Common Drug Review
Clinical Review Report

June 2016

Drug	Dulaglutide (Trulicity)
Indication	For the once-weekly treatment of adult patients with type 2 diabetes mellitus to improve glycemic control, in combination with: • diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance. • metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control. • metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control. • prandial insulin with metformin, when diet and exercise plus basal or basal-bolus insulin therapy (up to two injections of basal or basal plus prandial insulin per day) with or without oral antihyperglycemic medications do not achieve adequate glycemic control
Reimbursement request	For the once-weekly treatment of adult patients with type 2 diabetes mellitus to improve glycemic control, in combination with: • metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control. • metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control.
Dosage form(s)	0.75 mg and 1.5 mg (subcutaneous injection, once-weekly)
NOC date	November 10, 2015
Manufacturer	Eli Lilly Canada Inc.

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

TABLE OF CONTENTS

Tables

Figures

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
BMI	body mass index
BP	blood pressure
CDA	Canadian Diabetes Association
CI	confidence interval
CrI	credible interval
CNS	central nervous system
CSR	clinical study report
CV	cardiovascular
DIC	deviance information criterion
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DPP-4	dipeptidyl peptidase-4
EMA	European Medicines Agency
ECG	electrocardiogram
ER	emergency room
EQ-5D	EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSG	fasting serum glucose
GLP-1	glucagon-like peptide 1
A1C	glycated hemoglobin
HF	heart failure
HRQoL	health-related quality of life
IDC	indirect comparison
ITT	intention-to-treat
IWQOL-Lite	Impact of Weight on Quality of Life–Lite questionnaire
LOCF	last observation carried forward
LDCL-C	low-density–lipoprotein cholesterol
LS	least squares
LSM	least squares mean
MCID	minimal clinically important difference
MD	mean difference
MI	myocardial infarction
MMRM	mixed-model repeated measures
NMA	network meta-analysis
NA	not applicable

NR	not reported
NYHA	New York Heart Association
OAM	oral antihyperglycemic medication
OR	odds ratio
PG	plasma glucose
PP	per-protocol
RCT	randomized controlled trial
REML	restricted maximum likelihood
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SE	standard error
SR	systematic review
SGLT-2	sodium/glucose cotransporter-2
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TIA	transient ischemic attack
ULN	upper limit of normal
VAS	visual analogue scale
WDAE	withdrawal due to adverse event
WHO	World Health Organization

EXECUTIVE SUMMARY

Introduction

Diabetes mellitus (DM) is a metabolic disease that is characterized by persistent elevations in blood glucose (hyperglycemia). This persistent elevated blood glucose causes damage to blood vessels on a microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (peripheral artery disease, cardiovascular (CV) disease) level. There are two main subtypes of DM: type 1 (T1DM), in which the primary problem is a lack of adequate insulin secretion from pancreatic beta cells, and type 2 (T2DM), in which cells are unresponsive to insulin. Dulaglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist that mimics the effect of endogenous GLP-1, thereby stimulating glucose-dependent insulin secretion, decreasing glucagon output, slowing gastric emptying, and inducing satiety.

Indication under review
For the once-weekly treatment of adult patients with T2DM to improve glycemic control, in combination with: • diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance. • metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control. • metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control. • prandial insulin with metformin, when diet and exercise plus basal or basal-bolus insulin therapy (up to two injections of basal or basal plus prandial insulin per day) with or without oral antihyperglycemic medications do not achieve adequate glycemic control
Listing criteria requested by sponsor
For the once-weekly treatment of adult patients with type 2 diabetes mellitus to improve glycemic control, in combination with: • metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control. • metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control.

The objective of this review was to perform a systematic review of the beneficial and harmful effects of dulaglutide for the treatment of adults with T2DM who have experienced inadequate glycemic control on diet and exercise plus therapy with metformin alone or with metformin and a sulfonylurea.

Results and Interpretation

Included Studies

Add-on to metformin

The evidence for this review, as it pertains to the use of dulaglutide for the second-line treatment of adults with T2DM, was drawn from two phase 3, multi-centre, active-controlled, non-inferiority trials. AWARD-5 was an adaptive, inferentially seamless phase 2/3 study that randomized 1,098 participants to one of four primary treatment arms: dulaglutide 0.75 mg, dulaglutide 1.5 mg, sitagliptin 100 mg, and placebo then sitagliptin (placebo/sitagliptin) for 24 months. AWARD-6 was an open-label study that randomized 599 participants to receive dulaglutide 1.5 mg or liraglutide 1.8 mg for 26 weeks. The primary efficacy outcome for both studies was the change from baseline in glycated hemoglobin (A1C), although it was primarily measured at 52 weeks in AWARD-5 versus 26 weeks in AWARD-6. The primary objective of AWARD-5 was to evaluate the non-inferiority of dulaglutide 1.5 mg against sitagliptin using

a non-inferiority margin of 0.25%, whereas, for AWARD-6, it was to evaluate the non-inferiority of dulaglutide 1.5 mg versus liraglutide 1.8 mg using a margin of 0.4%. Other outcomes of interest that were collected across both trials include mortality, the percentage of participants achieving target A1C < 7%, change from baseline in fasting plasma glucose (FPG), body weight, blood pressure, health-related quality of life (HRQoL) using the EuroQol 5-Dimensions Health-Related Quality of Life (EQ-5D), as well as adverse events (AEs), serious adverse events (SAEs), and notable harms. HRQoL was additionally measured using the Impact of Weight on Quality of Life–Lite (IWQOL-Lite) questionnaire in AWARD-5, which also evaluated health care resource utilization.

Add-on to metformin and a sulfonylurea

The evidence for this review, as it pertains to the use of dulaglutide for the third-line treatment of adults with T2DM, was drawn from one phase 3, multi-centre, active-controlled, non-inferiority trial. AWARD-2 was an open-label trial, although double-blind with respect to the dulaglutide assignments, which randomized 810 participants to dulaglutide 0.75 mg, dulaglutide 1.5 mg, or insulin glargine for 78 weeks. The primary efficacy outcome for this study was the change from baseline in A1C at 52 weeks. The primary objective was to evaluate the non-inferiority of dulaglutide 1.5 mg against insulin glargine using a non-inferiority margin of 0.4%. Other outcomes of interest were mortality, the percentage of participants achieving target A1C < 7%, change from baseline in fasting serum glucose (FSG), body weight, blood pressure, and HRQoL using the EQ-5D, as well as AEs, SAEs, and notable harms.

Efficacy

The efficacy results for the second-line studies — i.e., add-on to metformin — are summarized in Table 1. The efficacy results for the third-line studies — i.e., add-on to metformin and a sulfonylurea — are summarized in Table 2. Only the outcome of change from baseline in A1C was considered in the pre-specified testing strategy, which means that the results of all other outcomes should be considered exploratory and be interpreted with caution, because they were not adjusted for multiplicity, which increases the risk of making a type 1 error.

Add-on to metformin

In AWARD-5, there were a total of four deaths, of which three were cardiovascular (CV) in nature — one each in the dulaglutide 1.5 mg, sitagliptin, and placebo/sitagliptin arms. No participant died in AWARD-6. In AWARD-5, four participants experienced treatment-emergent diabetic retinopathy — one receiving dulaglutide 0.75 mg group, two receiving dulaglutide 1.5 mg, and one receiving sitagliptin. More participants receiving dulaglutide 1.5 mg experienced treatment-emergent diabetic nephropathy than individuals in other treatment groups, while more participants receiving dulaglutide 0.75 mg experienced treatment-emergent diabetic neuropathy than individuals in other treatment groups. Further, a total of four patients suffered a non-fatal stroke or a transient ischemic attack (TIA) in this trial, of whom three were receiving dulaglutide 0.75 mg and one was receiving the dulaglutide 1.5 mg. Moreover, a total of six patients suffered a non-fatal myocardial infarction (MI) in this study. In AWARD-6, one participant receiving dulaglutide 1.5 mg experienced treatment-emergent diabetic retinopathy, while another in the same group experienced diabetic neuropathy, and one participant receiving dulaglutide 1.8 mg suffered a non-fatal MI.

In AWARD-5, among participants randomized during stage 1 or 2, there was a greater reduction from baseline in A1C at week 52 in the dulaglutide 0.75 and 1.5 mg groups compared with the sitagliptin group: least squares mean difference (LS MD) (nominal 95% confidence interval [CI]) of –0.47 (–0.63 to –0.31) ($P < 0.001$) and –0.71 (–0.87 to –0.55) ($P < 0.001$), respectively. In AWARD-6, dulaglutide 1.5 mg was statistically non-inferior versus liraglutide 1.8 mg with respect to the change in A1C from baseline to

week 26, as indicated by an LS MD (nominal 95% CI) of –0.06 (–0.19 to 0.07) ($P < 0.001$). The results were consistent across the different statistical models, populations used, and at the longest follow-up time point. Further, there did not seem to be any important interactions between subgroups of interest and treatment across the two trials. In AWARD-5, at 52 weeks, more participants receiving dulaglutide 0.75 mg (48.8%) and 1.5 mg (57.6%) achieved A1C < 7.0% than those receiving sitagliptin (33.0%) ($P < 0.001$). In AWARD-6, at 26 weeks, there was no statistically significant difference in the percentage of participants who achieved A1C < 7.0% between those receiving dulaglutide 1.5 mg (68.3%) and liraglutide 1.8 mg (67.9%)

In AWARD-5, participants receiving dulaglutide 0.75 mg and 1.5 mg experienced greater reduction in FPG at week 52 than those receiving sitagliptin: LS MD (95% CI) of –0.73 mmol/L (–1.07 to –0.39) ($P < 0.001$) and –1.47 mmol/L (–1.82 to –1.13) ($P < 0.001$), respectively. In AWARD-6, there was no statistically significant difference in reduction from baseline in FPG at week 26 between the dulaglutide 1.5 mg and liraglutide 1.8 mg groups: LS MD (95% CI) of –0.03 mmol/L (–0.32 to 0.25) ($P = 0.828$).

In AWARD-5, participants receiving dulaglutide 0.75 mg and 1.5 mg lost more weight at week 52 than those receiving sitagliptin: LS MD (95% CI) of –1.07 kg (–1.65 to –0.48) ($P < 0.001$) and –1.50 kg (–2.08 to –0.92) ($P < 0.001$), respectively. In AWARD-6, participants receiving dulaglutide 1.5 mg lost less weight at week 26 than those receiving liraglutide 1.8 mg: LS MD (95% CI) of 0.71 kg (0.17 to 1.26) ($P < 0.001$).

In AWARD-5, although statistical significance was not tested, there appeared to be a small increase (from baseline to week 52) in each of the mean scores of the EQ-5D visual analogue scale (VAS), EQ-5D UK, and US population-based Index Scores, as well as the total score on the IWQOL-Lite (Table 31). In AWARD-6, there were no statistically significant differences in changes in HRQoL at week 26 between participants receiving dulaglutide and sitagliptin or liraglutide

In AWARD-5, there were no statistically significant differences observed across the treatment groups at 52 weeks in the number of participants reporting at least one emergency room (ER) visit and no ER visits since the last visit. AWARD-6 did not assess health care resource utilization.

Add-on to metformin and a sulfonylurea

In AWARD-2, there were a total of three deaths, of which two were CV in nature — one each in the dulaglutide 0.75 mg and insulin glargine treatment arms. Four participants (all receiving dulaglutide 0.75 mg) experienced treatment-emergent diabetic retinopathy, while two individuals (both receiving insulin glargine) experienced treatment-emergent diabetic neuropathy. More participants receiving insulin glargine experienced a non-fatal stroke or TIA or MI than those in the other treatment groups.

At 52 weeks, with respect to the primary efficacy end point of the change in A1C from baseline, dulaglutide 0.75 mg was statistically non-inferior to insulin glargine — LS MD (nominal 95% CI) of –0.13 (–0.29 to 0.02) ($P < 0.001$) — and dulaglutide 1.5 mg was statistically superior to insulin glargine — LS MD (nominal 95% CI) of –0.45 (–0.60 to –0.29) ($P < 0.001$). The above results were consistent across the different statistical models, populations used, and at 104 weeks. There was a statistically significant interaction between treatment and duration of diabetes at baseline, specifically with respect to a difference in change in A1C from baseline to week 52. Further, there was no statistically significant difference in the percentage of participants who achieved A1C < 7.0% between those receiving dulaglutide 0.75 mg (37.1%) and insulin glargine (30.9%). There were, however, significantly more participants receiving dulaglutide 1.5 mg (53.2%) than those receiving insulin glargine who achieved A1C < 7.0%.

Participants receiving insulin glargine experienced greater reduction in FPG at week 52 than those receiving dulaglutide 0.75 mg — LS MD not reported — although the difference was not statistically significant when compared with those receiving dulaglutide 1.5 mg.

Participants receiving dulaglutide 0.75 mg and 1.5 mg lost more weight at week 52 than those receiving insulin glargine — LS MD not reported, but the 95% CIs ranged from 2.17 kg to 3.36 kg ($P < 0.001$), and 2.71 kg to 3.90 kg ($P < 0.001$) for the respective comparisons.

There were no statistically significant differences in reduction of blood pressure at week 52 between participants receiving dulaglutide and insulin glargine.

In AWARD-2, participants receiving dulaglutide experienced little or no change in HRQoL, whereas those receiving insulin glargine experienced a slight decrease, thus resulting in a statistically greater decrease in HRQoL with insulin glargine relative to dulaglutide.

Harms

The harms results for the second-line studies — i.e., add-on to metformin — are summarized in Table 3. The harms results for the third-line studies — i.e., add-on to metformin and a sulfonylurea — are summarized in Table 4.

Add-on to metformin

In AWARD-5, over the entire 24-month treatment period, at least 75% of participants in each treatment group experienced a treatment-emergent AE. A greater proportion of participants receiving dulaglutide 0.75 mg (84.4%) and 1.5 mg (85.2%) experienced an AE than those receiving sitagliptin (76.8%). The two most common AEs across the four treatment arms were nasopharyngitis and hyperglycemia. A greater proportion of participants receiving either dose of dulaglutide experienced nausea, diarrhea, and vomiting than those in the other treatment groups. A smaller proportion of participants receiving dulaglutide 1.5 mg experienced hyperglycemia than those in the other treatment groups. In AWARD-6, over the entire 26-week treatment period, more than 60% of participants in each treatment group experienced an AE, with a seemingly equal proportion in each arm. The most common AE across the treatment arms was nausea, followed by diarrhea, headache, and vomiting. There were no differences in the occurrence of AEs between participants receiving dulaglutide 1.5 mg and liraglutide 1.8 mg.

In AWARD-5, a smaller proportion of participants receiving dulaglutide 0.75 mg (7.5%) experienced an SAE when compared with those receiving dulaglutide 1.5 mg (11.8%), sitagliptin (10.2%), and placebo/sitagliptin (9.0%) over 24 months. In AWARD-6, a greater proportion of participants receiving liraglutide 1.8 mg (3.7%) experienced a SAE than those receiving dulaglutide 1.5 mg (1.7%) over 26 weeks.

In AWARD-5, at least 20% of participants in each treatment group discontinued from the study prior to 24 months, due to a death or an AE, with an approximately equal proportion of such withdrawals in each group. In AWARD-6, a smaller proportion of participants receiving dulaglutide 1.5 mg (2.0%) experienced an AE that led to discontinuation of study treatment versus those receiving liraglutide 1.8 mg (4.7%). However, a greater proportion of participants receiving dulaglutide 1.5 mg (4.3%) discontinued from the study prior to 26 weeks due to an AE, when compared with those receiving liraglutide 1.8 mg (1.7%)

In AWARD-5, over the entire 24-month treatment period, the proportion of participants who experienced hypoglycemia (plasma glucose [PG] ≤ 3.9 mmol/L) ranged from 4.5% (placebo/sitagliptin) to 12.8% (dulaglutide 1.5 mg). A greater proportion of participants in the dulaglutide 1.5 mg treatment group experienced hypoglycemia and documented symptomatic hypoglycemia than those in the dulaglutide 0.75 mg group. There were no differences in the proportion of participants who experienced other notable harms — specifically, injection-site reactions, pancreatitis, and pancreatic and thyroid cancer — across the four treatment groups. In AWARD-6, over the entire 26-week treatment period, a greater proportion of participants receiving dulaglutide 1.5 mg (8.7%) experienced hypoglycemia than those receiving liraglutide 1.8 mg (5.7%). There did not appear to be any differences in the proportion of participants who experienced other notable harms across the two treatment groups.

Add-on to metformin and a sulfonylurea

In AWARD-2, over the entire 78-week treatment period, approximately 70% of participants in each treatment group experienced an AE. The most common AE across the treatment arms were diarrhea and nausea, both of which occurred more commonly among participants receiving either dose of dulaglutide versus insulin glargine. A greater proportion of participants receiving the higher dose of dulaglutide experienced AEs, like diarrhea, nausea, nasopharyngitis, and headache, than those receiving the lower dose. Moreover, a greater proportion of participants receiving insulin glargine experienced nasopharyngitis than those receiving either dose of dulaglutide.

At least 10% of participants in each treatment group experienced an SAE over 78 weeks. A greater proportion of participants receiving insulin glargine (12.2%) experienced an SAE than those receiving either dulaglutide dose.

No participant receiving insulin glargine discontinued from study medication due to an AE and continued in the study prior to 78 weeks; this is in contrast to approximately 6% of participants who did so while receiving either of the dulaglutide doses. A greater proportion of participants who received either dose of dulaglutide discontinued from the study due to an AE prior to 78 weeks when compared with those receiving insulin glargine.

More than half of the participants in each treatment group experienced hypoglycemia (PG ≤ 3.9 mmol/L), with a greater proportion of those receiving insulin glargine (71.4%) than either dulaglutide dose (56.6% for 0.75 mg, 58.6% for 1.5 mg). This trend was consistent with those observed with respect to the occurrence of documented symptomatic hypoglycemia and nocturnal hypoglycemia across the three treatment groups. There did not appear to be any differences in the proportion of participants who experienced other notable harms across the groups.

Conclusions

Add-on to metformin

Two phase 3, multi-centre, active-controlled, non-inferiority trials met the inclusion criteria for this review, specifically as it pertained to the use of dulaglutide for the second-line treatment of adults with T2DM. AWARD-5 was an adaptive, inferentially seamless phase 2/3 study that randomized participants to dulaglutide 0.75 mg, dulaglutide 1.5 mg, sitagliptin 100 mg, and placebo/sitagliptin over 24 months. AWARD-6 was an open-label study that randomized 599 participants to receive dulaglutide 1.5 mg or liraglutide 1.8 mg over 26 weeks. Limitations of the two trials included a failure to control the type 1 error rate with all outcomes other than A1C, exclusion of some subgroups that limit the generalizability of findings, and the design of the trials which did not assess the impact of dulaglutide on microvascular or macrovascular complications of diabetes. The study populations across both trials were, however,

generally reflective of Canadian practice. With respect to the primary efficacy outcome, change from baseline in A1C, results from the two trials suggested that dulaglutide 0.75 mg and 1.5 mg were likely clinically superior to sitagliptin 100 mg up to 104 weeks, and that dulaglutide 1.5 mg was statistically non-inferior to liraglutide 1.8 mg up to 52 weeks. More than half of the participants across the treatment arms in each trial experienced an AE, and there were no apparent differences between dulaglutide and the comparators in the overall rates of AE. The manufacturer-submitted network meta-analysis (NMA) suggested clinically important reductions in A1C with dulaglutide 0.75 mg or 1.5 mg versus dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium/glucose cotransporter-2 (SGLT-2) inhibitors, thiazolidinediones, acarbose, and meglitinides; no differences were found against other GLP-1 agonists, sulfonylureas, and insulin. The results may be limited by the fact that all drugs (in the NMA) within a class were grouped and analyzed together, except for dulaglutide, without testing for evidence that the within-class treatment effects were similar. Another NMA evaluated the relative effects of various GLP-1 agonists as second-line therapy for T2DM, and generally found no within-class differences in efficacy or safety.

Add-on to metformin and a sulfonylurea

One phase 3, multi-centre, active-controlled, non-inferiority trial met the inclusion criteria for this review, specifically as it pertained to the use of dulaglutide for the third-line treatment of adults with T2DM. AWARD-2 was an open-label trial that randomized participants to dulaglutide 0.75 mg, dulaglutide 1.5 mg, and insulin glargine over 78 weeks (participants were blinded to dose of dulaglutide). Important limitations of this study included a failure to control the type 1 error rate with all outcomes other than A1C and the suboptimal manner in which insulin glargine may have been administered. The study population in this trial was generally reflective of Canadian practice, although the exclusion of certain subgroups of patients limits the generalizability of the findings. The trial duration was insufficient to adequately evaluate the CV risk profile of dulaglutide. With respect to the primary efficacy outcome, change from baseline in A1C, dulaglutide 0.75 mg and 1.5 mg were statistically non-inferior and superior, respectively, to insulin glargine up to 78 weeks. More than 70% of participants in each treatment group experienced an AE, and a greater proportion of participants who received insulin glargine than dulaglutide experienced hypoglycemia. The manufacturer-submitted NMA suggested clinically important reductions in A1C with dulaglutide 0.75 mg or 1.5 mg versus DPP-4 inhibitors and thiazolidinediones; no differences were found against other GLP-1 agonists, SGLT-2 inhibitors, basal insulin, biphasic insulin, and bolus insulin. The results of the NMA may be limited by the fact that all drugs (in the NMA) within a class were grouped and analyzed together, except for dulaglutide, without testing for evidence that the within-class treatment effects were similar.

TABLE 1: SUMMARY OF EFFICACY RESULTS (ADD-ON TO METFORMIN)

Outcome (Statistical Model/Analysis Population)	AWARD-5				AWARD-6	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/Sitagliptin	Dulaglutide 1.5 mg	Liraglutide 1.8 mg
A1C, % (ANCOVA/ITT for AWARD-5; MMRM/ITT for AWARD-6)						
Baseline, N	302	303	314	177	299	300
Baseline, mean (SD)	8.19 (1.11)	8.12 (1.05)	8.09 (1.09)	[redacted]	8.06 (0.81)	8.05 (0.79)
26 weeks, N					[redacted]	[redacted]
26 weeks, change from baseline, LS mean (SE)					–1.42 (0.05)	–1.36 (0.05)
26 weeks, LS mean difference (nominal 95% CI)					–0.06 (–0.19 to 0.07)	
P value for non-inferiority					< 0.001	
P value for superiority					0.186	
52 weeks, N	297	301	311	176		
52 weeks, change from baseline, LS mean (SE)	–0.87 (0.06)	–1.10 (0.06)	–0.39 (0.06)	[redacted]		
52 weeks, LS mean difference vs. sitagliptin (nominal 95% CI)	–0.47 (–0.63 to –0.31)	–0.71 (–0.87 to –0.55)				
P value for non-inferiority vs. sitagliptin	< 0.001	< 0.001				
P value for superiority vs. sitagliptin	< 0.001	< 0.001				
A1C, achieve < 7.0% (ITT for AWARD-5 and AWARD-6)						
26 weeks, N					[redacted]	[redacted]
26 weeks, n (%)					200 (68.3)	199 (67.9)
26 weeks, adjusted OR (95% CI); *P* value					[redacted]	
52 weeks, N	297	302	312	176		
52 weeks, n (%)	145 (48.8)	174 (57.6)	103 (33.0)	61 (34.7)		
52 weeks, adjusted OR (95% CI) vs. sitagliptin; *P* value	[redacted]	[redacted]				
FPG (mmol/L) (MMRM/ITT for AWARD-5; ANCOVA/ITT for AWARD-6)						
Baseline, N	296	297	308	176	299	300
Baseline, mean (SD)	9.68 (2.94)	9.75 (3.27)	9.56 (2.80)	9.86 (3.15)	9.28 (2.16)	9.16 (2.32)
26 weeks, N					[redacted]	[redacted]
26 weeks, adjusted change from baseline, LSM (SE)					–1.93 (0.12)	–1.90 (0.12)
26 weeks, LS mean difference (95% CI); *P* value					–0.03 (0.32 to 0.25); *P* = 0.828	
52 weeks, N	247	239	244	117		
52 weeks, adjusted change from baseline, LSM (SE)	–1.63 (0.13)	–2.38 (0.13)	–0.90 (0.13)	–0.92 (0.18)		

Outcome (Statistical Model/Analysis Population)	AWARD-5				AWARD-6	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/Sitagliptin	Dulaglutide 1.5 mg	Liraglutide 1.8 mg
52 weeks, LS mean difference vs. sitagliptin (95% CI); *P* value	[redacted]	[redacted]				
Body weight (kg) (ANCOVA/ITT for AWARD-5 and AWARD-6)						
Baseline, N	302	304	315	[redacted]	299	300
Baseline, mean (SD)	86.22 (17.99)	86.67 (17.45)	85.97 (16.91)	[redacted]	93.82 (18.23)	94.35 (18.96)
26 weeks, N					299	299
26 weeks, adjusted change from baseline, LSM (SE)					–2.90 (0.22)	–3.61 (0.22)
26 weeks, LS mean difference (95% CI); *P* value					0.71 (0.17 to 1.26); *P* = 0.010	
52 weeks, N	299	303	314	[redacted]		
52 weeks, change from baseline, LSM (SE)	–2.60 (0.23)	–3.03 (0.22)	–1.53 (0.22)	–1.61 (0.29)		
52 weeks, LS mean difference vs. sitagliptin (95% CI); *P* value	–1.07 (–1.65 to –0.48); *P* < 0.001	–1.50 (–2.08 to –0.92); *P* < 0.001				
Blood pressure, seated systolic (mm Hg) (MMRM/ITT for AWARD-5 and AWARD-6)						
Baseline, N	302	304	315	[redacted]	299	300
Baseline, mean (SD)	127.50 (14.12)	128.57 (12.78)	[redacted]	[redacted]	132.20 (14.97)	130.94 (15.14)
26 weeks, N					[redacted]	[redacted]
26 weeks, adjusted change from baseline, LSM (SE)					–3.36 (0.7)	–2.82 (0.7)
26 weeks, LS mean difference (95% CI); *P* value					[redacted]	
52 weeks, N	255	246	253	121		
52 weeks, change from baseline, LS mean (SE)	–0.53 (0.67)	–0.79 (0.67)	[redacted]	[redacted]		
52 weeks, LS mean difference vs. sitagliptin (95% CI); *P* value	[redacted]	[redacted]				
Blood pressure, seated diastolic (mm Hg) (MMRM/ITT for AWARD-5 and AWARD-6)						
Baseline, N	302	304	315	[redacted]	299	300
Baseline, mean (SD)	77.65 (8.63)	77.86 (8.26)	77.32 (8.66)	77.68 (8.16)	79.88 (9.45)	79.10 (9.19)
26 weeks, N					[redacted]	[redacted]
26 weeks, change from baseline, LSM (SE)					–0.22 (0.4)	–0.31 (0.4)
26 weeks, LS mean difference (95% CI); *P* value					[redacted]	
52 weeks, N	[redacted]	[redacted]	[redacted]	[redacted]		
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]		

Outcome (Statistical Model/Analysis Population)	AWARD-5				AWARD-6	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/Sitagliptin	Dulaglutide 1.5 mg	Liraglutide 1.8 mg
52 weeks, LS mean difference vs. sitagliptin (95% CI); *P* value	[redacted]	[redacted]				

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; FPG = fasting plasma glucose; ITT = intention-to-treat; LS = least squares; LSM = least squares mean; MMRM = mixed-model repeated measures; OR = odds ratio; PP = per-protocol; SD = standard deviation; SE = standard error.

TABLE 2: SUMMARY OF EFFICACY RESULTS (ADD-ON TO METFORMIN AND A SULFONYLUREA)

Outcome (Statistical Model/Analysis Population)	AWARD-2		
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Insulin Glargine
A1C, % (ANCOVA/ITT)			
Baseline, N	272	273	262
Baseline, mean (SD)	8.13 (0.98)	8.18 (1.03)	8.10 (0.95)
52 weeks, N	[redacted]	[redacted]	[redacted]
52 weeks, change from baseline, LS mean (SE)	–0.76 (0.06)	–1.08 (0.06)	–0.63 (0.06)
52 weeks, LS mean difference vs. insulin glargine (nominal 95% CI)	[redacted]	[redacted]	
P value for non-inferiority vs. insulin glargine	[redacted]	[redacted]	
P value for superiority vs. insulin glargine	[redacted]	[redacted]	
< 7.0% (ITT)			
52 weeks, N	[redacted]	[redacted]	[redacted]
52 weeks, n (%)	[redacted]	[redacted]	[redacted]
52 weeks, adjusted OR (95% CI) vs. insulin glargine; *P* value	[redacted]	[redacted]	
FSG (mmol/L) (MMRM/ITT)			
Baseline, N	272	273	262
Baseline, mean (SD)	8.96 (2.70)	9.16 (2.73)	9.08 (2.66)
52 weeks, N	[redacted]	[redacted]	[redacted]
52 weeks, change from baseline, LS mean (SE)	–0.87 (0.14)	–1.50 (0.14)	–1.76 (0.14)
52 weeks, LS mean difference vs. insulin glargine (95% CI); *P* value	[redacted]	[redacted]	
Body weight (kg) (ANCOVA/ITT)			
Baseline, N	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	86.4 (18.01)	85.2 (17.81)	87.6 (19.69)
52 weeks, N	[redacted]	[redacted]	[redacted]

Outcome (Statistical Model/Analysis Population)	AWARD-2		
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Insulin Glargine
52 weeks, change from baseline, LS mean (SE)	–1.33 (0.24)	–1.87 (0.24)	1.44 (0.24)
52 weeks, LS mean difference vs. insulin glargine (95% CI); *P* value	[redacted]	[redacted]	
Blood pressure, seated systolic (mm Hg) (MMRM/ITT)			
Baseline, N	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
52 weeks, N	[redacted]	[redacted]	[redacted]
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]
52 weeks, LS mean difference vs. insulin glargine (nominal 95% CI); *P* value	[redacted]	[redacted]	
Blood pressure, seated diastolic (mm Hg) (MMRM/ITT)			
Baseline, N	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
52 weeks, N	[redacted]	[redacted]	[redacted]
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]
52 weeks, LS mean difference vs. insulin glargine (nominal 95% CI); *P* value	[redacted]	[redacted]	

ANCOVA = analysis of covariance; CI = confidence interval; FSG = fasting serum glucose; A1C = glycated hemoglobin; ITT = intention-to-treat; LS = least squares; MMRM = mixed-model repeated measures; NR = not reported; OR = odds ratio; PP = per-protocol; SD = standard deviation; SE = standard error.

TABLE 3: SUMMARY OF HARMS RESULTS (ADD-ON TO METFORMIN)

	AWARD-5 (24 months)				AWARD-6 (26 weeks)	
	Dulaglutide 0.75 mg (N = 302)	Dulaglutide 1.5 mg (N = 304)	Sitagliptin (N = 315)	Placebo/Sitagliptin (N = 177)	Dulaglutide 1.5 mg (N = 299)	Liraglutide 1.8 mg (N = 300)
SAEs						
Participants with > 0 SAEs, n (%)	23 (7.6)	36 (11.8)	32 (10.2)	[redacted]	5 (1.7)	11 (3.7)
WDAEs						
Discontinuation of study drug, n (%)	NR	NR	NR	[redacted]	[redacted]	[redacted]
Discontinuation of study, n (%)	64 (21.2)	64 (21.2)	67 (21.3)	[redacted]	[redacted]	[redacted]

	AWARD-5 (24 months)				AWARD-6 (26 weeks)	
	Dulaglutide 0.75 mg (N = 302)	Dulaglutide 1.5 mg (N = 304)	Sitagliptin (N = 315)	Placebo/Sitagliptin (N = 177)	Dulaglutide 1.5 mg (N = 299)	Liraglutide 1.8 mg (N = 300)
Notable Harms						
Participants with > 0 notable harms, n (%)						
Hypoglycemia (PG ≤ 3.9 mmol/L)	26 (8.6)	39 (12.8)	27 (8.6)	[redacted]	26 (8.7)	17 (5.7)
Documented symptomatic hypoglycemia (PG ≤ 3.9 mmol/L)	19 (6.3)	33 (10.9)	18 (5.7)	[redacted]	8 (2.7)	8 (2.7)
Nocturnal hypoglycemia (PG ≤ 3.9 mmol/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycemia SAE	0	0	0	[redacted]	0	0
Injection-site reactions	3 (1.0)	4 (1.3)	3 (1.0)	[redacted]	1 (0.3)	2 (0.7)
Pancreatitis	0	0	2 (0.6)	[redacted]	0	0
Pancreatitis (acute)	0	0	0	[redacted]	0	0
Pancreatitis (chronic)	1 (0.3)	1 (0.3)	0	[redacted]	0	0
Pancreatic cancer	NR	NR	NR	[redacted]	0	0
Thyroid cancer	0	1 (0.3)	0	[redacted]	0	1 (0.3)

AE = adverse event; NR = not reported; PG = plasma glucose; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

TABLE 4: SUMMARY OF HARMS RESULTS (ADD-ON TO METFORMIN AND A SULFONYLUREA)

	AWARD-2		
	Dulaglutide 0.75 mg (N = 272)	Dulaglutide 1.5 mg (N = 273)	Insulin Glargine (N = 262)
SAEs			
Participants with > 0 SAEs, n (%)	28 (10.3)	32 (11.7)	32 (12.2)
WDAEs			
Discontinuation of study drug and continued in the study, n (%)	[redacted]	[redacted]	[redacted]
Discontinuation of study, n (%)	8 (2.9)	9 (3.3)	5 (1.9)
Notable Harms			
Participants with > 0 notable harms, n (%)			
Hypoglycemia (PG ≤ 3.9 mmol/L)	154 (56.6)	160 (58.6)	187 (71.4)
Documented symptomatic hypoglycemia (PG ≤ 3.9 mmol/L)	106 (39.0)	110 (40.3)	134 (51.1)
Nocturnal hypoglycemia	63 (23.2)	70 (25.6)	104 (39.7)
Hypoglycemia SAE	0	2 (0.7)	2 (0.8)
Injection-site reactions	[redacted]	[redacted]	[redacted]
Pancreatitis (acute and chronic)	1 (0.4)	2 (0.7)	1 (0.4)
Pancreatitis	1 (0.4)	1 (0.4)	1 (0.4)
Pancreatitis (chronic)	0	1 (0.4)	0
Pancreatic cancer	NR	NR	NR
Thyroid cancer	0	1 (0.4)	0
Thyroid neoplasm	0	1 (0.4)	1 (0.4)

AE = adverse event; NR = not reported; PG = plasma glucose; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Diabetes mellitus (DM) is a metabolic disease that is characterized by persistent elevations in blood glucose (hyperglycemia). This persistent elevated blood glucose causes damage to blood vessels on a microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (peripheral artery disease, cardiovascular [CV] disease) level. There are two main subtypes of DM: type 1 (T1DM), in which the primary problem is a lack of adequate insulin secretion from pancreatic beta cells, and type 2 (T2DM), in which cells are unresponsive to insulin. T2DM is more common than T1DM, accounting for approximately 90% of cases of DM.[2] The etiology of T1DM is unknown, although onset is typically early in life. In contrast, onset of T2DM is typically later in life, although this is changing with the current epidemic of childhood obesity in Western societies. Poor diet and minimal exercise, and associated weight gain, are considered to be risk factors for T2DM.[3] There is overlap between the two conditions, most notably that patients with T2DM, who, in the initial stages of their disease, are able to secrete insulin, or may be hyperinsulinemic, eventually progress to a stage where insulin secretion is reduced, similar to T1DM.

Diabetes is a chronic, metabolic disease with significant health impact. The incidence of diabetes is increasing at a dramatic rate around the world. The International Diabetes Federation estimated that 371 million people had diabetes in 2012, and the prevalence is expected to increase to 552 million by 2030.[4] In Canada, the prevalence of diabetes was 6.8% (2.4 million Canadians) in 2009, and is expected to rise to 3.7 million people by 2019.[5] People with diabetes are more likely to be hospitalized, and to experience complications requiring specialist care. By 2020, the diabetes-associated costs to the Canadian health care system will be an estimated $16.9 billion per year.[6]

1.2 Standards of Therapy

There are many classes of drugs used in treating T2DM (see Table 5 and Table 6). Metformin is widely considered to be the first-line drug of choice, with other drug classes added to metformin or used in combination with each other in patients unable to achieve therapeutic targets.[7] These therapies include the sulfonylureas and the incretins, which comprise dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists. Other drug classes include the thiazolidinediones, which have had considerable safety issues, prescribing restrictions, and market withdrawals since their arrival on the market in the 1990s, the meglitinides, which act in a similar manner to the sulfonylureas, and the alpha-glucosidase inhibitors, which have a simple mechanism (block glucose absorption) and are typically used in combination with other drugs. Insulin and insulin analogues can be used in rapid-acting, intermediate or longer-acting forms, and are all administered by injection.

1.3 Drug

Dulaglutide is a long-acting GLP-1 receptor agonist that mimics the effect of endogenous GLP-1, thereby stimulating glucose-dependent insulin secretion, decreasing glucagon output, slowing gastric emptying, and inducing satiety.[8] The recommended starting dose of dulaglutide is 0.75 mg once weekly, administered subcutaneously. The dose may be increased to 1.5 mg once weekly for additional glycemic control. The maximum recommended dose is 1.5 mg once weekly. Other GLP-1 receptor agonists currently approved in Canada are albiglutide, exenatide, and liraglutide.

Indication under review
For the once-weekly treatment of adult patients with T2DM to improve glycemic control, in combination with: • diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance. • metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control. • metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control. • prandial insulin with metformin, when diet and exercise plus basal or basal-bolus insulin therapy (up to two injections of basal or basal plus prandial insulin per day) with or without oral antihyperglycemic medications, do not achieve adequate glycemic control
Listing criteria requested by sponsor
For the once-weekly treatment of adult patients with T2DM to improve glycemic control, in combination with: • metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control. • metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control.

TABLE 5: KEY CHARACTERISTICS OF GLP-1 ANALOGUES, THIAZOLIDINEDIONES, DPP-4 INHIBITORS, INSULIN

	GLP-1 Analogues	Thiazolidinediones (Pioglitazone)	DPP-4 Inhibitors	Insulin or Insulin Analogues
Mechanism of Action	Stimulates GLP-1, which leads to: • Insulin secretion • Inhibits glucagon release • Delays gastric emptying • Reduces food intake	PPAR-γ agonists • Increase uptake of FFA • Increase uptake of glucose • Reduce glucose synthesis	Increase GLP-1 by inhibiting the DPP-4 enzyme, which inactivates GLP-1 and leads to: • Insulin secretion • Inhibits glucagon release • Delays gastric emptying • Reduces food intake	Substitute for endogenously secreted insulin
Indication[a]	Liraglutide: T2DM in combination with metformin or metformin and a sulfonylurea, when these drugs, with diet and exercise, do not provide adequate glycemic control; T2DM in combination with metformin and a basal insulin, when liraglutide and metformin, with diet and exercise, do not provide adequate glycemic control	T2DM that cannot be adequately controlled by diet and exercise alone. May be used as monotherapy or in combination with a sulfonylurea or metformin when monotherapy fails to adequately control blood glucose.	Saxagliptin: T2DM in combination with metformin 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	Patients with DM who require insulin for control of hyperglycemia

	GLP-1 Analogues	Thiazolidinediones (Pioglitazone)	DPP-4 Inhibitors	Insulin or Insulin Analogues
	Albiglutide: T2DM that cannot be adequately controlled by diet and exercise alone. May be used as monotherapy or in combination with metformin, metformin and a sulfonylurea, or basal insulin with oral antidiabetic therapies. Exenatide (twice daily): T2DM that cannot be adequately controlled by diet and exercise alone. May be used as monotherapy or in combination with metformin, a sulfonylurea, or metformin and a sulfonylurea. Exenatide (extended-release, once weekly): T2DM that cannot be adequately controlled by diet and exercise alone. May be used in combination with metformin, a sulfonylurea, metformin and a sulfonylurea, or insulin glargine. Dulaglutide: T2DM that cannot be adequately controlled by diet and exercise alone. May be used in combination with metformin, metformin and a sulfonylurea, or prandial insulin with metformin.		(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	
Route of Administration	Subcutaneous	Oral	Oral	Subcutaneous

	GLP-1 Analogues	Thiazolidinediones (Pioglitazone)	DPP-4 Inhibitors	Insulin or Insulin Analogues
Recommended Dose	Varies by drug	15 to 30 mg once daily	Varies by drug	Titrated
Serious Side Effects / Safety Issues	Warnings and precautions: • Thyroid cancer • Prolonged PR interval • Hypoglycemia (when combined with sulfonylurea) • Pancreatitis Contraindications: Personal or family history of MTC and in patients with MEN2	Serious warnings: Bone fractures in women Fluid retention Warnings and precautions: • Bladder cancer • Heart failure • Hepatitis or hepatic failure	Contraindications: • DKA • Warnings and precautions: • Heart failure • Pancreatitis • Immune suppression	Serious warnings and precautions: • Hypoglycemia • Immune responses

DKA = diabetic ketoacidosis; DM = diabetes mellitus; DPP-4 = dipeptidyl peptidase 4; FFA = free fatty acid; GLP-1 = glucagon-like peptide 1; MEN2 = multiple endocrine neoplasia syndrome type 2; MTC = medullary thyroid carcinoma; PPAR = peroxisome proliferator-activated receptor; T2DM = type 2 diabetes mellitus.
[a] Health Canada indication.
Source: Product monographs from e-CPS.[9]

TABLE 6: KEY CHARACTERISTICS OF SGLT-2 INHIBITORS, METFORMIN, SULFONYLUREAS

	SGLT-2 Inhibitors	Biguanides (Metformin)	Sulfonylureas
Mechanism of Action	Inhibits the SGLT-2 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 (SUR1)
Indication[a]	Canagliflozin In T2DM: • As monotherapy in patients for whom metformin is inappropriate • In combination with metformin or a sulfonylurea when diet and exercise plus monotherapy with one of these drugs does not provide adequate glycemic control • In combination with metformin and either a sulfonylurea or pioglitazoneb when diet, exercise, and dual therapy (with metformin plus either a sulfonylurea or pioglitazone) do not provide	• T2DM that cannot be controlled by proper dietary management, exercise, and weight reduction, or when insulin therapy is not appropriate • Treatment of obese patients with diabetes	T2DM in adults, alone or in combination with other antihyperglycemic drugs as an adjunct to exercise and diet

	SGLT-2 Inhibitors	Biguanides (Metformin)	Sulfonylureas
	adequate glycemic control. • Combination therapy with insulin (with or without metformin) when diet and exercise, and therapy with insulin (with or without metformin) do not provide adequate glycemic control.		
Route of Administration	Oral	Oral	Oral
Recommended Dose	100 mg to 300 mg once daily	850 mg to 1,000 mg twice daily	Varies by drug
Serious Side Effects / Safety Issues	Contraindications: Renally impaired patients with eGFR less than 45 mL/min/ 1.73 m^2, end-stage renal disease or patients on dialysis. 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 DKA • Severe renal impairment Warnings: • Lactic acidosis (rare)	Contraindications: • Ketoacidosis • Severe liver or renal impairment Precautions: • Hypoglycemia

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

[a] Health Canada indication.

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

Source: Product monographs from e-CPS.[9]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of dulaglutide for the treatment of adults with T2DM who have experienced inadequate glycemic control on diet and exercise plus therapy with metformin alone or with metformin and a sulfonylurea.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 7.

TABLE 7: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with T2DM who have experienced inadequate glycemic control on diet and exercise plus therapy with metformin alone or with metformin and a sulfonylurea. **Subgroups** • Age • Baseline A1C • eGFR • T2DM duration
Intervention	Dulaglutide at a dose of 0.75 mg/0.5 mL or 1.5 mg/0.5 mL mg (subcutaneous injection, once-weekly)[a]
Comparators	**When used in combination with metformin alone** • Placebo • SGLT-2 inhibitors • Incretins (DPP-4 inhibitors, GLP-1 analogues) • Thiazolidinediones • Meglitinides • Insulin or insulin analogues • Alpha-glucosidase inhibitors • Sulfonylureas **When used in combination with metformin and a sulfonylurea** • Placebo • SGLT2 inhibitors • Incretins (DPP-4 inhibitors, GLP-1 analogues) • Thiazolidinediones • Meglitinides • Insulin or insulin analogues • Alpha-glucosidase inhibitors
Outcomes	**Key efficacy outcomes** • Mortality • Diabetes-related morbidity (macrovascular, microvascular) • Glycemic control (A1C, FPG)[b] • Health-related quality of life[b] • Body weight[b] • Blood pressure[b]

	Other outcomes • Treatment satisfaction or preference • Fear of injections • Health care resource utilization **Harms outcomes** • AEs, SAEs, WDAEs • Notable harms: hypoglycemia, injection-site reactions, pancreatitis, and pancreatic and thyroid cancers
Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; DB = double-blind; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide 1; FPG = fasting plasma glucose; A1C = glycated hemoglobin; RCT = randomized controlled trial; SAE = serious adverse event; SGLT-2 = sodium/glucose cotransporter 2; T2DM = type 2 diabetes mellitus; WDAE = withdrawal due to adverse event.
[a] In combination with metformin alone or with metformin and a sulfonylurea.
[b] Identified 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 (1946–) with in-process records and daily updates via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Trulicity (Dulaglutide).

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

The initial search was completed on January 27, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on May 18, 2016. 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/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Devices Regulatory Approvals, Advisories and Warnings, Drug Class Review, Databases (free), Internet Search. 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 8 and Table 9; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings From the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 8 and Table 9, and described in section 3.2: Included Studies. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

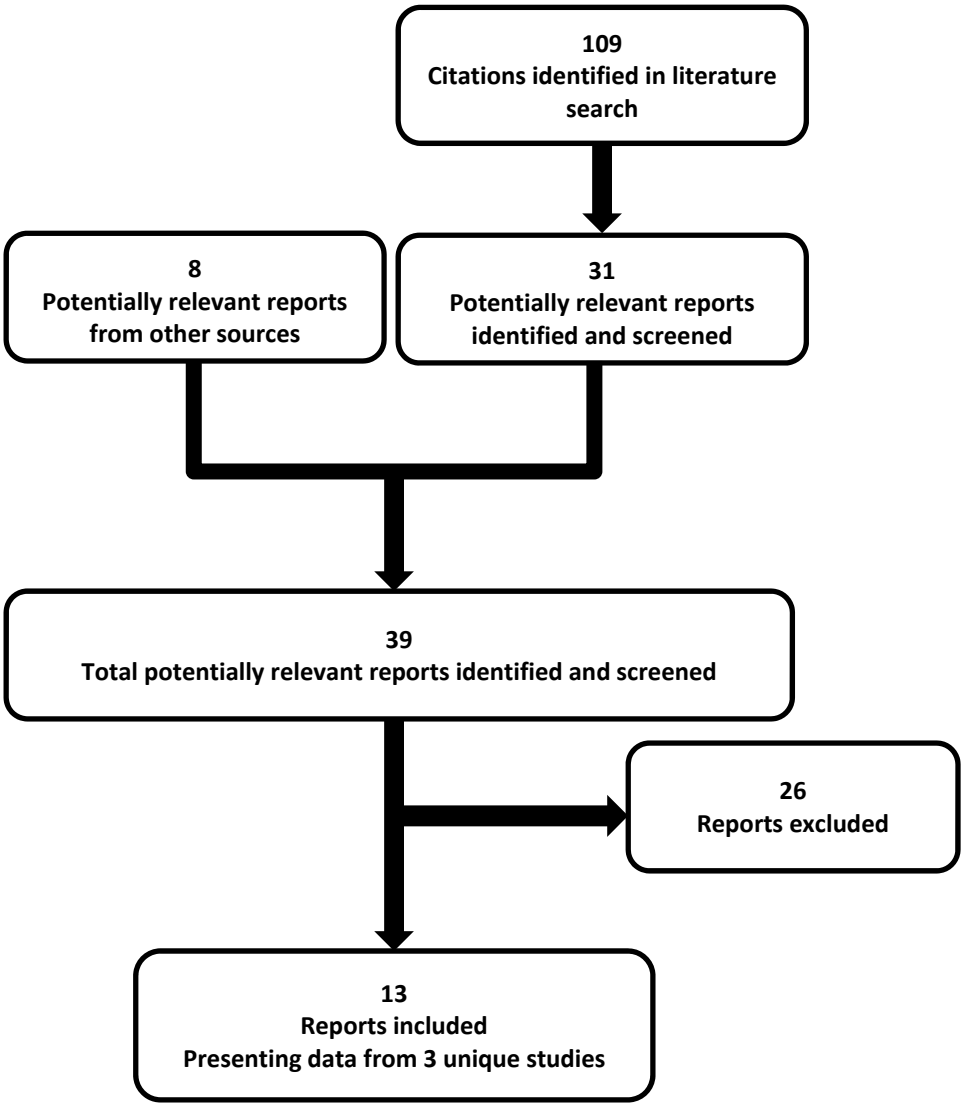


TABLE 8: DETAILS OF INCLUDED STUDIES (ADD-ON TO METFORMIN)

		AWARD-5	AWARD-6
DESIGNS & POPULATIONS	**Study Design**	Adaptive, inferentially seamless, multi-centre, double-blind (up to 12 months), double-dummy phase 2/3 non-inferiority RCT stratified by country	Multi-centre, open-label, active-controlled phase 3 non-inferiority RCT stratified by country and baseline A1C at randomization
	Locations	Canada, France, India, South Korea, Puerto Rico, Russia, Taiwan	Czech Republic, Hungary, Slovakia
		Germany, Mexico, Poland, Romania, Spain, United States	
	Randomized (N)	1,202 (stage 1 or 2)	599
	Inclusion Criteria	• Age 18 to 75 years • Been treated with diet and exercise alone, or taking metformin or another OAM as monotherapy, or taking metformin in combination with another OAM at screening • Must have been able to tolerate metformin at a dose ≥ 1,500 mg/day for ≥ 6 weeks prior to randomization • A1C value ≥ 7.0% to ≤ 9.5% at screening, except patients on diet and exercise therapy, who must have had A1C values > 8.0% to ≤ 9.5% • BMI ≥ 25 to ≤ 40 kg/m^2	• Age ≥ 18 years • Not optimally controlled with diet and exercise and metformin ≥ 1,500 mg/day and had been at a stable dose ≥ 3 months prior to screening • A1C value ≥ 7.0% to ≤ 10.0% at screening • BMI ≤ 45 kg/m^2
		Male or non-pregnant females with T2DM per WHO criteria; stable weight (± 5%) for ≥ 3 months prior to screening	
	Exclusion Criteria	• History of > 2 episodes of ketoacidosis or hyperosmolar state requiring hospitalization in the 6 months prior to study entry • Treatment with a GLP-1 receptor agonist within 6 months prior to study entry • Receipt of CNS stimulant; clinically relevant CV events within 6 months of study entry or between study entry and randomization • Poorly controlled hypertension at study entry or randomization • Abnormal ECG reading • Significant liver or kidney disease or a significant active uncontrolled endocrine or autoimmune abnormality	• History of ≥ 1 episode of ketoacidosis or hyperosmolar state or coma • Treatment with any OAMs (other than metformin) at screening or within 3 months prior; insulin use within 3 months prior to screening • Acute MI, NYHA Class III or IV HF, or TIA within 2 months prior to screening • Any self or family history of type 2A or type 2B multiple endocrine neoplasia in the absence of known C-cell hyperplasia • Any self or family history of medullary C-cell hyperplasia, focal hyperplasia, carcinoma; serum calcitonin ≥ 5.84 pmol/L at screening • Contraindication for the use of dulaglutide, metformin, or liraglutide

		AWARD-5	AWARD-6
			• Hematological condition that may have interfered with A1C measurement
		• T1DM • Acute or chronic hepatitis, signs and symptoms of any other liver disease, or ALT ≥ 3x ULN at screening • History of chronic pancreatitis or acute idiopathic pancreatitis • Use of weight loss drugs • Receipt of chronic (> 14 days) systemic glucocorticoid therapy or receipt of such therapy within 4 weeks prior to screening • Known clinically significant gastric emptying abnormality or undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery • Serum creatinine ≥ 132.6 µmol/L (male) or ≥ 123.76 µmol/L (female), or a creatinine clearance < 60 mL/minute at screening • Evidence of a significant, uncontrolled endocrine abnormality • Evidence of a significant, active autoimmune abnormality • History of a transplanted organ • History of an active or untreated malignancy, or were in remission from a clinically significant malignancy during last 5 years of screening	
DRUGS	**Intervention(s)**	Dulaglutide, 0.75 mg (subcutaneous injection, once weekly) plus metformin, ≥ 1,500 mg/day (tablet)[a] Dulaglutide, 1.5 mg (subcutaneous injection, once weekly) plus metformin, ≥ 1,500 mg/day (tablet)[a]	Dulaglutide, 1.5 mg (subcutaneous injection, once weekly) plus metformin, ≥ 1,500 mg/day (tablet)
	Comparator(s)	Sitagliptin, 100 mg (tablet, once daily) plus metformin, ≥ 1,500 mg/day (tablet) Placebo (tablet, once daily) plus metformin, ≥ 1,500 mg/day (tablet) (placebo switched to sitagliptin, 100 mg [tablet, once daily] after 6 months of treatment)	Liraglutide, 1.8 mg (subcutaneous injection, once daily) plus metformin, ≥ 1,500 mg/day (tablet)
DURATION	Phase		
	Screening and lead-in	Lead-in: 11 weeks	Screening: 2 weeks
	Treatment	24 months	26 weeks
	Safety follow-up	30 days	4 weeks

		AWARD-5	AWARD-6
OUTCOMES	**Primary End Point**	Change from baseline in A1C at 52 weeks (primary hypothesis to evaluate non-inferiority of dulaglutide 1.5 mg against sitagliptin using non-inferiority margin of 0.25%)	Change from baseline in A1C at 26 weeks (primary hypothesis to evaluate non-inferiority against liraglutide using non-inferiority margin of 0.4%)
	Other End Points	IWQOL-Lite, health care resource utilization	(No unique end points)
		Mortality, % of participants achieving target A1C < 7%; change from baseline in FPG, body weight, blood pressure, EQ-5D, harms	
NOTES	**Publications**	Nauck et al. 2014,[10] Weinstock et al. 2015[11]	Dungan et al. 2014[12]

A1C = glycated hemoglobin; ALT = alanine aminotransferase; BMI = body mass index; CNS = central nervous system; CV = cardiovascular; ECG = electrocardiogram; EQ-5D = EuroQol-5 Dimensions Health-Related Quality of Life Questionnaire; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; HF = heart failure; IWQOL-Lite = Impact of Weight on Quality of Life–Lite; MI = myocardial infarction; NYHA = New York Heart Association; OAM = oral antihyperglycemic medication; RCT = randomized controlled trial; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack; ULN = upper limit of normal; WHO = World Health Organization.

[a] Dulaglutide 0.75 mg and 1.5 mg were doses used in the phase 3 stage of the trial.

Note: Six additional reports were included: CADTH Common Drug Review submission,[15] FDA medical review,[16] FDA statistical review,[17] Health Canada Biologics safety and efficacy assessment report,[18] Health Canada Notice of Deficiency,[19] Yu et al. 2015.[20]

Source: AWARD-5 Clinical Study Report(CSR)[13], AWARD-6 CSR.[14]

TABLE 9: DETAILS OF INCLUDED STUDIES (ADD-ON TO METFORMIN AND A SULFONYLUREA)

		AWARD-2
DESIGNS & POPULATIONS	**Study Design**	Multi-centre, open-label (double-blind with respect to dulaglutide assignment), active-controlled phase 3 non-inferiority RCT stratified by country and baseline A1C at randomization
	Locations	Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Spain, France, Greece, Croatia, Hungary, India, Italy, South Korea, Mexico, Poland, Romania, Sweden, Slovakia, Taiwan
	Randomized (N)	810
	Inclusion Criteria	• Male or non-pregnant females ≥ 18 years with T2DM per WHO criteria not optimally controlled with 1, 2, or 3 OAMs (at least 1 of which must have been metformin or a sulfonylurea) • A1C value ≥ 7.0% to ≤ 11.0% at screening and on the minimal monotherapy required dose or higher for metformin (≥ 1,500 mg/day) and glimepiride (≥ 4 mg/day) • Stable weight (± 5%) for ≥ 3 months prior to screening • BMI ≥ 23 ≤ 45 kg/m^2
	Exclusion Criteria	• A1C value ≤ 6.5% at randomization • T1DM

		AWARD-2
		• Prior chronic insulin therapy or therapy with any GLP-1 receptor agonist in the 3 months prior to screening • Use of weight loss drugs • Receipt of chronic (> 14 days) systemic glucocorticoid therapy or receipt of such therapy within 4 weeks prior to screening • Acute MI, NYHA Class III or IV HF, or TIA within 2 months prior to screening • Clinically significant gastric emptying abnormality; acute or chronic hepatitis, signs and symptoms of any other liver disease, or ALT ≥ 3x ULN at screening • Acute or chronic pancreatitis • Serum creatinine ≥ 132.6 µmol/L (male) or ≥ 123.76 µmol/L (female), a creatinine clearance < 60 mL/minute at screening • Significant, uncontrolled endocrine abnormality • Self or family history of type 2A or type 2B multiple endocrine neoplasia, medullary C-cell hyperplasia, focal hyperplasia, or carcinoma • Serum calcitonin ≥ 5.84 pmol/L • Organ transplantation other than corneal transplants • Hematological condition that may interfere with A1C measurement
DRUGS	**Intervention(s)**	Dulaglutide, 1.5 mg (subcutaneous injection, once weekly) plus metformin, ≥ 1,500 mg/day (tablet) and glimepiride, ≥ 4 mg/day (tablet) Dulaglutide, 0.75 mg (subcutaneous injection, once weekly) plus metformin, ≥ 1,500 mg/day (tablet) and glimepiride, ≥ 4 mg/day (tablet)
	Comparator(s)	Insulin glargine, titrated-to-target (subcutaneous injection, once daily) plus metformin, ≥ 1,500 mg/day (tablet) and glimepiride, ≥ 4 mg/day (tablet)
DURATION	Phase	
	Lead-in	10 weeks
	Treatment	78 weeks
	Safety follow-up	4 weeks
OUTCOMES	**Primary End Point**	Change from baseline in A1C at 52 weeks (primary hypothesis to evaluate non-inferiority of dulaglutide 1.5 mg against insulin glargine using non-inferiority margin of 0.4%)
	Other End Points	Mortality, % of participants achieving target A1C < 7%; change from baseline in FSG, body weight, blood pressure, EQ-5D, harms

		AWARD-2
NOTES	**Publications**	Giorgino et al. 2015[21]

A1C = glycated hemoglobin; ALT = alanine aminotransferase; BMI = body mass index; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; FSG = fasting serum glucose; GLP-1 = glucagon-like peptide-1; HF = heart failure; MI = myocardial infarction; NYHA = New York Heart Association; OAM = oral antihyperglycemic medication; RCT = randomized controlled trial; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack; ULN = upper limit of normal; WHO = World Health Organization.

Note: Six additional reports were included: CADTH Common Drug Review (CDR) submission Trulicity,[15] FDA medical review,[16] FDA statistical review,[17] Health Canada Biologics safety and efficacy assessment report,[18] Health Canada Notice of Deficiency,[19] Yu et al. 2015.[20]

Source: AWARD-2 Clinical Study Report.[22]

3.2 Included Studies

3.2.1 Description of Studies

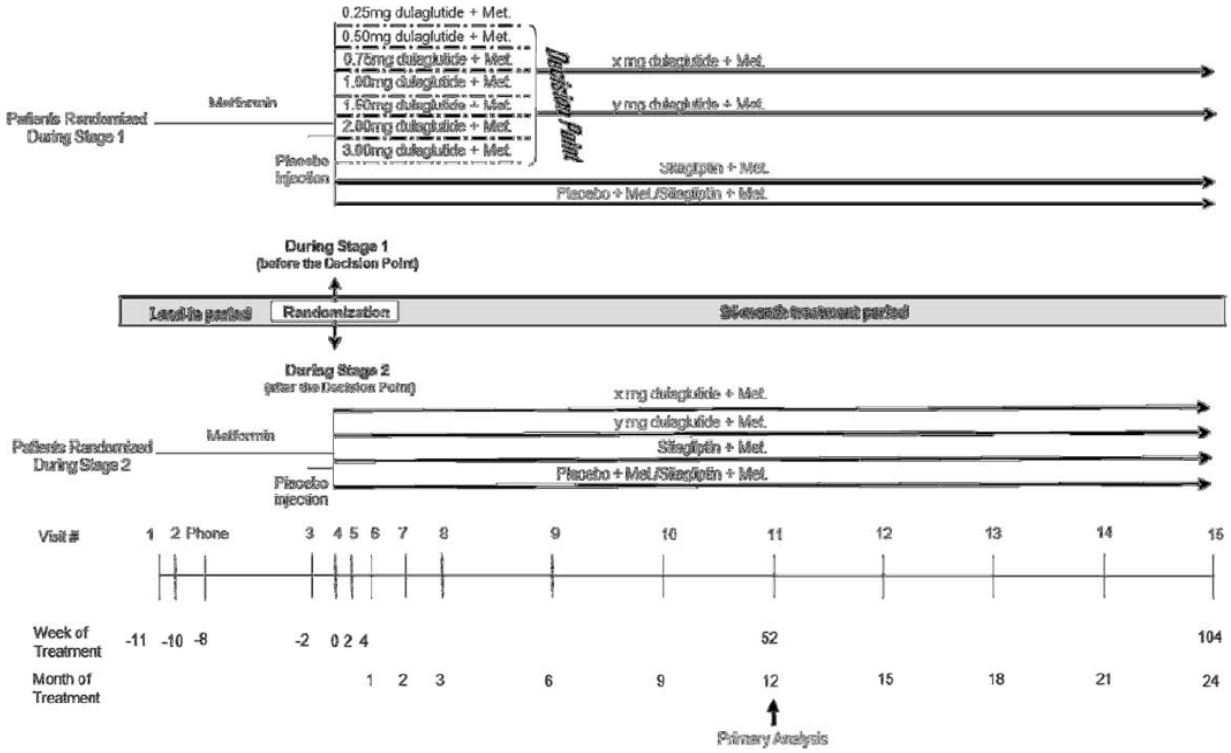
a) Add-on to metformin

AWARD-5 was an adaptive, inferentially seamless phase 2/3 study that consisted of two stages (Table 8, Figure 2). Stage 1 was a dose-finding, phase 2 trial during which participants were randomly assigned in a 1:1:3 ratio to one of the following nine treatment arms: placebo then sitagliptin (placebo/sitagliptin) sequence which comprised placebo for six months and then a switch to sitagliptin, sitagliptin, or one of seven doses of dulaglutide (dose range from 0.25 to 3.0 mg). To reiterate, 60% of participants were randomized to receive one of the seven dulaglutide doses. Participants who were assigned to the seven dulaglutide treatment arms were done so using a dynamic allocation scheme, which accumulated pre-specified safety and efficacy data, and preferentially assigned higher randomization probabilities (updated every two weeks) to doses that were considered more desirable. The randomization probabilities for the sitagliptin and placebo/sitagliptin treatment arms remained constant.

The objective of stage 1 was to identify two doses of dulaglutide at the Decision Point (i.e., the end of stage 1) which could be carried forward into stage 2 based on a Clinical Utility Index that captured the risk-benefit profile of the different doses. Stage 2 was a phase 3 trial that seamlessly followed stage 1 and during which participants on the two doses of dulaglutide selected at the Decision Point (0.75 mg and 1.5 mg) continued to receive their assigned treatments. Those participants in the non-selected dulaglutide arms were discontinued from the study. Participants who received placebo or sitagliptin during stage 1 continued to stage 2. When the Decision Point was reached, the randomization scheme switched to a block randomization scheme through which participants were assigned 2:2:2:1 to four primary treatment arms: dulaglutide 1.5 mg, dulaglutide 0.75 mg, sitagliptin, and placebo/sitagliptin until the desired sample size was reached.

Randomization was conducted using an interactive voice response system (IVRS), and stratified by country. Overall, the study enrolled participants with T2DM from 13 countries, including Canada. It comprised a lead-in period that lasted up to 11 weeks, which included one week for screening and 10 weeks for dose titration and stabilization of metformin dose (≥ 1,500 mg/day for six weeks or more prior to randomization) and discontinuation of other oral antihyperglycemic medications, a treatment period of 24 months, and a safety follow-up of 30 days. During the lead-in period, participants were trained on how to self-administer weekly injections, and were provided with diabetes treatment education.

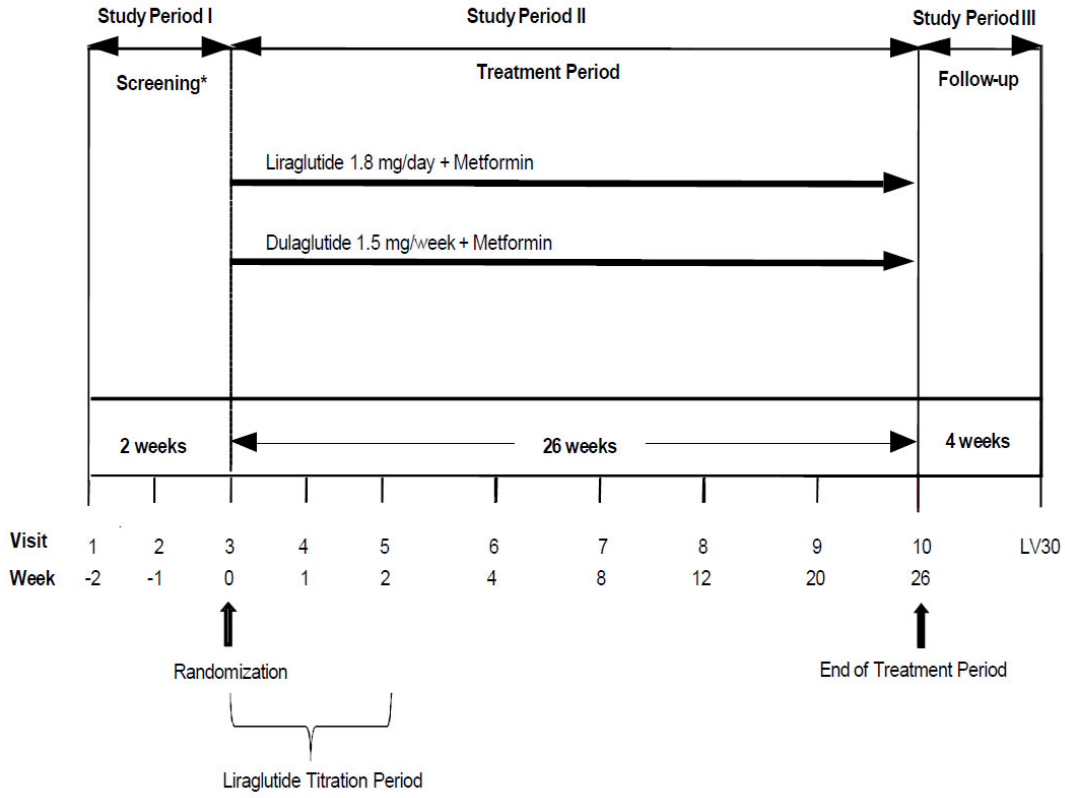
FIGURE 2: SCHEMATIC FOR AWARD-5



Source: AWARD-5 Clinical Study Report.[13]

AWARD-6 was an open-label, active-controlled phase 3 non-inferiority trial (Table 8). Randomization was according to a computer-generated random sequence using an IVRS. It was stratified by country and baseline A1C (≤ 8.5% vs. > 8.5%). The study enrolled participants with T2DM from nine countries, none of which was Canada. It comprised a screening period of two weeks, a treatment period of 26 weeks, and a safety follow-up of four weeks (Figure 3). During the screening period, participant eligibility was established, and those who were eligible for the study were educated by study personnel on diet and exercise, blood glucose monitoring, and hypoglycemic or hyperglycemic events, and were instructed on subcutaneous injections and performed a practice injection. Participants were randomized (1:1) to receive subcutaneously injected once-weekly dulaglutide 1.5 mg or subcutaneously injected once-daily liraglutide 1.8 mg.

FIGURE 3: SCHEMATIC FOR AWARD-6

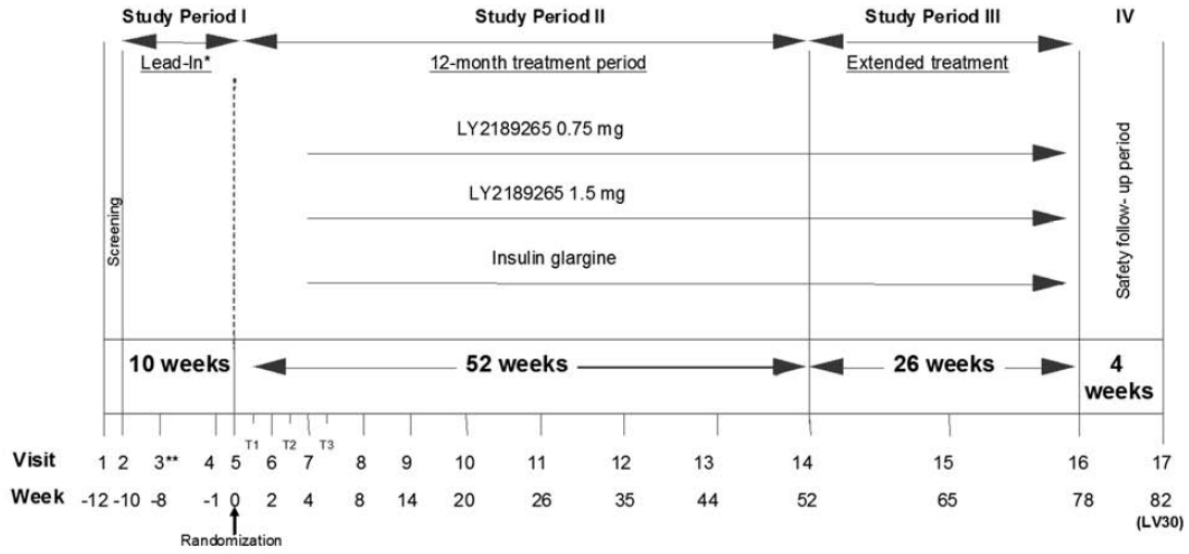


Source: AWARD-6 Clinical Study Report.[14]

b) Add-on to metformin and a sulfonylurea

AWARD-2 was an open-label (although double-blind with respect to the dulaglutide assignments), active-controlled phase 3 non-inferiority trial (Table 9). Randomization was according to a computer-generated random sequence using an IVRS. It was stratified by country and baseline A1C; i.e., ≤ 8.5% versus > 8.5%. The study enrolled participants with T2DM from 20 countries, including Canada. It comprised a lead-in period of 10 weeks, a treatment period of 78 weeks, and a safety follow-period of four weeks (Figure 4). During the lead-in period, participants were educated by study personnel on diet and exercise, blood glucose monitoring, study drug injection, and the management of hypoglycemic and hyperglycemic events. Participants were randomized (1:1:1) to receive subcutaneously injected once-weekly dulaglutide 0.75 mg, dulaglutide 1.5 mg, or once-daily insulin glargine.

FIGURE 4: SCHEMATIC FOR AWARD-2



Source: AWARD-2 Clinical Study Report.[22]

3.2.2 Populations

a) Inclusion and exclusion criteria

Add-on to metformin

In AWARD-5, eligible participants were adults with an A1C ≥ 7.0 to ≤ 9.5%, except those on diet and exercise therapy who required an A1C > 8.0 to ≤ 9.5%, body mass index (BMI) ≥ 25 to ≤ 40 kg/m^2, and stable weight (± 5%) for three months or more (Table 8). Participants at screening were required to have been treated with diet and exercise alone, or having taken metformin or another oral antihyperglycemic medication (OAM) as monotherapy, or metformin in combination with another OAM. During the lead-in period, participants were asked to discontinue any other OAMs, and metformin (≥ 1,500 mg/day) therapy was initiated for six or more weeks prior to randomization to maintain eligibility prior to randomization.

In AWARD-6, eligible participants were adults with an A1C ≥ 7.0 to ≤ 10.0%, and BMI ≤ 45 kg/m^2, who were receiving a stable dose of metformin (≥ 1,500 mg/day) for three months or more (Table 8).

Add-on to metformin and a sulfonylurea

In AWARD-2, eligible participants at screening were adults with an A1C ≥ 7.0 to ≤ 11.0%, BMI ≥ 23 to ≤ 45 kg/m^2, and stable weight (± 5%) for three months or more who were not optimally controlled with one, two, or three OAMs, of which at least one must have been metformin or a sulfonylurea (Table 9). During the lead-in period, participants were asked to discontinue any other OAMs, and metformin and glimepiride were initiated and/or adjusted until they reached maximum tolerated doses, but not higher than the maximum locally approved doses and not lower than the minimal required doses; i.e., ≥ 1,500 mg/day for metformin, and ≥ 4 mg/day for glimepiride. The OAM doses were stabilized for approximately six to eight weeks before randomization, at which point a qualifying A1C ≥ 6.5% was required for ongoing eligibility in the trial.

b) Baseline characteristics

Add-on to metformin

In AWARD-5, the mean age of study participants randomized during stage 1 or 2 was approximately 54 years, with no meaningful differences between the treatment arms (Table 10). An apparent discrepancy was that despite having an upper limit of age of 75 years as an inclusion criterion, the oldest participant in the sitagliptin arm was reportedly 76.29 years. More than half of participants were female, while more than half were Caucasian or white, and approximately 25% of participants were Asian or Hispanic. There did not appear to be any meaningful differences in other relevant baseline characteristics between participants receiving the different treatments in this trial. [redacted]

In AWARD-6, participants appeared to be slightly older than those enrolled in AWARD-5, although the difference was negligible. Moreover, they appeared to have greater mean values for weight, BMI, and seated systolic and diastolic blood pressure (BP) than participants from AWARD-5. The average duration of diabetes (approximately seven years) as well as mean A1C values (slightly greater than 8%) appeared to be similar among participants enrolled in both studies.

Add-on to metformin and a sulfonylurea

In AWARD-2, the mean age of study participants was approximately 57 years, and there were slightly more males than females (Table 11). About 70% of participants were white, while less than a fifth of all individuals were Asian. There appeared to be no meaningful differences in baseline characteristics between participants receiving the different treatments in this trial. The average duration of diabetes of participants enrolled in this trial was approximately nine years, which was about two years greater than those in AWARD-5 and AWARD-6.

TABLE 10: SUMMARY OF BASELINE CHARACTERISTICS (ADD-ON TO METFORMIN)

Characteristic	AWARD-5[a]				AWARD-6[b]	
	Dulaglutide 0.75 mg (N = 302)	Dulaglutide 1.5 mg (N = 304)	Sitagliptin (N = 315)	Placebo/Sitagliptin (N = 177)	Dulaglutide 1.5 mg (N = 299)	Liraglutide 1.8 mg (N = 300)
Age (y)						
Mean (SD)	54.35 (9.81)	53.66 (10.02)	53.75 (10.27)	54.91 (9.05)	56.49 (9.34)	56.81 (9.91)
Median	55.40	54.30	54.46	55.47	57.32	58.01
Min, max	19.81, 73.68	20.79, 75.37	23.98, 76.29	25.29, 74.46	19.31, 74.31	28.25, 79.54
Gender, n (%)						
Male	134 (44.4)	146 (48.0)	151 (47.9)	90 (50.8)	138 (46.2)	149 (49.7)
Race, n (%)						
African or African-American or black	12 (4.0)	16 (5.3)	7 (2.2)	9 (5.1)	21 (7.0)	16 (5.3)
Caucasian or white	162 (53.6)	157 (51.6)	158 (50.2)	91 (51.4)	256 (85.6)	259 (86.3)
Asian	77 (25.5)	77 (25.3)	80 (25.4)	39 (22)	1 (0.3)	0
Hispanic	51 (16.9)	54 (17.8)	67 (21.3)	38 (21.5)	0	0
Other	0	0	2 (0.6)	0	21 (7.0)	25 (8.4)
Weight (kg)						
Mean (SD)	86.22 (17.99)	86.67 (17.45)	85.97 (16.91)	87.07 (16.86)	93.82 (18.23)	94.35 (18.96)
Median	83.55	85.15	84.00	85.00	92.50	93.10
Min, max	53.10, 155.40	54.00, 136.00	49.50, 156.20	57.40, 137.60	57.4, 162.0	53.3, 159.0
BMI (kg/m^2)						
Mean (SD)	31.15 (4.44)	31.40 (4.57)	31.02 (4.20)	31.37 (4.25)	33.50 (5.07)	33.62 (5.16)
Median	30.55	30.95	30.40	31.20	33.23	33.60
Min, max	23.60, 42.90	22.90, 51.20	23.50, 43.50	23.90, 40.10	23.27, 50.53	21.17, 44.98
Seated systolic BP (mm Hg)						
Mean (SD)	127.50 (14.12)	128.57 (12.78)	127.11 (12.53)	128.16 (13.40)	132.20 (14.97)	130.94 (15.14)
Median	128.00	128.00	126.30	127.30	131.67	129.33
Min, max	85.00, 182.00	85.00, 168.00	89.30, 167.70	99.00, 172.30	94.00, 174.67	94.67, 174.00
Seated diastolic BP (mm Hg)						
Mean (SD)	77.65 (8.63)	77.86 (8.26)	77.32 (8.66)	77.68 (8.16)	79.88 (9.45)	79.10 (9.19)
Median	78.30	78.30	77.70	78.70	80.00	78.83

Characteristic	AWARD-5[a]				AWARD-6[b]	
	Dulaglutide 0.75 mg (N = 302)	Dulaglutide 1.5 mg (N = 304)	Sitagliptin (N = 315)	Placebo/Sitagliptin (N = 177)	Dulaglutide 1.5 mg (N = 299)	Liraglutide 1.8 mg (N = 300)
Min, max	52.30, 106.30	49.00, 100.70	50.00, 104.70	58.00, 100.70	53.00, 109.33	55.00, 109.67
Diabetes duration (y)						
Mean (SD)	7.34 (4.92)	6.95 (5.50)	7.16 (4.89)	6.96 (5.43)	7.13 (5.41)	7.28 (5.41)
Median	6.65	6.00	6.00	5.80	6.00	6.00
Min, max	1.00, 26.00	1.00, 34.00	1.00, 27.00	1.00, 33.00	0.33, 42.00	0.25, 32.00
A1C (%)						
Mean (SD)	8.19 (1.11)	8.12 (1.05)	8.09 (1.09)	8.10 (1.14)	8.06 (0.81)	8.05 (0.79)
Median	8.00	7.90	7.90	7.90	7.90	7.90
Min, max	6.30, 13.90	5.10, 13.20	6.00, 12.80	4.90, 12.10	6.5, 10.5	6.4, 10.1
CV history, n (%)						
Hyperlipidemia	265 (87.7)	258 (84.9)	261 (82.9)	140 (79.1)	NR	NR
Hypertension	229 (75.8)	214 (70.4)	245 (77.8)	126 (71.2)	189 (63.2)	199 (66.3)
Prior MI	NR	NR	NR	NR	9 (3.0)	12 (4.0)
Prior stroke	NR	NR	NR	NR	3 (1.0)	7 (2.3)
Prior TIA	NR	NR	NR	NR	2 (0.7)	4 (1.3)
Coronary artery disease	NR	NR	NR	NR	18 (6.0)	11 (3.7)

A1C = glycated hemoglobin; BMI = body mass index; BP = blood pressure; CV = cardiovascular; ITT = intention-to-treat; MI = myocardial infarction; SD = standard deviation; TIA = transient ischemic attack.

[a] ITT population randomized during stage 1 or stage 2.

[b] ITT population.

Source: AWARD-5 Clinical Study Report (CSR),[13] AWARD-6 CSR.[14]

TABLE 11: SUMMARY OF BASELINE CHARACTERISTICS (ADD-ON TO METFORMIN AND A SULFONYLUREA)

Characteristic	AWARD-2[a]		
	Dulaglutide 0.75 mg (N = 272)	Dulaglutide 1.5 mg (N = 273)	Insulin Glargine (N = 262)
Age (y)			
Mean (SD)	56.56 (9.27)	56.24 (9.76)	57.21 (9.38)
Median	57.37	56.54	58.10
Min, max	29.75, 77.02	27.03, 86.55	32.27, 79.40

Characteristic	AWARD-2[a]		
	Dulaglutide 0.75 mg (N = 272)	Dulaglutide 1.5 mg (N = 273)	Insulin Glargine (N = 262)
Gender, n (%)			
Male	136 (50.0)	144 (52.7)	134 (51.1)
Race, n (%)			
American-Indian or Alaska Native	31 (11.4)	29 (10.6)	29 (11.1)
Asian	46 (16.9)	48 (17.6)	43 (16.4)
Black or African-American	1 (0.4)	1 (0.4)	2 (0.8)
Multiple	1 (0.4)	2 (0.7)	4 (1.5)
White	193 (71.0)	193 (70.7)	184 (70.2)
Weight (kg)			
Mean (SD)	86.18 (18.15)	85.13 (17.90)	87.66 (19.62)
Median	84.75	83.00	86.60
Min, max	51.20, 142.00	50.00, 152.50	46.60, 145.00
BMI (kg/m^2)			
Mean (SD)	31.51 (5.41)	31.23 (5.21)	31.91 (5.76)
Median	31.29	30.80	31.49
Min, max	20.96, 45.67	21.21, 45.66	21.41, 45.47
Seated systolic BP (mm Hg)			
Mean (SD)	130.93 (13.83)	131.81 (15.82)	130.43 (15.61)
Median	130.00	130.00	130.00
Min, max	90.00, 170.00	91.00, 190.00	90.00, 185.00
Seated diastolic BP (mm Hg)			
Mean (SD)	78.86 (9.23)	78.72 (8.51)	78.01 (9.28)
Median	80.00	78.00	78.00
Min, max	51.00, 106.00	56.00, 109.00	51.00, 105.00
Diabetes duration (y)			
Mean (SD)	9.28 (5.93)	9.13 (6.22)	8.87 (5.98)
Median	8.00	8.00	8.00
Min, max	0.30 , 38.00	0.70, 36.00	0.50, 35.00
A1C (%)			
Mean (SD)	8.13 (0.98)	8.18 (1.03)	8.10 (0.95)

Characteristic	AWARD-2[a]		
	Dulaglutide 0.75 mg (N = 272)	Dulaglutide 1.5 mg (N = 273)	Insulin Glargine (N = 262)
Median	8.00	8.10	8.00
Min, max	6.60, 13.30	6.60, 12.50	6.60, 10.90
History of CV disease, n (%)[b,c]			
Yes	19 (9.2)	18 (8.5)	25 (12.0)
Prior MI, n (%)[b]			
Yes	4 (1.9)	6 (2.8)	5 (2.4)
Prior stroke, n (%)[b]			
Yes	1 (0.5)	2 (0.9)	2 (1.0)
Prior TIA, n (%)[b]			
Yes	2 (1.0)	1 (0.5)	3 (1.4)
Documented coronary artery disease, n (%)[b]			
Yes	13 (6.3)	8 (3.8)	10 (4.8)
Hypertension, n (%)[b]			
Yes	132 (63.8)	129 (61.1)	124 (59.6)
Hyperlipidemia, n (%)			
Yes	NR	NR	NR

A1C = glycated hemoglobin; BMI = body mass index; BP = blood pressure; CV = cardiovascular; MI = myocardial infarction; SD = standard deviation; TIA = transient ischemic attack.

[a] ITT population.

[b] 78-week per-protocol population.

[c] History of CV disease is defined as having a history of at least one of the following: MI, coronary revascularization, hospitalization for unstable angina or heart failure, stroke or TIA, peripheral arterial disease, lower extremity or carotid artery revascularization, or documented coronary artery disease.

Source: AWARD-2 Clinical Study Report.[22]

3.2.3 Interventions

a) Add-on to metformin

In AWARD-5, participants in the primary treatment arms were randomized to receive subcutaneously injected once-weekly dulaglutide 0.75 mg or 1.5 mg, once-daily tablet of sitagliptin 100 mg, or a once-daily placebo tablet, which was switched (in a blinded manner) to sitagliptin 100 mg after six months. This study used a double-blind, double-dummy design, as a result of which participants could have received one active injectable and one oral placebo drug, one placebo injectable and one active oral drug, or two placebo drugs at matching administration schedules. However, the double-blind design was only maintained up until the 12-month primary end point database lock, after which select members of the sponsor study team were unblinded. All medications were self-injected, and participants received training on how to self-administer the medications prior to randomization. No details on training provided, or whether participants were screened out due to their inability to self-inject.

In AWARD-6, participants were randomized to receive subcutaneously injected once-weekly dulaglutide 1.5 mg or subcutaneously injected once-daily liraglutide 1.8 mg. Participants who were randomized to receive liraglutide were initiated at a dose of 0.6 mg/day, which was titrated to 1.2 mg/day after one week, and 1.8 mg/day after another week. This was an open-label study in which the investigators and participants were aware of their assigned treatment.

In both studies, all participants were also required to take metformin ≥ 1,500 mg/day, but not higher than the maximum approved dose in the local label in participating countries, throughout the treatment period.

b) Add-on to metformin and a sulfonylurea

In AWARD-2, participants were randomized to receive subcutaneously injected once-weekly dulaglutide 0.75 mg or 1.5 mg, or once-daily insulin glargine. Dosing for insulin glargine started at 10 units daily, and participants were instructed to follow a standard titration algorithm (Figure 5). Specifically, the dose was adjusted every three to four days during the first four weeks of the treatment period, then once weekly through the eighth week, all while participants were targeting a fasting plasma glucose (FPG) of < 5.6 mmol/L. It is not clear whether the adjustments were self-directed or completed by study personnel or clinicians. Following this early period, participants were asked to self-adjust their dose per the standard algorithm through the end of the treatment period. Although the study was open-label, it was double-blind with respect to the dulaglutide assignments. In addition to the treatment to which they were randomized, all participants received metformin (≥ 1,500 mg/day, but not higher than the maximum approved dose according to the local label in participating countries) and glimepiride (≥ 4 mg/day, but not higher than the maximum approved dose according to the the local label in participating countries).

FIGURE 5: STANDARD TITRATION ALGORITHM FOR INSULIN GLARGINE IN AWARD-2

Fasting PG (SMPG) (mean of previous 3 days)	Insulin Glargine Dose Change
≥100 and <120 mg/dL (5.6-6.7 mmol/L)	0-2 IU
≥120 and <140 mg/dL (6.7-7.8 mmol/L)	↑ 2 IU
≥140 and <160 mg/dL (7.8-8.9 mmol/L)	↑ 4 IU
≥160 and <180 mg/dL (8.9-10 mmol/L)	↑ 6 IU
≥180 mg/dL (10 mmol/L)	↑ 8 IU
If mean fasting SMPG <70 mg/dL (3.8 mmol/L)	↓ dose to previous lower dose

Abbreviations: PG = plasma glucose (measured as plasma glucose); SMPG = self-monitored plasma glucose.

Source: AWARD-2 Clinical Study Report.[22]

3.2.4 Outcomes

a) Add-on to metformin

The primary efficacy outcome in AWARD-5 and AWARD-6 was the change from baseline in A1C, although it was measured at 52 weeks in AWARD-5 versus 26 weeks in AWARD-6. The primary objective of AWARD-5 was to evaluate the non-inferiority of dulaglutide 1.5 mg against sitagliptin using a non-inferiority margin of 0.25%, whereas for AWARD-6, it was to evaluate non-inferiority of dulaglutide against liraglutide using a margin of 0.4%. Other outcomes of interest collected in the two trials included mortality, the percentage of participants achieving target A1C < 7%, change from baseline in FPG, body weight, and seated BP (systolic and diastolic).

Health-related quality of life (HRQoL) was measured in both studies using the EuroQol 5-Dimensions Health-Related Quality of Life questionnaire (EQ-5D), but also using the Impact of Weight on Quality of Life Questionnaire–Lite (IWQOL-Lite) in AWARD-5. The EQ-5D is a generic quality-of-life instrument that may be applied to a wide range of health conditions and treatments (Appendix 5). A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights. The second part is a 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 is a self-administered, condition-specific instrument that assesses quality of life across five domains: physical function, self-esteem, sexual life, public distress, and work. There are five levels upon which to rate each item ranging from "always true" to "never true." Each level is assigned a score from 1 to 5, where "always true" is given a score of 5 and "never true" is given a score of 1. The sum of scores for each item in its respective domain provides the domain score, and the sum of scores for each domain provides the total score, with higher scores associated with a poorer quality of life. Domain and total scores may also be transformed to a 0 to 100 range, with lower scores indicating greater impairment. The minimal clinically important differences (MCIDs) for patients with type 2 diabetes were not identified for the EQ-5D or the IWQOL-Lite.

Health care resource utilization, by means of the number of emergency room (ER) visits reported by participants, was also measured in AWARD-5.

Both studies captured harms, including adverse events (AEs), serious adverse events (SAEs), and notable harms, specifically hypoglycemia, injection-site reactions, pancreatitis, and pancreatic and thyroid cancers.

b) Add-on to metformin and a sulfonylurea

The primary efficacy outcome in AWARD-2 was the change from baseline in A1C at 52 weeks. The primary objective was to evaluate the non-inferiority of dulaglutide 1.5 mg against insulin glargine using a non-inferiority margin of 0.4%. Other outcomes of interest included mortality, the percentage of participants achieving target A1C < 7%, change from baseline in fasting serum glucose (FSG), body weight, and seated BP (systolic and diastolic). HRQoL was measured using the EQ-5D.

In AWARD-2, harms were also assessed as with the two above-mentioned studies.

3.2.5 Statistical Analysis

Add-on to metformin

In AWARD-5, approximately 200 to 1,566 participants were planned for enrolment. The final sample size depended on the findings of stage 1, during which the study investigators planned to adaptively randomize participants to the nine treatment arms until a decision (regarding selection of doses to carry forward to stage 2) could be reached. If there was "strong evidence" that there were no doses that would meet the predefined selection criteria, then the study was planned to be stopped early due to futility, although the definition of strong evidence was unclear. The maximum planned enrolment for stage 1 was 400 participants. Moreover, if a decision could not be reached by 400 participants, then the study was also planned to be stopped early. As a result, if the study was stopped early due to futility during stage 1, the sample size would be smaller than if it continued into stage 2. The sample size calculation was based on enrolling a sufficient number of participants to power the study, as well as a sufficient number of participants to achieve 300 participants exposed to dulaglutide for 24 months (assuming a 25% dropout rate). The power was estimated at approximately 89%, based on a simulation study and assuming a 20% dropout rate (missing completely at random) at 12 months, and an enrolment of five participants per week. Based on pre-specified criteria, given that the predictive power of superiority of the higher dulaglutide dose selected in stage 1 — i.e., 1.5 mg — exceeded 85%, a minimum total sample size of 263 participants (across stages 1 and 2) were needed in each of the dulaglutide and sitagliptin arms. This was contextualized by comparing the calculations in a traditional clinical trial design, in which 263 participants per treatment arm would have provided approximately 93% power for a one-sided 0.025 alpha level test based on a two-sample t-statistic, assuming no true difference, a 20% dropout rate, a standard deviation (SD) of 1.2%, and a non-inferiority margin of 0.25% for A1C. At the Decision Point, the 0.75 mg dulaglutide arm had the smallest number of participants (n = 20) of the four primary arms, as a result of which 243 participants were added to each of the active arms and 122 participants were added to the placebo/sitagliptin sequence arm to ensure a total of at least 263 participants in each active arm and 131 participants in the placebo/sitagliptin sequence arm.

The primary and key secondary analyses for the efficacy measure of A1C change from baseline compared the two selected dulaglutide doses (0.75 mg and 1.5 mg) to sitagliptin at 12 months and placebo at six months. Dulaglutide results at six months were compared with placebo at six months, and dulaglutide 12-month data were compared with sitagliptin 12-month data. This analysis specifically examined six ordered hypotheses (one primary and five key secondary objectives) using a tree-gatekeeping testing strategy to control the family-wise type 1 error rate at one-sided level of 0.025 (Figure 6). Only the outcome of change from baseline in A1C was considered in the testing strategy. These analyses were performed on data from participants assigned to the primary treatment arms in both the intention-to-treat (ITT) and per-protocol (PP) populations, although the ITT population was used as the primary population to evaluate the ordered hypotheses. A nominal alpha level of 0.02 was used in the analysis of stage 1 and stage 2 combined to mitigate possible inflation of type 1 error.

FIGURE 6: ORDERED EFFICACY HYPOTHESES FOR AWARD-5

(Figure deleted based on manufacturer's request)

Source: AWARD-5 Clinical Study Report.[13]

The primary statistical analysis model (for the primary efficacy outcome) was based on an analysis of covariance (ANCOVA) of the change from baseline in A1C with fixed effects for treatment, country, and baseline A1C as a continuous covariate. Missing end points were imputed with the last post-baseline observation carried forward. If there were no data after the date of randomization, the end point was considered missing. Therefore, for those with no readings past baseline, baseline values were not carried forward; these patients were excluded from analysis. A secondary analysis (for the primary efficacy outcome) used a restricted maximum likelihood (REML)-based mixed-model repeated measures (MMRM) approach. This model included the fixed effects of treatment, country, visit, and treatment by visit interaction, as well as the covariate of baseline A1C, and participant as random effect. An unstructured covariance structure was used to model the within-participant errors. If this analysis failed to converge, the following covariance structures were tested in the following order: toeplitz, autoregressive, compound symmetry with heterogeneous variances by visit, and compound symmetry without heterogeneous variances by visit; the covariance structure that first converged was used. Unlike the ANCOVA model, in which missing data were imputed using the last outcome carried forward (LOCF) approach, the MMRM model was used without imputing for missing data. The ANCOVA and MMRM models were built using data from participants assigned to the primary treatment arms in the ITT (primary) and PP (secondary) populations. Non-inferiority of dulaglutide 1.5 mg versus sitagliptin for A1C was demonstrated if the hypothesis of inferiority at a margin of 0.25% was rejected with a nominal alpha of 0.02, one-sided, based on stage 1 and stage 2 data, or a nominal alpha of 0.025, one-sided, based on stage 2 data alone. The choice of margin was guided by discussions with the Food and Drug Administration (FDA) and the Committee for Medicinal Products for Human Use, and by observations from previous manufacturer-sponsored clinical trials with sitagliptin as an active comparator.

Analyses for the other efficacy outcomes were conducted in a manner similar to that for the primary efficacy outcome. Specifically, changes from baseline in FPG and BP were analyzed using mixed-model repeated measure (MRMM) only, while change from baseline in body weight was analyzed using ANCOVA and MRMM. No multiplicity adjustments were made for the efficacy analyses outside the pre-specified testing strategy or safety analyses. Relevant pre-specified subgroups of ITT participants included age (< 65 and ≥ 65 years) and duration of diabetes at baseline (< median and ≥ median). In particular, for A1C, the subgroup analyses were performed by examining the interaction of the primary treatment arms versus the subgroup effects using the change from baseline in the ANCOVA (LOCF) models. The models included the effects of treatment, subgroup, subgroup-by-treatment interaction, and baseline measurement as the covariate. The interaction effects were evaluated using an unadjusted significance level of 0.10.

In AWARD-6, approximately 592 participants (296 randomized to each treatment arm) were planned for enrolment. The primary analysis evaluated whether dulaglutide 1.5 mg was non-inferior versus liraglutide 1.8 mg as measured by change in A1C from baseline at 26 weeks. To demonstrate non-inferiority with 90% power, 444 completers (222 per arm) at 26 weeks were required, assuming no true difference in A1C between the two treatments, 0.4% margin of non-inferiority, common SD of 1.3% for change from baseline in A1C, 0.05 two-sided significance level, and 25% dropout rate at 26 weeks. If non-inferiority was met, serial gatekeeping was used to examine the hypothesis that dulaglutide was superior to liraglutide using the same efficacy outcome. The non-inferiority margin of 0.4% was guided

by clinical and statistical factors, the latter of which was based on the results of three placebo-controlled studies of liraglutide in which the effect of liraglutide versus placebo ranged from 0.9% to 1.6%. As with AWARD-5, two analysis models were used for the primary efficacy outcome, except that the REML-based MMRM was the primary model, while the ANCOVA model was the secondary. The MMRM model used in this trial was identical to the one from AWARD-5, and so was the selection of the convergence structure for the model. Consistent with AWARD-5, the primary analysis was conducted using the ITT population, although secondary analyses were also conducted (using the MMRM and ANCOVA models) with data from the PP and Completers populations.

Analyses for the other efficacy outcomes were conducted using the ITT population, although the type of model — i.e., ANCOVA or MMRM — differed by the outcome assessed. [redacted]
Altogether, apart from the primary efficacy analyses, no multiplicity adjustments were made for the analyses. To this end, tests were conducted at a two-sided alpha level of 0.05 and confidence intervals (CIs) were calculated at 95%, two-sided. As with AWARD-5, relevant subgroups of participants evaluated were those by age (< 65 and ≥ 65 years) and duration of diabetes at baseline (< median and ≥ median), and the manner in which they were analyzed, including the significance level, was identical across the two trials.

Add-on to metformin and a sulfonylurea

In AWARD-2, the primary analysis evaluated whether dulaglutide 1.5 mg was non-inferior versus insulin glargine as measured by change in A1C from baseline at 52 weeks. To show non-inferiority with 90% power, 279 participants per arm were required, assuming no difference between the two treatments, a 0.4% margin of non-inferiority, a common SD of 1.3% for change from baseline in A1C, a 0.05 two-sided significance level, and 20% dropout rate at 52 weeks. The required number of completers was 223 per arm. The following key secondary objectives were tested between dulaglutide and insulin glargine with respect to change in A1C from baseline:

1. To demonstrate that dulaglutide 0.75 mg was non-inferior to insulin glargine at 52 weeks
2. To demonstrate that dulaglutide 1.5 mg was superior to insulin glargine at 52 weeks
3. To demonstrate that dulaglutide 0.75 mg was superior to insulin glargine at 52 weeks.

The choice of the non-inferiority margin was guided by clinical and statistical factors, although the specifics of the latter were unclear. The analyses for the four ordered hypotheses mentioned above (one primary and three key secondary objectives) were conducted using a tree-gatekeeping testing strategy to control the family-wise type 1 error rate at one-sided level of 0.025. As with AWARD-5, the primary statistical model for the primary efficacy outcome analysis was an ANCOVA in which missing end points were imputed using the LOCF method (post-baseline only), while the secondary model was an REML-based MMRM. The manner in which the models were built in this study was identical to the AWARD-5 and AWARD-6 trials. This tree-gatekeeping procedure was applied to the ITT population as the primary analysis, and to the PP populations as a sensitivity analysis. Consistent with the above trials, the analyses for the other efficacy outcomes were conducted using the ITT population, although the type of model — i.e., ANCOVA or MMRM — differed by the outcome assessed. [redacted]
Tests were conducted at a two-sided alpha level of 0.05 and CIs were calculated at 95%, two-sided. As with the above trials, relevant subgroups of participants evaluated were those by age (< 65 and ≥ 65 years) and duration of diabetes at baseline (< median and ≥ median), and the manner in which they were analyzed, including

the significance level, was identical across the two trials. An additional subgroup of interest included participants by baseline A1C; i.e., ≤ 8.5 and > 8.5.

a) Analysis populations

Add-on to metformin

In AWARD-5, the ITT population was defined as all randomized participants. [redacted] The safety population included all the participants in the ITT population.

In AWARD-6, the modified intention-to-treat (mITT) population was defined as all randomized participants who took at least one dose of the assigned study drug. Participants who received rescue therapy were included in the ITT population, but only measurements obtained prior to the rescue were included in the efficacy analyses. [redacted] The Completers population was composed of all participants in the ITT population who completed the study without receiving rescue medication for severe, persistent hyperglycemia and without receiving alternative antihyperglycemic medication following discontinuation of study drug.

Add-on to metformin and a sulfonylurea

In AWARD-2, the mITT population was defined as in AWARD-6. The two trials were also identical in the manner in which they treated participants who received rescue therapy. The PP population comprised randomized participants who completed the study through 52 weeks (78 weeks for the secondary efficacy analysis) of active treatment, had an overall compliance with study treatment across visits of at least 75%, and had no significant protocol violations.

3.3 Patient Disposition

3.3.1 Add-on to metformin

In AWARD-5, a total of 2,195 participants entered trial screening for stages 1 or 2. Of these, 724 discontinued (689 did not meet entry criteria, 34 participant decision, one adverse event) before the lead-in period, and 269 discontinued during the lead-in period; however, 104 of these participants were randomized to the non-selected dulaglutide doses during stage 1, and were discontinued from the study after stage 1, thus leaving 1,098 participants who were randomized to the four primary treatment arms in stages 1 or 2. There appeared to be a higher proportion of participants in the placebo/sitagliptin arm who continued from stage 1 than those in the remaining groups (Table 12). A total of 441 participants (40.1%) discontinued from the study prior to the end of the treatment period. More participants appeared to discontinue from the study prior to 12 and 24 months in the placebo/sitagliptin treatment arm than the remaining groups. The most common reason for study discontinuation prior to 24 months was AE. A numerically larger proportion of participants who were receiving sitagliptin or the placebo/sitagliptin sequence appeared to have decided to discontinue from the study prior to 24 months than those receiving either dulaglutide dose.

In AWARD-6, 814 individuals were screened for eligibility. Of the 215 individuals who were not randomized, 193 (89.8%) did not meet the protocol entry criteria. Dropout rates were relatively lower than those observed in AWARD-5, and were similar across the dulaglutide 1.5 mg and liraglutide 1.8 mg arms — a total of 22 (7.4%) and 18 (6.0%) participants discontinued from the study prior to 26 weeks in the respective arms (Table 12). The most common reason for study discontinuation was AEs.

3.3.2 Add-on to metformin and a sulfonylurea

In AWARD-2, 1,300 individuals were screened for eligibility, of whom 27 were excluded because the study site at which they were enrolled had significant Good Clinical Practice non-compliance issues, 252 failed screening, and 211 discontinued during the lead-in period. Correspondence with the manufacturer highlighted that participants were discontinued during the lead-in period if the maximum tolerated doses of metformin or glimepiride were lower than the minimum protocol-specified doses. In addition, participants who achieved optimal glycemic control, in the opinion of the investigator and based on their self-monitoring plasma glucose data, were also discontinued. Finally, participants with A1C values lower than 6.5% were also excluded from randomization. A total of 810 participants were randomized, although three participants who were assigned to the insulin glargine group discontinued before receiving the first dose. Altogether, a total of 84 participants (10.4%) discontinued from the study before the end of the treatment period (Table 13). A similar proportion of participants discontinued from the study across the treatment arms at the 52- and 78-week end points, with the most common reason (at both times) being participant decision, followed by AEs. There were three deaths in the study, of which one was in the dulaglutide 0.75 mg group, while two were in the insulin glargine treatment group.

TABLE 12: PARTICIPANT DISPOSITION (ADD-ON TO METFORMIN)

	AWARD-5[a]				AWARD-6	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/Sitagliptin	Dulaglutide 1.5 mg	Liraglutide 1.8 mg
Screened, N	2,195 (stage 1 or stage 2)				814	
Randomized, N (%)	1,098 (126 from stage 1)				299	300
	302 (21 from stage 1)	304 (25 from stage 1)	315 (42 from stage 1)	177 (38 from stage 1)		
Discontinued study prior to 26 weeks, n (%)					22 (7.4)	18 (6.0)
AE					13 (4.3)	5 (1.7)
Protocol violation					1 (0.3)	1 (0.3)
Participant decision					5 (1.7)	8 (2.7)
Physician decision					1 (0.3)	1 (0.3)
Lost to follow-up					2 (0.7)	3 (1.0)
Discontinued study prior to 12 months, n (%)	59 (19.5)	66 (21.7)	77 (24.4)	65 (36.7)		
Discontinued study prior to 24 months, n (%)	118 (39.1)	112 (36.8)	129 (41.0)	82 (46.3)		
AE	64 (21.2)	63 (20.7)	65 (20.6)	39 (22.0)		
Participant decision	24 (7.9)	18 (5.9)	36 (11.4)	21 (11.9)		
Lost to follow-up	11 (3.6)	13 (4.3)	9 (2.9)	4 (2.3)		
Physician decision	11 (3.6)	4 (1.3)	9 (2.9)	9 (5.1)		
Lack of efficacy	0	4 (1.3)	4 (1.3)	6 (3.4)		
Protocol violation	3 (1.0)	4 (1.3)	3 (1.0)	1 (0.6)		
Entry criteria not met	3 (1.0)	5 (1.6)	1 (0.3)	1 (0.6)		
Death	0	1 (0.3)	2 (0.6)	1 (0.6)		
Sponsor decision	2 (0.7)	0	0	0		
mITT, N	302	304	315	177	299	300
26-week PP, N					[redacted]	[redacted]
Completers, N					274	275
12-month PP, N	[redacted]	[redacted]	[redacted]	[redacted]		
24-month PP, N	[redacted]	[redacted]	[redacted]	[redacted]		
Safety, N	302	304	315	177	299	300

AE = adverse event; ITT = intention-to-treat; mITT = modified intention-to-treat; PP = per-protocol.

[a] From stage 2 only, unless otherwise specified.

Source: AWARD-5 Clinical Study Report (CSR),[13] AWARD-6 CSR.[14]

TABLE 13: PARTICIPANT DISPOSITION (ADD-ON TO METFORMIN AND A SULFONYLUREA)

	AWARD-2		
	Dulaglutide 0.75 mg	**Dulaglutide 1.5 mg**	**Insulin Glargine**
Screened, N	1300		
Randomized, N	272	273	265
Discontinued study prior to 52 weeks, n (%)	20 (7.4)	25 (9.2)	25 (9.4)
Discontinued study prior to 78 weeks, n (%)	29 (10.7)	31 (11.4)	27 (11.3)
Participant decision	7 (2.6)	11 (4.0)	8 (3.1)
AE	8 (2.9)	9 (3.3)	5 (1.9)
Lost to follow-up	3 (1.1)	3 (1.1)	3 (1.1)
Physician decision	3 (1.1)	3 (1.1)	3 (1.1)
Entry criteria not met	2 (0.7)	3 (1.1)	0
Non-compliance with study drug	2 (0.7)	1 (0.4)	2 (0.8)
Death	1 (0.4)	0	2 (0.8)
Protocol violation	2 (0.7)	0	1 (0.4)
Lack of efficacy	1 (0.4)	1 (0.4)	0
mITT, N	272	273	262
52-week PP, N	[redacted]	[redacted]	[redacted]
78-week PP, N	[redacted]	[redacted]	[redacted]
Safety, N	272	273	262

AE = adverse event; ITT = intention-to-treat; PP = per-protocol.
Note: ITT population.
Source: AWARD-2 Clinical Study Report.[22]

3.4 Exposure to Study Treatments

3.4.1 Add-on to metformin

a) Extent of exposure to study drugs

In AWARD-5, although the extent of exposure to dulaglutide 0.75 mg and 1.5 mg was similar — approximately 81 weeks — it was slightly longer than that to sitagliptin, for which the average treatment duration was about two weeks shorter (Table 14). [redacted]

In AWARD-6, the mean treatment duration across the dulaglutide 1.5 mg and liraglutide 1.8 mg arms were similar at approximately 24 weeks (Table 14).

TABLE 14: EXTENT OF EXPOSURE TO STUDY DRUGS (ADD-ON TO METFORMIN)

	AWARD-5[a]				AWARD-6	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/ Sitagliptin	Dulaglutide 1.5 mg	Liraglutide 1.8 mg
Treatment duration, weeks						
N	302	304	315	177	299	300
Mean (SD)	81.6 (33.6)	80.7 (35.4)	78.8 (35.4)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation.
Note: Intention-to-treat participants randomized during stage 1 or stage 2.
Source: AWARD-5 Clinical Study Report (CSR),[13] AWARD-6 CSR.[14]

In both AWARD-5 and AWARD-6, there did not appear to be any meaningful differences in mean daily dose of metformin, which was approximately 2,000 mg/day, across the treatment arms at baseline and follow-up (Table 15).

TABLE 15: SUMMARY OF METFORMIN DAILY DOSE (ADD-ON TO METFORMIN)

	AWARD-5[a]				AWARD-6	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/Sitagliptin	Dulaglutide 1.5 mg	Liraglutide 1.8 mg
Baseline (mg/day)						
N	302	304	315	177	294	298
Mean (SD)	1976.7 (413.22)	1955.8 (407.19)	1938.3 (399.16)	1927.0 (393.77)	2020.7 (418.16)	2067.8 (451.66)
Min, max	1500, 3000	1500, 3000	1500, 3000	1500, 3000	NR	NR
26 weeks (mg/day)						
N					275	279
Mean (SD)					2013.3 (422.92)	2069.2 (466.33)
Min, max					NR	NR
12 months (mg/day)						
N	256	247	254	121		
Mean (SD)	1956.0 (448.97)	1930.6 (413.92)	1924.0 (423.59)	1929.1 (460.37)		
Min, max	**0, 3000**	**500, 3000**	**0, 3000**	**1000, 3000**		
24 months (mg/day)						
N	196	200	192	96		
Mean (SD)	1963.6 (489.32)	1913.5 (426.00)	1933.6 (419.06)	1965.9 (468.36)		
Min, max	0, 3000	500, 3000	1000, 3000	1250, 3000		

Max = maximum, min = minimum; SD = standard deviation.
[a] Intention-to-treat participants randomized during stage 1 or stage 2.
Source: AWARD-5 Clinical Study Report (CSR),[13] AWARD-6 CSR.[14]

b) Rescue therapy

In AWARD-5, participants who developed persistent or worsening hyperglycemia, and would need rescue therapy, were discontinued from the study.

In AWARD-6, during the 26-week treatment period, a total of 19 participants (3.2%) received rescue therapy for any reason: six (2.0%) receiving dulaglutide 1.5 mg, and 13 (4.3%) receiving liraglutide 1.8 mg. Of these participants, one (0.3%) participant receiving dulaglutide 1.5 mg and three (1.0%) receiving liraglutide 1.8 mg received rescue therapy for severe, persistent hyperglycemia.

c) Treatment compliance

In AWARD-5, treatment compliance was defined as taking at least 75% each of the injection solution and oral study drug (tablets) dispensed; for injectable solution (dulaglutide or placebo), compliance was further defined as not missing more than two consecutive weekly injections within each visit interval. It was not clear whether the dose had to be taken on the same day and time each week in order to be considered compliant. [redacted]

In AWARD-6, treatment compliance was defined as taking at least 75% of the required full doses of study drug for each visit. Over the entire 26-week treatment period, overall treatment compliance was similar across the dulaglutide 1.5 mg (98.2%) and liraglutide 1.8 mg and (97.5%) arms (*P* = 0.413).

d) Concomitant medication use

[redacted]

In AWARD-6, almost 70% of participants were receiving antihypertensives, while fewer than half of participants were receiving lipid-lowering drugs, anticoagulant drugs, anti-inflammatory drugs, and cardiac therapy (Table 16).

TABLE 16: SUMMARY OF CONCOMITANT MEDICATION USE (ADD-ON TO METFORMIN)

	AWARD-5 (Stabilization Period, Visit 3 or 4)				AWARD-6 (During 26-Week Treatment Period)	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/Sitagliptin	Dulaglutide 1.5 mg	Liraglutide 1.8 mg
Concomitant medication category, N (%)						
Antihypertensives	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lipid-lowering drugs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anticoagulant drugs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-inflammatory drugs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Source: AWARD-5 Clinical Study Report (CSR),[13] AWARD-6 CSR.[14]

3.4.2 Add-on to metformin and a sulfonylurea

a) Extent of exposure to study drugs

[redacted] (Table 17).

TABLE 17: EXTENT OF EXPOSURE TO STUDY DRUGS (ADD-ON TO METFORMIN AND A SULFONYLUREA)

	AWARD-2		
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Insulin Glargine
Treatment duration, weeks			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]

SD = standard deviation.
Source: AWARD-2 Clinical Study Report.[22]

At week 52, which represented the time point for the primary efficacy analyses in AWARD-2, the mean (SD) daily dose of insulin glargine was 29.40 units (25.85) or 0.33 units/kg (0.24) (Figure 7). [redacted]

FIGURE 7: MEAN INSULIN GLARGINE DOSE DURING AWARD-2

(Figure deleted based on manufacturer's request)

[redacted]

Source: AWARD-2 Clinical Study Report.[22]

In AWARD-2, the mean daily dose of metformin and glimepiride appeared to be similar at baseline across the treatment groups, at approximately 2,400 mg/day and slightly greater than 6 mg/day, respectively (Table 18). The average dose of metformin that participants in this study were receiving was greater than that in AWARD-5 and AWARD-6. Further, there appeared to be a small decrease in the average dose of both metformin and glimepiride over the course of the trial, although the difference was not clinically meaningful, according to the clinical expert.

TABLE 18: SUMMARY OF METFORMIN AND SULFONYLUREA DAILY DOSE (ADD-ON TO METFORMIN AND A SULFONYLUREA)

	AWARD-2		
Dose mg/day	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Insulin Glargine
N	272	273	262
Metformin			
Baseline — mean (SD)	2411.76 (494.93)	2379.03 (480.08)	2419.18 (475.34)
Baseline — min, max	0, 4000	850, 3000	1000, 3000
52 weeks[a] — mean (SD)	2397.33 (470.68)	2332.33 (553.09)	2390.08 (497.08)
52 weeks[a] — min, max	1000, 3000	0, 3000	0, 3000
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Glimepiride			
Baseline — mean (SD)	6.32 (1.60)	6.25 (1.68)	6.24 (1.57)
Baseline — min, max	0, 8	0, 8	0, 8
52 weeks[a] — mean (SD)	5.58 (2.22)	5.41 (2.32)	5.39 (2.30)
52 weeks[a] — min, max	0, 8	0, 8	0, 8
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Max = maximum; min = minimum; SD = standard deviation.
[a] Last observation carried forward.
Source: AWARD-2 Clinical Study Report.[22]

a) Rescue therapy

In AWARD-2, during the 78-week treatment period, a total of 90 participants (11.2%) received rescue medication for any reason: 31 (11.4%) received dulaglutide 1.5 mg, 43 (15.8%) received dulaglutide 0.75 mg, and 16 (6.1%) received insulin glargine. Of these participants, 24 (8.8%) in the dulaglutide 1.5 mg group, 34 (12.5%) in the dulaglutide 0.75 mg group, and 16 (6.1%) in the insulin glargine group received rescue therapy for severe, persistent hyperglycemia. Rescue therapy was not defined.

b) Treatment compliance

[redacted]

c) Concomitant medication use

[redacted]

[redacted]

TABLE 19: SUMMARY OF CONCOMITANT MEDICATION USE (ADD-ON TO METFORMIN AND A SULFONYLUREA)

	AWARD-2		
	Dulaglutide 0.75 mg (N = 272)	Dulaglutide 1.5 mg (N = 273)	Insulin Glargine (N = 265)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Note: At baseline.
Source: AWARD-2 Clinical Study Report.[22]

3.5 Critical Appraisal

3.5.1 Internal Validity

a) Add-on to metformin

AWARD-5 and AWARD-6 were randomized, active-controlled, parallel-group, non-inferiority trials with appropriate randomization and allocation concealment processes. AWARD-5 used a double-blind, double-dummy design, although this was maintained only until the 12-month primary end point database lock, after which select members of the sponsor study team were unblinded. While the participants were not unblinded from this point forward, there appeared to be a greater number of participants in the sitagliptin and placebo/sitagliptin arms who decided to discontinue from the study prior to 24 months than in the dulaglutide arms. AWARD-6 maintained an open-label design throughout the study. While lack of blinding is not a key concern for interpreting the results of the primary efficacy outcome, lack of blinding is potentially biasing for some of the secondary efficacy and for the safety outcomes in both trials, because these outcomes were not measured objectively; e.g., HRQoL.
Baseline characteristics were similar across treatment groups in both trials, although in AWARD-5, there were statistically significant differences in some variables — i.e., race, baseline A1C, and percentage of participants with hypertension and hyperlipidemia — among participants randomized during stage 1 versus stage 2. Despite pre-specifying a subgroup analysis to assess whether treatment effects significantly differed across the participants enrolled in stage 1 versus stage 2, no such analysis was conducted. Instead, participants enrolled in stage 2 only were analyzed separately (Table 27), and their results were compared with those who were randomized during stage 1 or 2. Thus, it remains uncertain whether the differences in baseline characteristics between participants randomized during stage 1 versus stage 2 impacted the results. Further, there appeared to be a disproportionate number of participants from stage 1 who continued to stage 2 across the four primary treatment arms; specifically, a greater proportion of participants in the placebo/sitagliptin arm appeared to have continued to stage 2 from stage 1 than those in the remaining groups, which might have introduced bias.

Both studies were designed as non-inferiority trials, although the choice of the non-inferiority margin was 0.25% in AWARD-5, and 0.4% in AWARD-6. Both margins are similar to margins used in previous T2DM trials, and consistent with the 2008 FDA draft guidance for diabetes mellitus, which accepts a non-margin of 0.3 or 0.4 A1C percentage units.[23] Neither the FDA[17] nor the Health Canada[18] reviews raised concerns regarding the choice of margins. Even though both studies were designed as non-

inferiority trials, the primary statistical model for the primary efficacy outcome was tested using data from the ITT population, which could potentially bias the results in favour of a finding of non-inferiority. AWARD-6 did not use a true ITT population, because rather than including all randomized participants, the ITT analysis set included only those participants who took at least one dose of the assigned study drug (i.e., an mITT population). [redacted]

AWARD-5 used a tree-gatekeeping testing strategy to examine six ordered hypotheses (one primary and five key secondary objectives) to control the family-wise type 1 error rate at a [redacted]. This is a common and appropriate strategy to account for multiplicity, and the manufacturer appears to have adhered to its pre-specified testing strategy, including appropriately testing for superiority after non-inferiority was established. It is important to note, however, that only the outcome of change from baseline in A1C was considered in the testing strategy, which means that the results of the outcomes outside of the gatekeeping procedure should be considered exploratory and be interpreted with caution, because they were not adjusted for multiplicity, which increases the risk of making a type 1 error.

Across both trials, two analysis models were used for the primary efficacy outcome — an REML-based MMRM and an ANCOVA model — although it was unclear why there was inconsistency in specifying the MMRM or ANCOVA model as primary. In the ANCOVA model, missing data were imputed using the LOCF approach, specifically using post-baseline data; in other words, participants for whom data after the date of randomization were missing were excluded from the analyses. Excluding these participants is inconsistent with the true definition of an ITT analysis, in which all participants are included, and may not preserve the integrity of randomization. However, this concern is minimized in AWARD-5, in which only 11 participants (1.0%) were excluded from the primary analysis (using the ITT population). Further, post-hoc analyses of the potential impact of missing data on the primary efficacy outcome in AWARD-5 were conducted by the FDA, and the results revealed no important limitations, thus providing reassurance regarding the statistical approach.[17] The impact of missing data on the results may be of greater concern in AWARD-6, in which the MMRM model (missing data not imputed) was used for the primary analysis — specifically, 48 of 599 (8.0%) participants (20 receiving dulaglutide 1.5 mg) did not contribute to the primary analysis in this model due to missing data. Nevertheless, the results of the MMRM model appeared to be similar to those from the other statistical models and analysis sets, including the ANCOVA model that used the ITT population (Figure 8). It is important to note, however, that the analyses using the ITT population excluded post-rescue efficacy measurements, which might explain why the ANCOVA model using data from the ITT analysis set excluded 13 participants (2.2%)

Although the number of discontinuations prior to 26 weeks in AWARD-6 was relatively minimal — i.e., less than 10% in each treatment arm — there was a larger percentage of participants who discontinued prior to 24 months in AWARD-5: from 39.1% in the dulaglutide 0.75 mg group to 46.3% in the placebo/sitagliptin group. Moreover, the rates of discontinuation appeared to be disproportional across the treatment groups, with more participants in the sitagliptin and placebo/sitagliptin arms discontinuing than those receiving either dose of dulaglutide.

Although both studies were adequately powered to evaluate the primary efficacy outcome, neither trial was powered to assess key outcomes such as impact on microvascular or macrovascular complications of diabetes, change in body weight, FPG, BP, or for harms outcomes. Further, although subgroup analyses were presented for a number of relevant subgroups, which were pre-specified, adjustments for

multiple comparisons did not appear to have been made for these analyses. These analyses (as well as the secondary efficacy outcomes and harms outcomes) should be treated as exploratory given that subgroups typically do not maintain randomization unless used as stratification variables for randomization, which was true of all subgroups except for baseline A1C in AWARD-6, and because of the increased likelihood of type 1 error.

b) Add-on to metformin and a sulfonylurea

Like the above trials, AWARD-2 was a randomized, active-controlled, parallel-group, non-inferiority trial with appropriate randomization and allocation concealment processes. Although the study used an open-label design, it was double-blind with respect to the dulaglutide assignments; as with AWARD-5 and AWARD-6, this necessitates caution when interpreting the results of analyses of subjective outcomes, such as HRQoL, in this study. More importantly, however, the open-label design raises concerns regarding the extent to which insulin glargine was optimally administered in this trial, especially as participants who were assigned to receive that treatment were asked to self-adjust their dose until their FPG had reached targets of < 5.6 mmol/L. Figure 7 indicates that participants may not have reached stable doses of insulin glargine by the end of the study. Only 24% [redacted] of participants assigned to receive insulin glargine had reached an FPG target of < 5.6 mmol/L at 52 weeks [redacted] A1C, due to the delay in seeing the effect of lowering plasma glucose on A1C, as well as the fact that the majority of patients did not achieve their target insulin dose over the course of the trial.

The choice of the non-inferiority margin in this trial was 0.4%, which was consistent with that in AWARD-6. Two models — an ANCOVA (primary) and an REML-MRMM (secondary) — were used to conduct the analyses. Consistent with the above trials, the primary analyses for the other efficacy outcomes were conducted using the ITT analysis set, which excluded post-rescue efficacy measurements, and the secondary analyses used data from the PP population. The same limitations, as above, with respect to the statistical models and analysis populations are relevant here. [redacted]. However, as more participants in the two dulaglutide arms (0.75 mg and 1.5 mg) received rescue therapy than participants in the insulin glargine arm, fewer participants contributed to the MRMM model in the dulaglutide groups than those receiving insulin glargine. Nevertheless, the results were consistent across the different statistical models and analysis sets, and as with AWARD-5, the FDA review concluded that the overall conclusions of the trial were robust to missing data.[17]

Like AWARD-5, this study used a tree-gatekeeping testing strategy to control the family-wise type 1 error rate at one-sided level of 0.025. The strategy here, however, tested four ordered hypotheses, unlike the six that were evaluated in AWARD-5. As above, only the outcome of change from baseline in A1C was considered in the testing strategy, which limits the ability to interpret the analyses of outcomes outside the gatekeeping procedure. Without controlling for multiplicity, analyses of all outcomes other than change in A1C and the subgroup analyses should be considered hypothesis-generating and interpreted with caution.

3.5.2 External Validity

a) Add-on to metformin

Across AWARD-5 and AWARD-6, the trial participants broadly reflected the characteristics of patients with T2DM who would be seen in usual Canadian practice and would require second-line treatment; i.e.,

those who experience inadequate glycemic control on diet and exercise plus therapy with metformin alone. In AWARD-5, approximately 50% of the participants were Caucasian or white, which, according to the consulting clinical expert on this review, appears to be more representative of the target population, versus AWARD-6, in which more than 85% of participants were Caucasian or white. [redacted] Across both trials, T2DM patients who were African, African-American, or black were underrepresented, while in AWARD-6, Asian and Hispanic patients were underrepresented. Discussions with the clinical expert highlighted that any differences in weight and BMI and BP between trials may be due, at least in part, to a significantly greater proportion of Caucasian or white participants enrolled in AWARD-5 than in AWARD-6, but that the observed values were still within the range of patients seen in usual clinical practice.

In AWARD-6, although participants were titrated on liraglutide, those who were randomized to receive dulaglutide were not, even though recommended initiating dose in the product monograph is 0.75 mg. This may limit generalizability to clinical practice, as the dosing regimen does not reflect how the drug would be initiated. Patients would also reach target dosing of dulaglutide more quickly and therefore achieve a larger reduction in blood glucose faster.

A few caveats were noted after discussions with the clinical expert, which limit the generalizability of the results to certain subgroups of patients with T2DM. First, AWARD-5 imposed an upper limit of age of 75 years as an inclusion criterion. This may be significant, as the prevalence of diagnosed diabetes generally increases with age. The Public Health Agency of Canada estimates that in 2008-2009, individuals aged 75 to 79 years were the highest proportion of people with diagnosed diabetes (23.1% of females, 28.5% of males).[24] Both trials also excluded participants with creatinine clearance < 60 mL/minute at screening, which reflected the contraindication of metformin. However, this may affect the generalizability of results to patients with reduced kidney function, as the clinical expert stated that metformin will often be used below this threshold at a lower dose. Both studies appeared to exclude participants with a recent history of clinically significant and potentially unstable cardiovascular (CV) disease. For example, AWARD-6 excluded participants with acute myocardial infarction (MI), New York Heart Association class III or IV heart failure, or transient ischemic attack (TIA) within two months prior to screening. This criterion, however, appears to be consistent with most other clinical development programs for T2DM. Nonetheless, the exclusion of such participants results in uncertainty regarding the safety and efficacy profile of the relevant study treatments in these populations. At 12 and 24 months, the maximum daily dose of metformin used across the four treatment arms in AWARD-5 was 3,000 mg/day, which exceeds the Health Canada–recommended maximum dose of 2,550 mg/day, further limiting the generalizability of the results. [25] No information was provided about the maximum daily dose of metformin in AWARD-6.

The choice and dose of comparator in both studies — i.e., sitagliptin 100 mg in AWARD-5, and liraglutide 1.8 mg in AWARD-6 — reflected treatment regimens that are available and used in Canada as second-line therapy for T2DM. An important limitation across the trials is the lack of data comparing dulaglutide to other drug classes used for second-line therapy, particularly sulfonylureas.

Both trials evaluated the efficacy and safety of the study treatments across a range of outcomes, many of which were important to patients. As well, the lengths of follow-up for both studies (104 weeks for AWARD-5, 26 weeks for AWARD-6) are considered acceptable to assess the efficacy (A1C) of antihyperglycemic drugs, although the long-term safety of dulaglutide, particularly the occurrence of microvascular and macrovascular events, remains uncertain.

b) Add-on to metformin and a sulfonylurea

[redacted]Correspondence with the manufacturer highlighted that participants were discontinued during the lead-in period if the maximum tolerated doses of metformin or glimepiride were lower than the minimum protocol-specified doses. In addition, participants achieving optimal glycemic control, in the opinion of the investigator and based on the participants' self-monitoring plasma glucose data, were also discontinued. Finally, participants with A1C values lower than 6.5% were also excluded from randomization. Nevertheless, the characteristics of the included patients broadly reflected those with T2DM who would be seen in usual Canadian practice and would require third-line treatment; i.e., those who experience inadequate glycemic control on diet and exercise plus therapy with metformin and a sulfonylurea. A total of 75 participants (9.3%) were enrolled from Canadian sites. Discussions with the consulting clinical expert highlighted limitations with respect to the generalizability of the results similar to those noted for the above trials. In particular, T2DM patients who were African, African-American, or black were underrepresented. Further, the trial, as above, also excluded participants with creatinine clearance < 60 mL/minute at screening, as well as those with a recent history of clinically significant and potentially unstable CV disease. The average duration of diabetes of participants enrolled in this trial was approximately nine years, which was about two years longer than those in AWARD-5 and AWARD-6. The consulting clinical expert noted that this was consistent with the fact that the trial had been designed to test third-line treatment for T2DM, whereas the other two trials focused on second-line treatment. At 52 weeks, the maximum daily doses of metformin and glimepiride across all three treatment arms were 3,000 mg/day and 8 mg/day. The metformin dose exceeds the maximum recommended dose by Health Canada, which is 2,550 mg/day, while the glimepiride dose is consistent with the Health Canada recommendations, which is 8 mg/day.[26] At 78 weeks, however, the maximum glimepiride dose in the dulaglutide 0.75 mg arm was 12 mg/day, which exceeds the Health Canada recommendation. These discrepancies further limit the generalizability of the results.

Insulin glargine was a relevant comparator, but the consulting clinical expert indicated that the titration schedule was overly aggressive — a point noted by the European Medicines Agency (EMA) as well.[27] The implications are challenging to quantify, however, as the trial may have been biased against insulin glargine, because there are concerns about whether participants receiving this treatment had reached stable doses by the end of the study. Further, participants were targeting an FPG of < 5.6 mmol/L, which is inconsistent with the recommendation by the Canadian Diabetes Association, which recommends a target of 4 to 7 mmol/L.[28] Further, the effects of dulaglutide against other regimens used for third-line therapy — i.e., SGLT2 inhibitors, thiazolidinediones, meglitinides, and alpha-glucosidase inhibitors — remain uncertain due to a lack of direct comparative evidence. As well, there were no data evaluating a background regimen that comprised a sulfonylurea other than glimepiride.

This trial also evaluated the efficacy and safety of the study treatments across a range of outcomes, many of which were important to patients, including glycemic control, body weight, and BP. As above, however, the long-term safety of dulaglutide, particularly the occurrence of microvascular and macrovascular events, remains uncertain.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 7).

3.6.1 Key efficacy outcomes

a) Mortality

Mortality was not considered an efficacy variable in the included studies, but rather as a safety variable.

Add-on to metformin

In AWARD-5, there were a total of four deaths — one in the dulaglutide 1.5 mg group, two in sitagliptin, and one in placebo/sitagliptin — over the entire 24-month treatment period. Three of the deaths were CV in nature — one each in the dulaglutide 1.5 mg, sitagliptin, and placebo/sitagliptin arms.

No participant died in AWARD-6.

Add-on to metformin and a sulfonylurea

In AWARD-2, there were a total of three deaths — one in the dulaglutide 0.75 mg group, and two in insulin glargine — over the entire 78-week treatment period. Two of the deaths were CV in nature — one each in the dulaglutide 0.75 mg and insulin glargine treatment arms.

b) Diabetes-related morbidity

Diabetes-related morbidity — i.e., select microvascular and macrovascular events — was not considered an efficacy variable in the included studies, but rather comprises several safety variables.

Add-on to metformin

In AWARD-5, over the entire 24-month treatment period, four participants experienced treatment-emergent diabetic retinopathy — one receiving dulaglutide 0.75 mg, two receiving dulaglutide 1.5 mg, and one receiving sitagliptin (Table 20). Over the same time interval, more participants receiving dulaglutide 1.5 mg experienced treatment-emergent diabetic nephropathy than individuals in other treatment groups [redacted]

[redacted]

TABLE 20: DIABETES-RELATED MORBIDITY (ADD-ON TO METFORMIN)

Outcome	AWARD-5				AWARD-6	
	Dulaglutide 0.75 mg (N = 302)	Dulaglutide 1.5 mg (N = 304)	Sitagliptin (N = 315)	Placebo/ Sitagliptin (N = 177)	Dulaglutide 1.5 mg (N = 299)	Liraglutide 1.8 mg (N = 300)
Diabetic retinopathy						
26 weeks, n (%)					[redacted]	[redacted]
24 months, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Diabetic nephropathy						
26 weeks, n (%)					[redacted]	[redacted]
24 months, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Diabetic neuropathy						
26 weeks, n (%)					[redacted]	[redacted]
24 months, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		

Outcome	AWARD-5				AWARD-6	
	Dulaglutide 0.75 mg (N = 302)	Dulaglutide 1.5 mg (N = 304)	Sitagliptin (N = 315)	Placebo/ Sitagliptin (N = 177)	Dulaglutide 1.5 mg (N = 299)	Liraglutide 1.8 mg (N = 300)
Non-fatal stroke or TIA (adjudicated)						
26 weeks, n (%)					[redacted]	[redacted]
24 months, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		
Non-fatal MI (adjudicated)						
26 weeks, n (%)					[redacted]	[redacted]
24 months, n (%)	[redacted]	[redacted]	[redacted]	[redacted]		

MI = myocardial infarction; NR = not reported; TIA = transient ischemic attack.
Source: AWARD-5 Clinical Study Report (CSR),[13] AWARD-6 CSR.[14]

Add-on to metformin and a sulfonylurea

In AWARD-2, over the entire 78-week treatment period, four participants (all receiving dulaglutide 0.75 mg) experienced treatment-emergent diabetic retinopathy, while two individuals (both receiving insulin glargine) experience treatment-emergent diabetic neuropathy (Table 21). More participants receiving insulin glargine experienced a non-fatal stroke or TIA or MI than those in the other treatment groups.

TABLE 21: DIABETES-RELATED MORBIDITY (ADD-ON TO METFORMIN AND A SULFONYLUREA)

Outcome	AWARD-2		
	Dulaglutide 0.75 mg (N = 272)	Dulaglutide 1.5 mg (N = 273)	Insulin Glargine (N = 262)
Diabetic retinopathy			
78 weeks, n (%)	[redacted]	[redacted]	[redacted]
Diabetic nephropathy			
78 weeks, n (%)	[redacted]	[redacted]	[redacted]
Diabetic neuropathy			
78 weeks, n (%)	[redacted]	[redacted]	[redacted]
Non-fatal stroke or TIA (adjudicated)			
78 weeks, n (%)	[redacted]	[redacted]	[redacted]
Non-fatal MI (adjudicated)			
78 weeks, n (%)	[redacted]	[redacted]	[redacted]

MI = myocardial infarction; TIA = transient ischemic attack.
Source: AWARD-2 Clinical Study Report.[22]

c) Glycated hemoglobin

A1C was considered an efficacy variable in the included studies. The results for this outcome are presented from the primary statistical model using the primary analysis population and at the primary end point in each study. Only the change in A1C from baseline was included in the pre-specified testing strategy, which means that the analyses of participants achieving A1C < 7.0% need to be considered exploratory, because they were not adjusted for multiplicity, and the results be interpreted with caution.

Add-on to metformin

Change in A1C from baseline: In AWARD-5, the primary efficacy end point was the change in A1C from baseline to week 52. The results demonstrated that there was a greater reduction from baseline in A1C at week 52 in the dulaglutide 0.75 and 1.5 mg groups than in the sitagliptin group: least squares mean difference (LS MD) (nominal 95% CI) of –0.47 (–0.63 to –0.31) ($P < 0.001$) and –0.71 (–0.87 to –0.55) ($P < 0.001$), respectively (Table 22). The results appeared to be consistent with the analysis of participants who were exclusively randomized during stage 2 (Table 27). However, no formal statistical tests were conducted to assess whether treatment effects significantly differed across the participants enrolled in stage 1 versus stage 2.

In AWARD-6, the primary efficacy end point was the change in A1C from baseline to week 26. The results demonstrated that dulaglutide 1.5 mg was statistically non-inferior versus liraglutide 1.8 mg with respect to the change in A1C from baseline to week 26, as indicated by an LS MD (nominal 95% CI) of –0.06 (–0.19 to 0.07) ($P < 0.001$) (Table 27).

The above results were consistent across the different statistical models, populations used, and at the longest follow-up time point (Figure 8). Further, there did not seem to be any important interactions between subgroups of interest and treatment across the two trials (Table 28, Table 29).

Achieving A1C < 7.0%: In AWARD-5, at 52 weeks, significantly more participants receiving dulaglutide 0.75 mg (48.8%) and 1.5 mg (57.6%) achieved A1C < 7.0% than those receiving sitagliptin (33.0%) ($P < 0.001$) (Table 22).

In AWARD-6, at 26 weeks, there was no statistically significant difference in the percentage of participants who achieved A1C < 7.0% between those receiving dulaglutide 1.5 mg (68.3%) and liraglutide 1.8 mg (67.9%) [redacted] (Table 22).

Add-on to metformin and a sulfonylurea

Change in A1C from baseline: In AWARD-2, the primary efficacy end point was the change in A1C from baseline to week 52. The results demonstrated that, with respect to this outcome, dulaglutide 0.75 mg was statistically non-inferior to insulin glargine — LS MD (nominal 95% CI) of –0.13 (–0.29 to 0.02) ($P < 0.001$) — and dulaglutide 1.5 mg was statistically superior to insulin glargine — LS MD (nominal 95% CI) of –0.45 (–0.60 to –0.29) ($P < 0.001$) (Table 23).

The above results were consistent across the different statistical models, populations used, and at the longest follow-up time point (Figure 8). There was statistically significant interaction between treatment and duration of diabetes at baseline, specifically with respect to a difference in change in A1C from baseline to week 52 (Table 30).

Achieving A1C < 7.0%: In AWARD-2, at 52 weeks, there was no statistically significant difference in the percentage of participants who achieved A1C < 7.0% between those receiving dulaglutide 0.75 mg (37.1%) and insulin glargine (30.9%) ($P = 0.098$) (Table 23). There were, however, significantly more participants receiving dulaglutide 1.5 mg (53.2%) than those receiving insulin glargine who achieved A1C < 7.0% ($P < 0.001$).

d) Fasting plasma glucose

FPG was considered an efficacy variable in the included studies. It is important to note, however, that this outcome was outside the pre-specified testing strategy, which means that the analyses need to be considered exploratory, and the results interpreted with caution.

Add-on to metformin

In AWARD-5, participants receiving dulaglutide 0.75 mg and 1.5 mg experienced a greater reduction in FPG at week 52 than those receiving sitagliptin: LS MD (95% CI) of –0.73 mmol/L (–1.07 to –0.39) (P < 0.001) and –1.47 mmol/L (–1.82 to –1.13) (P < 0.001), respectively (Table 22).

In AWARD-6, there was no statistically significant difference in reduction from baseline in FPG at week 26 between the dulaglutide 1.5 mg and liraglutide 1.8 mg groups: LS MD (95% CI) of –0.03 mmol/L (–0.32 to 0.25) (P = 0.828) (Table 22).

Add-on to metformin and a sulfonylurea

In AWARD-2, participants receiving insulin glargine experienced a greater reduction in FPG at week 52 than those receiving dulaglutide 0.75 mg — LS MD was not reported, and the 95% CI ranged from 0.51 mmol/L to 1.27 mmol/L (P < 0.001) — although the difference was not significant when compared with those receiving dulaglutide 1.5 mg (Table 23).

e) Body weight

Body weight was not considered an efficacy variable in the included studies, but rather as a safety variable. It is important to note, however, that this outcome was outside the pre-specified testing strategy, which means that the analyses need to be considered exploratory, and the results interpreted with caution.

Add-on to metformin

In AWARD-5, participants receiving dulaglutide 0.75 mg and 1.5 mg lost more weight at week 52 than those receiving sitagliptin: LS MD (95% CI) of –1.07 kg (–1.65 to –0.48) (P < 0.001) and –1.50 kg (–2.08 to –0.92) (P < 0.001), respectively (Table 22).

In AWARD-6, participants receiving dulaglutide 1.5 mg lost less weight at week 26 than those receiving liraglutide 1.8 mg: LS MD (95% CI) of 0.71 kg (0.17 to 1.26) (P < 0.001) (Table 22).

Add-on to metformin and a sulfonylurea

In AWARD-2, participants receiving dulaglutide 0.75 mg and 1.5 mg lost more weight at week 52 than those receiving insulin glargine — LS MD was not reported, and the 95% CIs ranged from 2.17 kg to 3.36 kg (P < 0.001), and 2.71 kg to 3.90 kg (P < 0.001) for the respective comparisons (Table 23).

f) Blood pressure

BP was not considered an efficacy variable in the included studies, but rather as a safety variable. It is important to note, however, that this outcome was outside the pre-specified testing strategy, which means that the analyses need to be considered as exploratory, and the results interpreted with caution.

Add-on to metformin

Across AWARD-5 and AWARD-6, there were no statistically significant differences in reduction of BP at week 52 and 26, respectively, between participants receiving dulaglutide and sitagliptin or liraglutide (Table 22).

Add-on to metformin and a sulfonylurea
In AWARD-2, there were no statistically significant differences in reduction of BP at week 52 between participants receiving dulaglutide and insulin glargine (Table 23).

g) Health-related quality of life
HRQoL was considered an efficacy variable in the included studies. The results for this outcome are presented in APPENDIX 4. It is important to note, however, that this outcome was outside the pre-specified testing strategy, which means that the analyses need to be considered as exploratory, and the results interpreted with caution.

Add-on to metformin
In AWARD-5, although statistical significance was not tested, there appeared to be a small increase (from baseline to week 52) in each of the mean scores of the EQ-5D VAS, EQ-5D UK, and US population-based Index Scores, as well as the total score on the IWQOL-Lite (Table 31). In AWARD-6, there were no statistically significant differences in changes in HRQoL at week 26 between participants receiving dulaglutide and sitagliptin or liraglutide.

Add-on to metformin and a sulfonylurea
In AWARD-2, participants receiving dulaglutide experienced little or no change in HRQoL, whereas those receiving insulin glargine experienced a slight decrease, thus resulting in a statistically greater decrease in HRQoL with insulin glargine relative to dulaglutide (Table 32).

3.6.2 Other Efficacy Outcomes

a) Treatment satisfaction and/or preference
None of the included studies assessed treatment satisfaction and/or preference.

b) Fear of injections
None of the included studies assessed fear of injections.

c) Health care resource utilization
Health care resource utilization was not considered an efficacy variable in the included studies, but rather as a safety variable. The results for this outcome are presented at the primary end point in each study. It is important to note, however, that this outcome was outside the pre-specified testing strategy, which means that the analyses need to be considered as exploratory, and the results interpreted with caution.

Add-on to metformin
In AWARD-5, there were no significant differences observed across the treatment groups at 52 weeks in the number of participants reporting at least one ER visit and no ER visits since the last visit.

AWARD-6 did not assess health care resource utilization.

Add-on to metformin and a sulfonylurea
AWARD-2 did not assess health care resource utilization.

TABLE 22: KEY EFFICACY OUTCOMES (ADD-ON TO METFORMIN)

Outcome (Statistical Model/Analysis Population)	AWARD-5				AWARD-6	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/Sitagliptin	Dulaglutide 1.5 mg	Liraglutide 1.8 mg
A1C, % (ANCOVA/ITT for AWARD-5; MMRM/ITT for AWARD-6)						
Baseline, N	302	303	314	[redacted]	299	300
Baseline, mean (SD)	8.19 (1.11)	8.12 (1.05)	8.09 (1.09)	[redacted]	8.06 (0.81)	8.05 (0.79)
26 weeks, N					[redacted]	[redacted]
26 weeks, change from baseline, LS mean (SE)					–1.42 (0.05)	–1.36 (0.05)
26 weeks, LS mean difference (nominal 95% CI)					–0.06 (–0.19 to 0.07)	
P value for non-inferiority					< 0.001	
P value for superiority					0.186	
52 weeks, N	297	301	311	176		
52 weeks, change from baseline, LS mean (SE)	–0.87 (0.06)	–1.10 (0.06)	–0.39 (0.06)	[redacted]		
52 weeks, LS mean difference vs. sitagliptin (nominal 95% CI)	–0.47 (–0.63 to –0.31)	–0.71 (–0.87 to –0.55)				
P value for non-inferiority vs. sitagliptin	< 0.001	< 0.001				
P value for superiority vs. sitagliptin	< 0.001	< 0.001				
A1C, achieve < 7.0% (ITT for AWARD-5 and AWARD-6)						
26 weeks, N					[redacted]	[redacted]
26 weeks, n (%)					200 (68.3)	199 (67.9)
26 weeks, adjusted OR (95% CI); *P* value					[redacted]	
52 weeks, N	297	302	312	176		
52 weeks, n (%)	145 (48.8)	174 (57.6)	103 (33.0)	61 (34.7)		
52 weeks, adjusted OR (95% CI) vs. sitagliptin; *P* value	[redacted]	[redacted]				
FPG (mmol/L) (MMRM/ITT for AWARD-5; ANCOVA/ITT for AWARD-6)						
Baseline, N	296	297	308	176	299	300
Baseline, mean (SD)	9.68 (2.94)	9.75 (3.27)	9.56 (2.80)	9.86 (3.15)	9.28 (2.16)	9.16 (2.32)
26 weeks, N					[redacted]	[redacted]
26 weeks, adjusted change from baseline, LSM (SE)					–1.93 (0.12)	–1.90 (0.12)
26 weeks, LS mean difference (95% CI); *P* value					–0.03 (–0.32 to 0.25); *P* = 0.828	
52 weeks, N	247	239	244	117		

Outcome (Statistical Model/Analysis Population)	AWARD-5				AWARD-6	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/Sitagliptin	Dulaglutide 1.5 mg	Liraglutide 1.8 mg
52 weeks, adjusted change from baseline, LSM (SE)	–1.63 (0.13)	–2.38 (0.13)	–0.90 (0.13)	–0.92 (0.18)		
52 weeks, LS mean difference vs. sitagliptin (95% CI); *P* value	[redacted]	[redacted]				
Body weight (kg) (ANCOVA/ITT for AWARD-5 and AWARD-6)						
Baseline, N	302	304	315	[redacted]	299	300
Baseline, mean (SD)	86.22 (17.99)	86.67 (17.45)	85.97 (16.91)	[redacted]	93.82 (18.23)	94.35 (18.96)
26 weeks, N					299	299
26 weeks, adjusted change from baseline, LSM (SE)					–2.90 (0.22)	–3.61 (0.22)
26 weeks, LS mean difference (95% CI); *P* value					0.71 (0.17 to 1.26); *P* = 0.010	
52 weeks, N	299	303	314	[redacted]		
52 weeks, change from baseline, LS mean (SE)	–2.60 (0.23)	–3.03 (0.22)	–1.53 (0.22)	–1.61 (0.29)		
52 weeks, LS mean difference vs. sitagliptin (95% CI); *P* value	–1.07 (–1.65 to –0.48); *P* < 0.001	–1.50 (–2.08 to –0.92); *P* < 0.001				
Blood pressure, seated systolic (mm Hg) (MMRM/ITT for AWARD-5 and AWARD-6)						
Baseline, N	302	304	315	[redacted]	299	300
Baseline, mean (SD)	127.50 (14.12)	128.57 (12.78)	[redacted]	[redacted]	132.20 (14.97)	130.94 (15.14)
26 weeks, N					[redacted]	[redacted]
26 weeks, adjusted change from baseline, LSM (SE)					–3.36 (0.7)	–2.82 (0.7)
26 weeks, LS mean difference (95% CI); *P* value					[redacted] *P* = 0.600	
52 weeks, N	255	246	253	121		
52 weeks, change from baseline, LS mean (SE)	–0.53 (0.67)	–0.79 (0.67)	[redacted]	[redacted]		
52 weeks, LS mean difference vs. sitagliptin (95% CI); *P* value	[redacted]	[redacted]				
Blood pressure, seated diastolic (mm Hg) (MMRM/ITT for AWARD-5 and AWARD-6)						
Baseline, N	302	304	315	[redacted]	299	300
Baseline, mean (SD)	77.65 (8.63)	77.86 (8.26)	77.32 (8.66)	77.68 (8.16)	79.88 (9.45)	79.10 (9.19)
26 weeks, N					[redacted]	[redacted]
26 weeks, change from baseline, LSM (SE)					–0.22 (0.4)	–0.31 (0.4)
26 weeks, LS mean difference (95% CI); *P* value					[redacted] *P* = 0.884	
52 weeks, N	[redacted]	[redacted]	[redacted]	[redacted]		

Outcome (Statistical Model/Analysis Population)	AWARD-5				AWARD-6	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/Sitagliptin	Dulaglutide 1.5 mg	Liraglutide 1.8 mg
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]		
52 weeks, LS mean difference vs. sitagliptin (95% CI); *P* value	[redacted]	[redacted]				

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; FPG = fasting plasma glucose; ITT = intention-to-treat; LS = least squares; MMRM = mixed-model repeated measures; OR = odds ratio; PP = per-protocol; SD = standard deviation; SE = standard error; vs. = versus.
Source: AWARD-5 Clinical Study Report (CSR),[13] AWARD-6 CSR.[14]

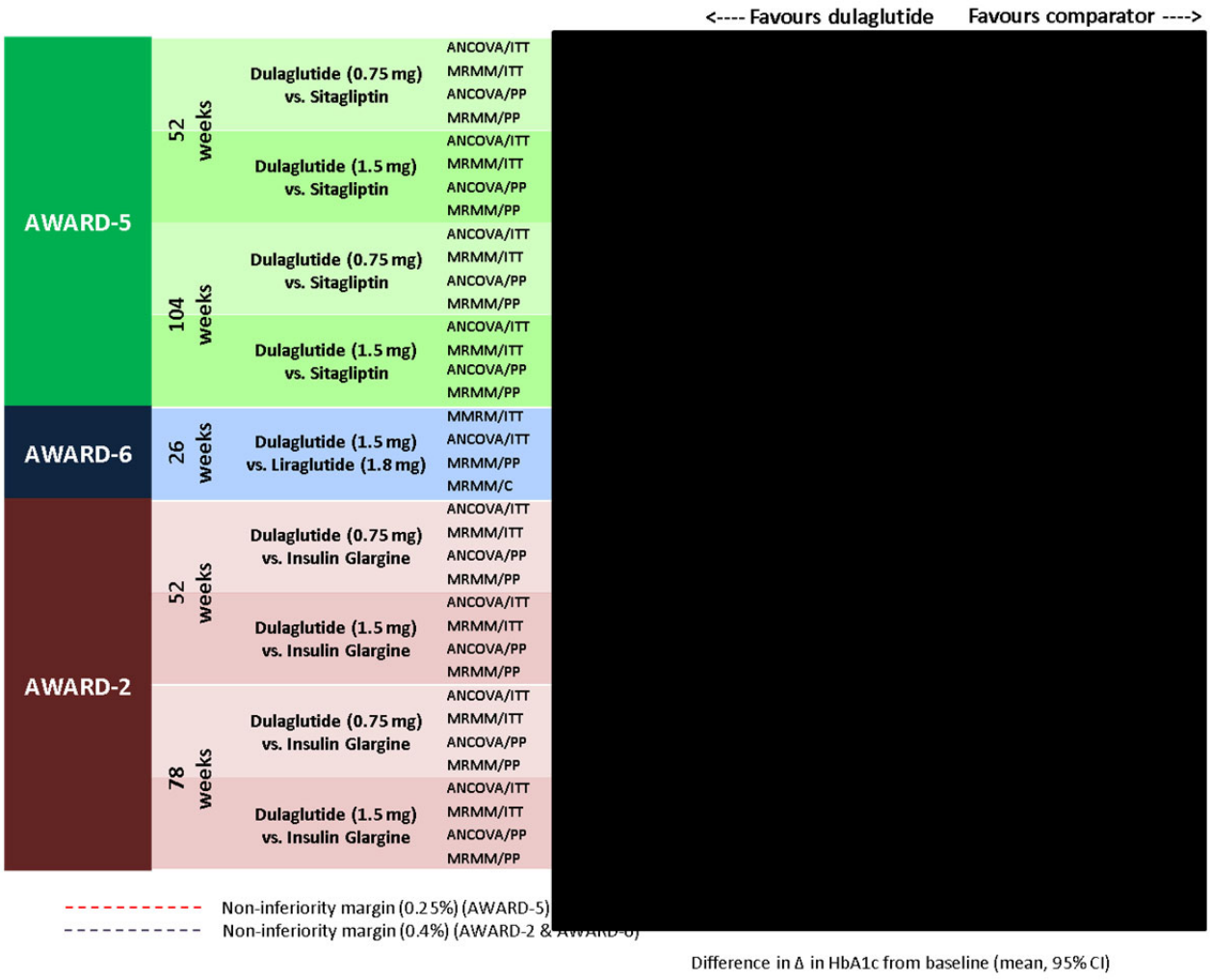
TABLE 23: KEY EFFICACY OUTCOMES (ADD-ON TO METFORMIN AND A SULFONYLUREA)

Outcome (Statistical Model/Analysis Population)	AWARD-2		
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Insulin Glargine
A1C, % (ANCOVA/ITT)			
Baseline, N	272	273	262
Baseline, mean (SD)	8.13 (0.98)	8.18 (1.03)	8.10 (0.95)
52 weeks, N	[redacted]	[redacted]	[redacted]
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	–0.63 (0.06)
52 weeks, LS mean difference vs. insulin glargine (nominal 95% CI)	[redacted]	[redacted]	
P value for non-inferiority vs. insulin glargine	[redacted]	[redacted]	
P value for superiority vs. insulin glargine	[redacted]	[redacted]	
A1C, achieve < 7.0% (ITT)			
52 weeks, N	[redacted]	[redacted]	[redacted]
52 weeks, n (%)	[redacted]	[redacted]	[redacted]
52 weeks, adjusted OR (95% CI) vs. insulin glargine; *P* value	[redacted]	[redacted]	
FSG (mmol/L) (MMRM/ITT)			
Baseline, N	272	273	262
Baseline, mean (SD)	8.96 (2.70)	9.16 (2.73)	9.08 (2.66)
52 weeks, N	[redacted]	[redacted]	[redacted]
52 weeks, change from baseline, LS mean (SE)	–0.87 (0.14)	–1.50 (0.14)	–1.76 (0.14)
52 weeks, LS mean difference vs. insulin glargine (95% CI); *P* value	[redacted]	[redacted]	
Body weight (kg) (ANCOVA/ITT)			
Baseline, N	270	272	259

Outcome (Statistical Model/Analysis Population)	AWARD-2		
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Insulin Glargine
Baseline, mean (SD)	86.4 (18.01)	85.2 (17.81)	87.6 (19.69)
52 weeks, N	[redacted]	[redacted]	[redacted]
52 weeks, change from baseline, LS mean (SE)	–1.33 (0.24)	–1.87 (0.24)	1.44 (0.24)
52 weeks, LS mean difference vs. insulin glargine (95% CI); *P* value	[redacted]	[redacted]	
Blood pressure, seated systolic (mm Hg) (MMRM/ITT)			
Baseline, N	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
52 weeks, N	[redacted]	[redacted]	[redacted]
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]
52 weeks, LS mean difference vs. insulin glargine (nominal 95% CI); *P* value	[redacted]	[redacted]	
Blood pressure, seated diastolic (mm Hg) (MMRM/ITT)			
Baseline, N	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
52 weeks, N	[redacted]	[redacted]	[redacted]
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]
52 weeks, LS mean difference vs. insulin glargine (nominal 95% CI); *P* value	[redacted]	[redacted]	

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; FSG = fasting serum glucose; ITT = intention-to-treat; LS = least squares; MMRM = mixed-model repeated measures; NR = not reported; OR = odds ratio; PP = per-protocol; SD = standard deviation; SE = standard error; vs. = versus.
Source: AWARD-2 Clinical Study Report.[22]

FIGURE 8: ANALYSIS OF CHANGE FROM BASELINE IN A1C AT PRIMARY AND LONGEST FOLLOW-UP TIME POINT, BY STATISTICAL MODEL (ALL STUDIES)



ANCOVA = analysis of covariance; CI = confidence interval; HbA1c = glycated hemoglobin; ITT = intention-to-treat; MMRM = mixed-model repeated measures; PP = per-protocol.
Source: AWARD-5 Clinical Study Report (CSR),[13] AWARD-6 CSR,[14] AWARD-2 CSR.[22]

3.7 Harms

Only those harms identified in the review protocol are reported below (Section 2.2, Table 7).

The results for all harms outcomes in this section are presented over the entire treatment period in each study rather than at the primary end point.

3.7.1 Adverse Events

a) Add-on to metformin

In AWARD-5, over the entire 24-month treatment period, at least 75% of participants in each treatment group experienced a treatment-emergent AE (Table 24). A greater proportion of participants receiving dulaglutide 0.75 mg (84.4%) and 1.5 mg (85.2%) experienced an AE than those receiving sitagliptin (76.8%). The two most common AEs across the four treatment arms — i.e., dulaglutide 0.75 mg, dulaglutide 1.5 mg, placebo/sitagliptin, and sitagliptin — were nasopharyngitis and hyperglycemia. There did not appear to be an association with any specific drug with the rate of nasopharyngitis across treatment arms. A smaller proportion of participants receiving dulaglutide 1.5 mg experienced hyperglycemia than those in the other treatment groups. A greater proportion of participants receiving either dose of dulaglutide experienced nausea, diarrhea, and vomiting than those in the other treatment groups.

In AWARD-6, over the entire 26-week treatment period, more than 60% of participants in each treatment group experienced an AE, with a seemingly equal proportion in each arm (Table 24). The most common AE across the dulaglutide 1.5 mg and liraglutide 1.8 mg treatment arms was nausea (20.4% in dulaglutide vs. 18.0% in liraglutide), followed by diarrhea (12.0% in each group), headache (7.4% dulaglutide vs. 8.3% liraglutide), and vomiting (7.0% dulaglutide vs. 8.3% liraglutide). There did not appear to be any meaningful differences in the occurrence of treatment-emergent AEs between participants receiving dulaglutide 1.5 mg and liraglutide 1.8 mg.

b) Add-on to metformin and a sulfonylurea

In AWARD-2, over the entire 78-week treatment period, approximately 70% of participants in each treatment group experienced an AE (Table 25). The most common AEs across the dulaglutide 0.75 mg and 1.5 mg, and insulin glargine arms were diarrhea and nausea, both of which occurred more commonly among participants receiving either dose of dulaglutide (diarrhea: 9.2% dulaglutide 0.75 mg, 10.6% dulaglutide 1.5 mg; nausea: 7.7% dulaglutide 0.75 mg, 15.4% dulaglutide 1.5 mg) versus insulin glargine (diarrhea: 5.7%, nausea: 1.5%). Further, there appeared to be a dose-dependent effect, as a greater proportion of participants receiving the higher dose of dulaglutide experienced AEs, like diarrhea, nausea, nasopharyngitis, and headache, than those receiving the lower dose. Moreover, a greater proportion of participants receiving insulin glargine experienced nasopharyngitis than those receiving either dose of dulaglutide.

3.7.2 Serious Adverse Events

a) Add-on to metformin

In AWARD-5, a smaller proportion of participants receiving dulaglutide 0.75 mg (7.5%) experienced a SAE than those receiving dulaglutide 1.5 mg (11.8%), sitagliptin (10.2%), and placebo/sitagliptin (9.0%) over 24 months (Table 24).

In AWARD-6, a greater proportion of participants receiving liraglutide 1.8 mg (3.7%) experienced a SAE than those receiving dulaglutide 1.5 mg (1.7%) over 26 weeks (Table 24).

b) Add-on to metformin and a sulfonylurea

In AWARD-2, at least 10% of participants in each treatment group experienced a SAE over 78 weeks (Table 25). A greater proportion of participants receiving insulin glargine (12.2%) experienced an SAE than those receiving either dulaglutide dose.

3.7.3 Withdrawals Due to Adverse Events

a) Add-on to metformin

In AWARD-5, at least 20% of participants in each treatment group discontinued from the study due to a death or an AE prior to 24 months, with an approximately equal proportion of such withdrawals in each group (Table 24).

In AWARD-6, fewer participants receiving dulaglutide 1.5 mg ([redacted]) experienced an AE that led to discontinuation of study treatment versus those receiving liraglutide 1.8 mg (4.7%) (Table 24). However, a greater proportion of participants receiving dulaglutide 1.5 mg (4.3%) discontinued from the study due to an AE prior to 26 weeks when compared with those receiving liraglutide 1.8 mg (1.7%).

b) Add-on to metformin and a sulfonylurea

In AWARD-2, no participant receiving insulin glargine discontinued from study medication due to an AE and continued in the study prior to 78 weeks; this is in contrast to approximately 6% of participants who did so while receiving either of the dulaglutide doses (Table 25). A greater proportion of participants who received either dose of dulaglutide discontinued from the study due to an AE prior to 78 weeks when compared with those receiving insulin glargine.

3.7.4 Notable Harms

a) Add-on to metformin

In AWARD-5, over the entire 24-month treatment period, the proportion of participants who experienced hypoglycemia (plasma glucose ≤ 3.9 mmol/L) ranged from 4.5% (placebo/sitagliptin) to 12.8% (dulaglutide 1.5 mg) (Table 24). There appeared to be a dose-dependent effect with respect to the occurrence of total hypoglycemia and documented symptomatic hypoglycemia across the two dulaglutide treatment groups, with a numerically greater proportion of participants in the dulaglutide 1.5 mg treatment group experiencing these events than those receiving dulaglutide 0.75 mg. There did not appear to be any differences in the proportion of participants who experienced other notable harms, specifically, injection-site reactions, pancreatitis, and pancreatic and thyroid cancer, across the four treatment groups.

In AWARD-6, over the entire 26-week treatment period, a numerically greater proportion of participants receiving dulaglutide 1.5 mg (8.7%) experienced hypoglycemia than those receiving liraglutide 1.8 mg (5.7%) (Table 24). There did not appear to be any differences in the proportion of participants who experienced other notable harms across the two treatment groups.

b) Add-on to metformin and a sulfonylurea

In AWARD-2, over the entire 78-week treatment period, more than half the participants in each treatment group experienced hypoglycemia, with a greater proportion of those receiving insulin glargine (71.4%) than either dulaglutide dose (56.6% for 0.75 mg, 58.6% for 1.5 mg) (Table 25). This trend was consistent with those observed with respect to the occurrence of documented symptomatic hypoglycemia and nocturnal hypoglycemia across the three treatment groups. There did not appear to be any differences in the proportion of participants who experienced other notable harms across the groups.

TABLE 24: HARMS (ADD-ON TO METFORMIN)

	AWARD-5[a] (24 months)				AWARD-6[b] (26 weeks)	
	Dulaglutide 0.75 mg (N = 302)	Dulaglutide 1.5 mg (N = 304)	Sitagliptin (N = 315)	Placebo/Sitagliptin (N = 177)	Dulaglutide 1.5 mg (N = 299)	Liraglutide 1.8 mg (N = 300)
AEs[b]						
Participants with > 0 AEs, N (%)	255 (84.4)	259 (85.2)	242 (76.8)	[redacted]	185 (61.9)	189 (63.0)
Most common AEs[c]						
Nasopharyngitis	47 (15.6)	42 (13.8)	45 (14.3)	[redacted]	23 (7.7)	21 (6.0)
Hyperglycemia	38 (12.6)	30 (9.9)	50 (15.9)	[redacted]		
Nausea	44 (14.6)	53 (17.4)	21 (6.7)	[redacted]	61 (20.4)	54 (18.0)
Diarrhea	36 (11.9)	49 (16.1)	18 (5.7)	[redacted]	36 (12.0)	36 (12.0)
Headache	27 (8.9)	29 (9.5)	26 (8.3)	[redacted]	22 (7.4)	25 (8.3)
Vomiting	25 (8.3)	41 (13.5)	11 (3.5)	[redacted]	21 (7.0)	25 (8.3)
Back pain	27 (8.9)	20 (6.6)	19 (6.0)	[redacted]	11 (3.7)	15 (5.0)
Urinary tract infection	22 (7.3)	20 (6.6)	19 (6.0)	[redacted]		
Upper respiratory tract infection	22 (7.3)	22 (7.2)	19 (6.0)	[redacted]		
Decreased appetite	17 (5.6)	29 (9.5)	10 (3.2)	[redacted]	16 (5.4)	20 (6.7)
Dyspepsia	19 (6.3)	18 (5.9)	14 (4.4)	[redacted]	24 (8.0)	18 (6.0)
Arthralgia	19 (6.3)	14 (4.6)	14 (4.4)	[redacted]		
Cough	11 (3.6)	19 (6.3)	16 (5.1)	[redacted]		
Influenza	18 (6.0)	16 (5.3)	13 (4.1)	[redacted]		
Abdominal pain	13 (4.3)	21 (6.9)	11 (3.5)	[redacted]		
Dizziness	18 (6.0)	7 (2.3)	14 (4.4)	[redacted]		
Constipation	16 (5.3)	14 (4.6)	4 (1.3)	[redacted]	11 (3.7)	17 (5.7)
Abdominal distension	15 (5.0)	13 (4.3)	3 (1.0)	[redacted]		
SAEs[b]						
Participants with > 0 SAEs, N (%)	23 (7.6)	36 (11.8)	32 (10.2)	[redacted]	5 (1.7)	11 (3.7)
WDAEs[b]						
Discontinuation of study drug, N (%)	NR	NR	NR	[redacted]	[redacted]	[redacted]
Discontinuation of study, N (%)	64 (21.2)	64 (21.2)	67 (21.3)	[redacted]	[redacted]	[redacted]

	AWARD-5[a] (24 months)				AWARD-6[b] (26 weeks)	
Notable Harms[b]						
Participants with > 0 notable harms, N (%)						
Hypoglycemia (PG ≤ 3.9 mmol/L)	26 (8.6)	39 (12.8)	27 (8.6)	[redacted]	26 (8.7)	17 (5.7)
Documented symptomatic hypoglycemia (PG ≤ 3.9 mmol/L)	19 (6.3)	33 (10.9)	18 (5.7)	[redacted]	8 (2.7)	8 (2.7)
Nocturnal hypoglycemia (PG ≤ 3.9 mmol/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycemia SAE	0	0	0	[redacted]	0	0
Injection-site reactions	3 (1.0)	4 (1.3)	3 (1.0)	[redacted]	1 (0.3)	2 (0.7)
Pancreatitis	0	0	2 (0.6)	[redacted]	0	0
Pancreatitis (acute)	0	0	0	[redacted]	0	0
Pancreatitis (chronic)	1 (0.3)	1 (0.3)	0	[redacted]	0	0
Pancreatic cancer	NR	NR	NR	[redacted]	0	0
Thyroid cancer	0	1 (0.3)	0	[redacted]	0	1 (0.3)

AE = adverse event; NR = not reported; PG = plasma glucose; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Participants randomized during stage 1 or stage 2 (intention-to-treat population); prior to 24 months.
[b] Includes deaths.
[c] Frequency > 5%.
Source: AWARD-5 Clinical Study Report (CSR),[13] AWARD-6 CSR.[14]

TABLE 25: HARMS (ADD-ON TO METFORMIN AND A SULFONYLUREA)

	AWARD-2 (78 weeks)		
	Dulaglutide 0.75 mg (N = 272)	Dulaglutide 1.5 mg (N = 273)	Insulin Glargine (N = 262)
AEs			
Participants with > 0 AEs, N (%)	188 (69.1)	201 (73.6)	192 (73.3)
Most common AEs[a]			
Diarrhea	25 (9.2)	29 (10.6)	15 (5.7)
Nausea	21 (7.7)	42 (15.4)	4 (1.5)
Nasopharyngitis	12 (4.4)	15 (5.5)	23 (8.8)
Headache	9 (3.3)	22 (8.1)	13 (5.0)
Upper respiratory tract infection	10 (3.7)	15 (5.5)	17 (6.5)

	AWARD-2 (78 weeks)		
Urinary tract infection	16 (5.9)	11 (4.0)	15 (5.7)
Influenza	13 (4.8)	12 (4.4)	13 (5.0)
Dyspepsia	9 (3.3)	19 (7.0)	6 (2.3)
Vomiting	10 (3.7)	18 (6.6)	3 (1.1)
Bronchitis	6 (2.2)	9 (3.3)	14 (5.3)
Abdominal pain upper	9 (3.3)	14 (5.1)	2 (0.8)
SAEs			
Participants with > 0 SAEs, N (%)	28 (10.3)	32 (11.7)	32 (12.2)
WDAEs			
Discontinuation of study drug and continued in the study, N (%)	[redacted]	[redacted]	[redacted]
Discontinuation of study, N (%)	8 (2.9)	9 (3.3)	5 (1.9)
Notable Harms			
Participants with > 0 notable harms, N (%)			
Hypoglycemia (PG ≤ 3.9 mmol/L)	154 (56.6)	160 (58.6)	187 (71.4)
Documented symptomatic hypoglycemia (PG ≤ 3.9 mmol/L)	106 (39.0)	110 (40.3)	134 (51.1)
Nocturnal hypoglycemia	63 (23.2)	70 (25.6)	104 (39.7)
Hypoglycemia SAE	0	2 (0.7)	2 (0.8)
Injection-site reactions	[redacted]	[redacted]	[redacted]
Pancreatitis (acute and chronic)	1 (0.4)	2 (0.7)	1 (0.4)
Pancreatitis	1 (0.4)	1 (0.4)	1 (0.4)
Pancreatitis (chronic)	0	1 (0.4)	0
Pancreatic cancer	NR	NR	NR
Thyroid cancer	0	1 (0.4)	0
Thyroid neoplasm	0	1 (0.4)	1 (0.4)

AE = adverse event; NR = not reported; PG = plasma glucose; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Frequency > 5%.
Source: AWARD-2 Clinical Study Report.[22]

4. DISCUSSION

4.1 Summary of Available Evidence

a) Add-on to metformin

The evidence for this review of dulaglutide for the second-line treatment of adults with T2DM was drawn from two phase 3, multi-centre, active-controlled, non-inferiority trials. AWARD-5 was an adaptive, inferentially seamless phase 2/3 study that randomized 1,098 participants to one of four primary treatment arms — dulaglutide 0.75 mg, dulaglutide 1.5 mg, sitagliptin 100 mg, and placebo/sitagliptin — for 24 months. AWARD-6 was an open-label study that randomized 599 participants to receive dulaglutide 1.5 mg or liraglutide 1.8 mg for 26 weeks. The primary efficacy outcome for both studies was the change from baseline in A1C, although it was primarily measured at 52 weeks in AWARD-5, versus 26 weeks in AWARD-6. Other outcomes of interest that were collected across both trials include mortality, the percentage of participants achieving target A1C < 7%, change from baseline in FPG or FSG, body weight, BP, HRQoL using the EQ-5D, as well as AEs, SAEs, and notable harms. HRQoL was additionally measured using the IWQOL-Lite in AWARD-5, which also evaluated health care resource utilization.

Both studies used appropriate methods to generate and conceal the randomization sequences. AWARD-5, in particular, used a double-blind, double-dummy design. In AWARD-5, there was a greater proportion of participants in the sitagliptin and placebo/sitagliptin arms who decided to discontinue from the study prior to 24 months than the dulaglutide arms, which may have introduced bias. Further, there was a large percentage of participants who discontinued from the study prior to 24 months in AWARD-5 — from 39.1% in the dulaglutide 0.75 mg group to 46.3% in the placebo/sitagliptin group. The high number of discontinuations is typically not a concern with a true ITT analysis; in this study, however, participants who did not have post-baseline observations were excluded from the primary analyses, which are inconsistent with the ITT principle, in which all randomized participants contribute to the analysis. However, the resulting risk of bias is minimal, given the relatively small number of participants who did not contribute to the analyses, as well as the FDA's analysis, which did not identify any impact of missing data on results. In AWARD-6, 8.0% of participants did not contribute to the primary analysis (MMRM) due to missing post-baseline data. However, the results were consistent across the other statistical approaches, including the ANCOVA model in which fewer participants were excluded, which provides some reassurance of the results.

In AWARD-5, baseline characteristics were similar across treatment groups in this trial [redacted]. Despite pre-specifying a subgroup analysis to assess whether treatment effects significantly differed across the participants enrolled in stage 1 versus stage 2, no such analysis was conducted. Instead, participants enrolled in stage 2 only were analyzed separately, and their results were compared with those who were randomized during stages 1 or 2 (Table 27). Thus, it remains uncertain whether the differences in baseline characteristics between participants randomized during stage 1 versus stage 2 impacted the results. In addition, there appeared to be a disproportionate number of participants from stage 1 who continued to stage 2 across some of the four primary treatment arms; specifically, a greater proportion of participants in the placebo/sitagliptin arm appeared to have continued to stage 2 from stage 1 than those in the remaining groups, which could introduce a potential source of bias.

The choices of the non-inferiority margin in both trials were consistent with previous clinical development programs for treatments for T2DM, and consistent with the 2008 FDA draft guidance. Both trials conducted analyses using multiple statistical models and multiple trial populations to provide reassurance for the main results. Although both studies were adequately powered to evaluate the primary efficacy outcome, neither trial was powered to assess key secondary efficacy outcomes such as changes in body weight, FPG, BP, HRQoL (for which change scores were not reported in AWARD-5), many of which were identified in the patient input, or for harms outcomes. Further, only the outcome of change from baseline in A1C was considered in the testing strategy, which means that the analyses of the outcomes outside of the gatekeeping procedure need to be considered exploratory, and the results interpreted with caution, because they were not adjusted for multiplicity. Interpretation of the subgroup analyses necessitates similar caution.

The consulting clinical expert confirmed that the study populations were generally reflective of Canadian practice, although both trials excluded participants with creatinine clearance < 60 mL/minute at screening, as well as those with recent history of clinically significant and potentially unstable CV disease. These exclusions result in uncertainty regarding the generalizability of the results to these subgroups of patients with T2DM. Further, AWARD-5 imposed an upper limit of age of 75 years as an inclusion criterion, which may further restrict the external validity of the results. AWARD-6 enrolled more participants who were Caucasian or white and fewer who were Asian or Hispanic than is typically seen in routine clinical practice in Canada. As well, across both trials, patients with T2DM who were African, African-American, or black were underrepresented. The choice and dose of comparator in both studies — i.e., sitagliptin 100 mg in AWARD-5, and liraglutide 1.8 mg in AWARD-6 — were reflective of current practice according to the clinical expert and reflected treatment regimens that are available and used in Canada as second-line therapy for T2DM. Last, besides incretins, — i.e., DPP-4 inhibitors (sitagliptin), and GLP-1 agonists (liraglutide) — there were no direct comparative data for dulaglutide versus other drug classes used for second-line therapy, including SGLT2 inhibitors, thiazolidinediones, meglitinides, insulin or insulin analogues, alpha-glucosidase inhibitors, and sulfonylureas, used in Canada.

b) Add-on to metformin and a sulfonylurea

The evidence for this review as it pertains to the use of dulaglutide for the third-line treatment of adults with T2DM was drawn from one phase 3, multi-centre, active-controlled, non-inferiority trial. AWARD-2 was an open-label trial, although double-blind with respect to the dulaglutide assignments, which randomized 810 participants to dulaglutide 0.75 mg, dulaglutide 1.5 mg, and insulin glargine for 78 weeks. The primary efficacy outcome for this study was the change from baseline in A1C at 52 weeks. Other outcomes of interest were mortality, the percentage of participants achieving target A1C < 7%, change from baseline in FPG and/or FSG, body weight, BP, HRQoL using the EQ-5D, as well as AEs, SAEs, and notable harms.

Although AWARD-2 used an open-label design, it was double-blind with respect to the dulaglutide assignments; this requires caution when interpreting the results of analyses of subjective outcomes; e.g., HRQoL. More importantly, the open-label design raises concerns with the extent to which insulin glargine was optimally administered. Particularly, participants who were randomized to receive insulin glargine were asked to self-adjust their dose until their FPG had reached target — i.e., < 5.6 mmol/L — although only 27.0% of participants reached target at 78 weeks and doses had not plateaued by the end of the trial. This would favour a conclusion of non-inferiority, as the comparator treatment may have been suboptimally administered. As doses were not stable at the end of the trial, the full effect of insulin glargine may not be reflected in the A1C at 78 weeks. As with the above studies, this study used a tree-

gatekeeping testing strategy to adjust for multiplicity, although it too included only the outcome of change from baseline in A1C, which limits the interpretation of the remaining outcomes and subgroup analyses

The consulting clinical expert confirmed that the study population in this trial was generally reflective of Canadian practice, although this study also excluded participants with creatinine clearance < 60 mL/minute at screening, as well as those with recent history of clinically significant and potentially unstable CV disease. These exclusions result in uncertainty regarding the generalizability of the results to these subgroups of patients with T2DM. As well, patients with T2DM who were African, African-American, or black were underrepresented. The consulting clinical expert indicated that the titration schedule for insulin glargine may have been overly aggressive, although not inappropriate. However, it is important to note that, because fewer than a third of participants reached target FPG at 78 weeks of the trial, the actual titration schedule might have been suboptimal. Lastly with the exception of insulin or insulin analogues (insulin glargine), there were no comparative data of dulaglutide versus other drug classes used for third-line therapy in Canada, which includes SGLT-2 inhibitors, thiazolidinediones, meglitinides, and alpha-glucosidase inhibitors.

4.2 Interpretation of Results

4.2.1 Efficacy

a) Add-on to metformin

In AWARD-5, both doses of dulaglutide (0.75 mg and 1.5 mg) were statistically superior to sitagliptin 100 mg with respect to change from baseline in A1C at 52 and 104 weeks. In AWARD-6, dulaglutide 1.5 mg was statistically non-inferior to liraglutide 1.8 mg with respect to change from baseline in A1C at 26 and 52 weeks. The findings were corroborated by the analyses of the percentage of participants who achieved A1C < 7.0% across the trials. The manufacturer submitted one network meta-analysis (NMA) comparing dulaglutide 0.75 mg and 1.5 mg to other drug classes for second-line therapy, including other GLP-1 agonists, SGLT2 inhibitors, DPP-4 inhibitors, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, sulfonylureas, basal insulin, biphasic insulin, and bolus insulin (0). Several methodological limitations with the manufacturer-submitted NMA were identified, including the fact that all drugs within a class were grouped and analyzed together, except for dulaglutide, without testing for evidence that the within-class treatment effects were similar. Still, the results were consistent with the findings from the two trials. In particular, per the NMA, dulaglutide 0.75 mg and 1.5 mg demonstrated statistically greater changes from baseline A1C compared with DPP-4 inhibitors, SGLT-2 inhibitors, acarbose, and meglitinides ([redacted]), while dulaglutide 1.5 mg also demonstrated superiority over thiazolidinediones ([redacted]). The magnitude of these effects appeared to be clinically important. No statistically significant differences were detected between either dose of dulaglutide and sulfonylureas, basal insulin, and biphasic insulin. Further, dulaglutide 1.5 mg and other GLP-1 agonists did not appear to be statistically different, which is consistent with the findings of AWARD-6, as well as another NMA by Kayaniyil et al. (summarized in 0) that evaluated the relative efficacy and safety of various GLP-1 agonists and found no within-class differences.[1]

In AWARD-5, one participant in each of the dulaglutide 1.5 mg and sitagliptin 100 mg treatment groups died as a result of CV causes, while no participant died in AWARD-6. Across both trials, there were few participants who experienced non-fatal macrovascular events and microvascular events. The small number of events and the insufficient length of follow-up are, however, not sufficient to make an adequate assessment of CV risk with dulaglutide. CV risk assessment with dulaglutide is ongoing with a CV outcomes study (titled REWIND) of approximately 9,600 participants who will be randomized to dulaglutide 1.5 mg or placebo.[29]

The results across the other outcomes in both trials should be hypothesis-generating only, given that none of the analyses were adjusted for multiplicity. In AWARD-6, liraglutide 1.8 mg was associated with a statistically greater reduction in body weight than dulaglutide 1.5 mg. Weight loss appears to be a class effect of GLP-1 agonists in T2DM patients, although results of the NMA by Kayaniyil et al. indicated no consistent differences between different GLP-1 receptor drugs (0).[1] This finding is also consistent with the results of the manufacturer-submitted NMA, in which there were no significant differences between dulaglutide (both doses) and other GLP-1 agonists. Per the NMA, however, both doses of dulaglutide demonstrated likely clinical superiority over sulfonylureas, thiazolidinediones, and insulin with respect to weight loss. In AWARD-5, the impact of weight on quality of life was assessed using the IWQOL-Lite questionnaire [redacted].

The results of the trials also indicated that there were no apparent differences between dulaglutide when and sitagliptin 100 mg (AWARD-5) or liraglutide 1.8 mg (AWARD-6) with respect to change in BP, HRQoL, and health care resource utilization between the treatments.

b) Add-on to metformin and a sulfonylurea

In AWARD-2, dulaglutide 0.75 mg and 1.5 mg were statistically non-inferior and superior to insulin glargine, respectively, with respect to change from baseline in A1C at 52 and 78 weeks. An analysis of the percentage of participants who achieved A1C < 7.0% in this trial was consistent with the primary results, as there was not a statistically significant difference in the number of responders between those receiving dulaglutide 0.75 mg and insulin glargine, although significantly more participants receiving dulaglutide 1.5 mg achieved target than those receiving insulin glargine. The manufacturer submitted one NMA comparing dulaglutide 0.75 mg and 1.5 mg to other drug classes for third-line therapy, including other GLP-1 agonists, SGLT2 inhibitors, DPP-4 inhibitors, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, basal insulin, biphasic insulin, and bolus insulin (0). The results of the NMA were somewhat inconsistent with the findings from AWARD-2, although these may be attributed to the fact that all drugs (in the NMA) within a class were grouped and analyzed together, except for dulaglutide, without testing for evidence that the within-class treatment effects were similar. In particular, per the NMA, no statistically significant differences were detected between dulaglutide 0.75 mg and basal insulin with respect to change from baseline in A1C, which is consistent with the results of AWARD-2. However, no statistically significant differences were detected between dulaglutide 1.5 mg and basal insulin either. Further, no statistically significant differences were observed between dulaglutide 0.75 mg and 1.5 mg compared with other GLP-1 agonists, SGLT2 inhibitors. Dulaglutide 0.75 mg ([redacted]) and dulaglutide 1.5 mg ([redacted]) demonstrated significantly greater changes from baseline A1C versus DPP-4 inhibitors. Dulaglutide 1.5 mg also showed statistically greater changes from baseline in A1C levels against thiazolidinediones ([redacted]) and acarbose ([redacted]).

In AWARD-2, one participant in each of the dulaglutide 0.75 mg and insulin glargine treatment groups died as a result of CV causes. As with AWARD-5 and AWARD-6, there were few participants who experienced non-fatal macrovascular events and microvascular events, with no apparent differences between dulaglutide and the comparator. Again, the small number of events is insufficient to make an adequate assessment of CV risk with dulaglutide as third-line treatment for T2DM patients, and results from the ongoing REWIND trial are needed to provide greater insights.

As above, the ability to interpret the results across the secondary outcomes in AWARD-2 is uncertain, given that none of the analyses were adjusted for multiplicity. In this study, participants receiving insulin

glargine appeared to experience significantly greater reductions in FSG at week 52 than those receiving dulaglutide 0.75 mg, although the clinical importance of the findings is negligible, per the consulting clinical expert. Moreover, the results of AWARD-2 demonstrated that participants receiving insulin glargine gained weight over the course of 52 weeks, while those receiving either dose of dulaglutide lost weight over the same time frame. The differences between treatment arms could be viewed as clinically meaningful, according to the clinical expert consulted, although since this trial did not assess the impact of weight loss on quality of life, as with AWARD-5, the importance to patients remains uncertain. The expert noted, however, that the magnitude of weight loss with dulaglutide was less than that observed in the second-line trials — i.e., AWARD-5 and AWARD-6 — suggesting that the impact on weight loss with dulaglutide as third-line therapy might be reduced as it may be used with drugs that cause weight gain in this role. The manufacturer-submitted NMA indicated that the effects of weight loss with dulaglutide (both doses) as third-line therapy were in line with the expectations of the consulting clinical expert, with the results suggesting no difference against SGLT2 inhibitors, DPP-4 inhibitors, and acarbose, but statistical (and likely clinical) superiority against thiazolidinediones and insulin (0). The clinical expert indicated that these differences are in line with the known effects of the different pharmacological drugs. Specifically, that thiazolidinediones and insulins are expected to cause weight gain, while the other drugs are weight neutral or reduce weight to a small extent; so, in comparison, dulaglutide would be expect to show little or no benefit compared with DPP-4 inhibitors, SGLT2 inhibitors, and acarbose, and weight loss compared with thiazolidinediones and insulin. Further, per the NMA, dulaglutide 0.75 mg appeared to be statistically inferior to other GLP-1 agonists with respect to weight loss, although this result is unlikely to be clinically important, while dulaglutide 1.5 mg seemed to show no statistical difference.

In AWARD-2, there were no apparent differences between dulaglutide (both doses) and insulin glargine, with respect to change in BP. Further, participants receiving dulaglutide 0.75 mg and 1.5 mg experienced significantly greater improvements [redacted] although, given the established psychometric properties of this instrument, the results do not appear to be clinically important.

4.2.2 Harms

a) Add-on to metformin

In AWARD-5, the vast majority (≥ 75%) of participants experienced an AE, with a greater proportion of events in the dulaglutide groups versus the sitagliptin 100 mg group. The most common AE in this trial across all treatment arms was nasopharyngitis. Hyperglycemia was also frequented reported by participants in this study, although it was more common among those receiving sitagliptin 100 mg than either dose of dulaglutide. In AWARD-6, greater than 60% of participants in each treatment group experienced an AE, with an approximately equal proportion of affected participants in each treatment group. Across both trials, other common AEs across all treatments included nausea, diarrhea, and vomiting; more participants receiving dulaglutide than sitagliptin 100 mg were affected in AWARD-5, which is consistent with the gastrointestinal risk profile of GLP-1 agonists.[30] The NMA by Kayaniyil et al. (APPENDIX 6) suggested that there are no differences between individual GLP-1 agonists with respect to the occurrence of nausea.[1]

Patients with T2DM have consistently indicated that hypoglycemia is an important factor to consider when choosing antihyperglycemic drugs, since their ability to achieve optimal glycemic control may be limited by the occurrence of hypoglycemia (0). Across both studies, a numerically greater proportion of participants receiving dulaglutide 1.5 mg experienced total hypoglycemia than those receiving sitagliptin 100 mg (AWARD-5) or liraglutide 1.8 mg (AWARD-6).In AWARD-5, there appeared to be a dose-

dependent effect with respect to the occurrence of total hypoglycemia and documented symptomatic hypoglycemia across the two dulaglutide treatment groups, with a numerically greater proportion of participants in the dulaglutide 1.5 mg treatment group experiencing these events than those receiving dulaglutide 0.75 mg. The evidence for safety in the manufacturer-submitted NMA was sparse, although the results were consistent with those from trials, [redacted]

There did not appear to be any differences in the proportion of participants receiving dulaglutide and the comparator who experienced SAEs or other notable harms, specifically, injection-site reactions, pancreatitis, and pancreatic and thyroid cancer. However, given that these are relatively rare outcomes, it is possible that the sample sizes and durations of the studies are insufficient to adequately capture these outcomes. The data from the trials are consistent with the results of the manufacturer-submitted NMA. Further, the results with respect to pancreatitis align with the findings of a previous systematic review, which suggested that GLP-1 agonists do not significantly increase the risk of pancreatitis among T2DM patients.[31]

b) Add-on to metformin and a sulfonylurea

In AWARD-2, approximately 70% of participants in each treatment group experienced an AE. The most common AEs across the treatment arms were diarrhea and nausea, both of which occurred more commonly among participants receiving dulaglutide than insulin glargine. Again, these results are consistent with the increased gastrointestinal risks associated with GLP-1 agonists.[30] There appeared to be a dose-dependent effect in this trial, as a greater proportion of participants receiving the higher dose of dulaglutide experienced AEs, such as diarrhea, nausea, nasopharyngitis, and headache, than those receiving the lower dose. These discrepancies are in contrast to the results observed in AWARD-5, in which there did not appear to be any dose-dependent effects with respect to these outcomes in particular. Moreover, a greater proportion of participants receiving insulin glargine experienced nasopharyngitis than those receiving either dose of dulaglutide.

Further, a greater proportion of participants who received insulin glargine than dulaglutide experienced hypoglycemia, which is an important outcome for patients in guiding choice of treatments (0). These discrepancies might be due to the overly aggressive titration schedule of insulin glargine, which was noted by the consulting clinical expert and the EMA, the latter of which alluded to the potential ensuing increased risk of hypoglycemia in its public assessment report. [27] Results from the manufacturer-submitted NMA indicated that there were no statistically significant differences with respect to the risk of hypoglycemia for dulaglutide versus other drug classes, although there appeared to be a trend toward increased risk with insulin (0). Data on the rate of hypoglycemia was sparse in the NMA, thus precluding meaningful conclusions.

There did not appear to be any meaningful differences with respect to the occurrence of SAEs among participants receiving dulaglutide or insulin glargine in this trial; this is consistent with the findings of the manufacturer-submitted NMA, although again the evidence for safety was sparse.

4.3 Potential Place in Therapy

The information in this section is based on information provided in draft form by the clinical expert whom CDR reviewers consulted for the purpose of this review.

Dulaglutide is likely to be popular across the full range of Health Canada–approved indications, not just those covered by this submission. The patient submission makes it clear that a majority (65%) of patients taking a GLP-1 agonist were satisfied with it and for these people the convenience of a once-weekly injection is likely to be considerable. For people who are unable to inject themselves, it offers the option of having a weekly injection given by a family member or community nurse. For people fearful of injections, it is a more attractive option than daily injections as an add-on to existing oral drugs. The risks of hypoglycemia and impact on weight are the same as other GLP-1 agonists. Dulaglutide is likely to become more attractive with time as fears of causing pancreatic and medullary cell cancers decrease with time from market launch.

5. CONCLUSIONS

Add-on to metformin

Two phase 3, multi-centre, active-controlled, non-inferiority trials met the inclusion criteria for this review, specifically as it pertained to the use of dulaglutide for the second-line treatment of adults with T2DM. AWARD-5 was an adaptive, inferentially seamless phase 2/3 study that randomized participants to dulaglutide 0.75 mg, dulaglutide 1.5 mg, sitagliptin 100 mg, and placebo/sitagliptin over 24 months. AWARD-6 was an open-label study that randomized 599 participants to receive dulaglutide 1.5 mg or liraglutide 1.8 mg over 26 weeks. Limitations of the two trials included a failure to control the type 1 error rate with all outcomes other than A1C, exclusion of some subgroups that limit the generalizability of findings, and the design of the trials which did not assess the impact of dulaglutide on microvascular or macrovascular complications of diabetes. The study populations across both trials were, however, generally reflective of Canadian practice. With respect to the primary efficacy outcome, change from baseline in A1C, results from the two trials suggested that dulaglutide 0.75 mg and 1.5 mg were likely clinically superior to sitagliptin 100 mg up to 104 weeks, and that dulaglutide 1.5 mg was statistically non-inferior to liraglutide 1.8 mg up to 52 weeks. More than half of the participants across the treatment arms in each trial experienced an AE, and there were no apparent differences between dulaglutide and the comparators in the overall rates of AE. The manufacturer-submitted network meta-analysis (NMA) suggested clinically important reductions in A1C with dulaglutide 0.75 mg or 1.5 mg versus dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium/glucose cotransporter-2 (SGLT-2) inhibitors, thiazolidinediones, acarbose, and meglitinides; no differences were found against other GLP-1 agonists, sulfonylureas, and insulin. The results may be limited by the fact that all drugs (in the NMA) within a class were grouped and analyzed together, except for dulaglutide, without testing for evidence that the within-class treatment effects were similar. Another NMA evaluated the relative effects of various GLP-1 agonists as second-line therapy for T2DM, and generally found no within-class differences in efficacy or safety.

Add-on to metformin and a sulfonylurea

One phase 3, multi-centre, active-controlled, non-inferiority trial met the inclusion criteria for this review, specifically as it pertained to the use of dulaglutide for the third-line treatment of adults with T2DM. AWARD-2 was an open-label trial that randomized participants to dulaglutide 0.75 mg, dulaglutide 1.5 mg, and insulin glargine over 78 weeks (participants were blinded to dose of dulaglutide). Important limitations of this study included a failure to control the type 1 error rate with all

outcomes other than A1C and the suboptimal manner in which insulin glargine may have been administered. The study population in this trial was generally reflective of Canadian practice, although the exclusion of certain subgroups of patients limits the generalizability of the findings. The trial duration was insufficient to adequately evaluate the CV risk profile of dulaglutide. With respect to the primary efficacy outcome, change from baseline in A1C, dulaglutide 0.75 mg and 1.5 mg were statistically non-inferior and superior, respectively, to insulin glargine up to 78 weeks. More than 70% of participants in each treatment group experienced an AE, and a greater proportion of participants who received insulin glargine than dulaglutide experienced hypoglycemia. The manufacturer-submitted NMA suggested clinically important reductions in A1C with dulaglutide 0.75 mg or 1.5 mg versus DPP-4 inhibitors and thiazolidinediones; no differences were found against other GLP-1 agonists, SGLT-2 inhibitors, basal insulin, biphasic insulin, and bolus insulin. The results of the NMA may be limited by the fact that all drugs (in the NMA) within a class were grouped and analyzed together, except for dulaglutide, without testing for evidence that the within-class treatment effects were similar.

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 provided feedback.

The Canadian Diabetes Association (the CDA) helps people with diabetes live healthy lives while work continues toward finding a cure. The CDA is supported in its efforts by a network of volunteers, employees, health care professionals, researchers, and partners. It provides education and services, advocates on behalf of people with diabetes, supports research, and translates research into practical applications. The CDA solicits and receives unrestricted educational grants from multiple manufacturers and vendors of pharmaceuticals, supplies, and devices for diabetes, including Eli Lilly — the manufacturer of the drug under consideration for this review. The CDA reported no conflicts of interest in the preparation of this submission.

2. Condition-Related Information
The submission is based on information obtained through two surveys distributed through social media and email. The first survey (October 2015) gathered information regarding the impacts of diabetes from 212 Canadians with type 2 diabetes and 61 caregivers. The second survey (December 2015) gathered information from Canadians with type 2 diabetes (n = 352) and their caregivers (n = 34) about current drug therapies and experience with dulaglutide and/or other glucagon-like peptide-1 (GLP-1) agonists. In the December survey, approximately 25% of respondents were aged 40 to 54 years, 53% were 55 to 69 years old, and 13% were 70 years and older. Among respondents, 20%, 42%, and 25% had had diabetes for six to 10 years, 11 to 20 years, or more than 20 years, respectively.

Type 2 diabetes is a chronic (progressive) condition that occurs when the pancreas does not produce enough insulin or when the body does not effectively use the insulin that is produced. Common symptoms of diabetes include fatigue, thirst, and weight change. High blood glucose levels can cause long-term complications such as blindness, heart disease, kidney problems, nerve damage, and erectile dysfunction. The goal of diabetes management is to keep glucose levels within the target range to minimize symptoms and avoid or delay the complications.

Diabetes requires considerable self-management, including healthy eating, regular physical activity, healthy body weight, taking diabetes medications as prescribed, monitoring blood glucose, and stress management. Poor glucose control can result in acute crises, and serious long-term complications. For the majority of survey respondents, diabetes has negatively affected all aspects of their lives and limited daily activities. Diabetes management is a “constant struggle” involving meal planning, testing blood glucose, and taking medications. It is also challenging to manage coexisting conditions or diabetes-related complications. The most commonly reported complications were high blood pressure (59%), high cholesterol (55%), foot problems (47%), hypoglycemia (42%) and eye problems (40%), and the frequency of coexisting conditions were generally similar across survey respondents in different age groups.

The patients and their caregivers who responded to the surveys indicated that diabetes had a psychological and emotional impact on their lives due to the necessary changes in diet and lifestyle, managing medications, stress and anxiety about hypoglycemia, strain on relationships, and financial

burden. One respondent said, "It is difficult to lead a normal life when you always need to be taking meds or checking your [blood glucose] levels and reading labels on all your food while your [blood glucose] levels change with or without food intake. The impact of diabetes on all your other organs is another huge problem, and when you treat one, you harm another. Most difficult disease to manage."

3. Current Therapy-Related Information

Many people with type 2 diabetes have difficulty achieving optimal glycemic control and are therefore at risk for both acute and chronic diabetes complications. The initial therapy they receive is most often metformin, but over time, most people will require the addition of a second or third drug to reach glycemic targets. Many of the currently available second-line therapies cause significant weight gain while their ability to achieve optimal glycemic control may be limited by hypoglycemia. It is important to have a selection of medications to accommodate the individual needs and preferences of patients, as different people require different options to help effectively manage their diabetes.

Among the 386 patients and caregivers who responded to the December 2015 survey, the majority (59%) indicated that they were "satisfied" or "very satisfied" with their current therapies, whereas 20% indicated dissatisfaction. More than half of respondents indicated that current therapies resulted in "better" or "much better" blood glucose and glycated hemoglobin (A1C) control than prior to treatment, and 47% stated that hypoglycemia had improved with current therapy. Among respondents, 63% reported that weight gain had not improved or had gotten worse, and 52% to 64% reported that gastrointestinal effects, dehydration, and urinary tract or yeast infections were "the same," "worse," or "much worse" with current therapies. In addition to controlling blood glucose without hypoglycemia, the aspects of diabetes that patients reported as being most important for medications to address included avoiding weight gain, reducing high blood pressure, and avoiding fluid retention, gastrointestinal effects, and urinary tract infections.

4. Expectations About the Drug Being Reviewed

Four survey respondents had experience with dulaglutide, out of a total of 71 respondents who reported having taken a drug from the same class ([GLP-1] receptor agonist) in combination with other antidiabetic medications. Overall, 65% of patients taking a GLP-1 agonist indicated satisfaction with their current therapy, primarily as a result of better blood glucose control (fasting, upon waking) and A1C control (70%), and post-prandial blood glucose levels (66%). About 50% indicated better or much better weight control versus 47% who reported "same" or "worse" results. Approximately 46% indicated that their hypoglycemia improved with current therapy, compared with 46% who saw no improvement; 67% reported same or worse gastrointestinal effects (versus 23% who saw improvement), 66% reported same or worse for dehydration (versus 16% who saw improvement), and 53% reported same or worse urinary tract or yeast infection (versus 20% who saw improvement). One individual reported an extremely negative experience with a GLP-1 agonist. One respondent taking dulaglutide reported that it was "very effective in weight loss and blood sugar control."

In the words of respondents with positive experience of GLP-1 agonists:

"*My quality of life and day-to-day feelings of wellness have dramatically improved since being on this drug."*

"It has helped to drastically reduce my blood glucose test results and brought my A1C down significantly, from 10.0 to 7.9, in just a few months."

"The GLP-1 drug that I have been taking was very life-changing: better numbers, better A1C, lost weight, feel better generally."

One individual reported an *"extremely negative experience with GLP-1 agonist."*

Among all survey respondents (n = 282), 45% believed it is important or very important that dulaglutide be made available, to provide another treatment option to Canadians with type 2 diabetes. In general, patients hope that new medications will offer affordable and accessible treatments, better diabetes control with minimal or no side effect (especially hypoglycemia), improvement to life and life expectancy without diabetes complications, less frequent medications with fewer needles and testing, weight loss or prevention of weight gain, and a cure for diabetes. The once-weekly injection of dulaglutide was seen as an advantage, especially if it could reduce or eliminate insulin or other injections and blood glucose monitoring. Patients expressed concern regarding the cost of treatments and being unable to access medications if they were not covered by patients' drug plans.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	January 27, 2016
Alerts:	Bi-weekly search updates until May 18, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.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
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(dulaglutide or Trulicity or LY-2189265 or LY2189265).ti,ab,ot,hw,kf,rn,nm.
2	(WTT295HSY5 or 923950-08-7 or 1198417-37-6).rn,nm.
3	1 or 2
4	3 use pmez
5	*dulaglutide/
6	(dulaglutide or Trulicity or LY-2189265 or LY2189265).ti,ab,kw.
7	5 or 6
8	conference abstract.pt.
9	7 not 8
10	9 use oemezd
11	4 or 10
12	remove duplicates from 11
13	exp animals/
14	exp animal experimentation/ or exp animal experiment/
15	exp models animal/
16	nonhuman/
17	exp vertebrate/ or exp vertebrates/
18	or/13-17
19	exp humans/
20	exp human experimentation/ or exp human experiment/
21	or/19-20
22	18 not 21
23	12 not 22

OTHER DATABASES	
PubMed	A limited PubMed search was performed 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:	January 22, 2016
Keywords:	Trulicity (Dulaglutide)/Type 2 Diabetes Mellitus
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
- Databases (free).

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Araki et al., 2015[32]	Wrong background therapy
Blonde et al., 2015[33]	Wrong background therapy
Dungan et al., 2014[34]	Not RCT
Dungan et al., 2016[35]	Wrong background therapy
Ferdinand et al., 2014[36]	Phase 2 RCT
Geiger et al., 2012[37]	No outcomes of interest
Grunberger et al., 2012[38]	Phase 2 RCT
Gurung et al., 2015[39]	Not RCT
Karagiannis et al., 2015[40]	Not RCT
Kuritzky et al., 2014[41]	Not RCT
Miyagawa et al., 2015[42]	Wrong background therapy
Monami et al., 2014[43]	Not RCT
Odawara et al., 2015[44]	Wrong background therapy
Onishi et al., 2015[45]	Not RCT
Reaney et al., 2015[46]	Wrong background therapy
Saulsberry et al., 2015[47]	Not RCT
Skrivanek et al., 2014[48]	Phase II RCT
Skrivanek et al., 2012[49]	Not RCT
Spencer et al., 2012[50]	Not RCT
Sun et al., 2015[51]	Not RCT
Terauchi et al., 2015[52]	Phase 2 RCT
Umpierrez et al., 2014[53]	Wrong background therapy
Umpierrez et al., 2011[54]	Phase 2 RCT
Wysham et al., 2014[55]	Wrong background therapy
Zaccardi et al., 2016[56]	Not RCT
Zhang et al., 2016[57]	Not RCT

RCT = randomized controlled trial.

APPENDIX 4: ADDITIONAL DATA

TABLE 26: COMPARISON OF PARTICIPANTS' CHARACTERISTICS BETWEEN STAGE 1 AND STAGE 2 IN AWARD-5

Characteristic	AWARD-5			
	Stage 1 (n = 126)	Stage 2 (n = 972)	MD (95% CI)	Overall *P* value
Age (y)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]		
Min, max	[redacted]	[redacted]		
Gender, n (%)				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)				
Aboriginal and/or Torres Strait Islander	[redacted]	[redacted]	[redacted]	[redacted]
African	[redacted]	[redacted]		
Caucasian	[redacted]	[redacted]		
East Asian	[redacted]	[redacted]		
Hispanic	[redacted]	[redacted]		
Native American	[redacted]	[redacted]		
West Indian (Indian subcontinent)	[redacted]	[redacted]		
Weight (kg)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]		
Min, max	[redacted]	[redacted]		
BMI (kg/m^2)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]		
Min, max	[redacted]	[redacted]		
Seated systolic BP (mm Hg)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]		

Characteristic	AWARD-5			
	Stage 1 (n = 126)	Stage 2 (n = 972)	MD (95% CI)	Overall *P* value
Min, max	[redacted]	[redacted]		
Seated diastolic BP (mm Hg)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]		
Min, max	[redacted]	[redacted]		
Diabetes duration (y)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]		
Min, Max	[redacted]	[redacted]		
A1C (%)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]		
Min, max	[redacted]	[redacted]		
Hypertension, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Hyperlipidemia, n (%)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; BMI = body mass index; BP = blood pressure; CI = confidence interval; MD = mean difference; NA = not applicable; SD = standard deviation.
Source: AWARD-5 Clinical Study Report.[13]

TABLE 27: ANALYSIS OF A1C OF PARTICIPANTS RANDOMIZED DURING STAGE 2 IN AWARD-5

Outcome	AWARD-5			
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/Sitagliptin
A1C, %[a]				
Baseline, N	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
52 weeks, N	[redacted]	[redacted]	[redacted]	[redacted]
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
52 weeks, LS mean difference vs. sitagliptin (nominal 95% CI)	[redacted]	[redacted]		
P value for non-inferiority vs. sitagliptin	[redacted]	[redacted]		
P value for superiority vs. sitagliptin	[redacted]	[redacted]		

A1C = glycated hemoglobin; CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error; vs. = versus.

[redacted]

Source: AWARD-5 Clinical Study Report.[13]

TABLE 28: ANALYSIS OF A1C BY SUBGROUPS IN AWARD-5

Outcome	AWARD-5				
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/Sitagliptin	Interaction Term *P* value
Baseline age: < 65 years					[redacted]
Baseline, N	[redacted]	[redacted]	[redacted]	[redacted]	
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	
52 weeks, N	[redacted]	[redacted]	[redacted]	[redacted]	
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	
52 weeks, LS mean difference — sitagliptin vs. dulaglutide (95% CI); *P* value	[redacted]	[redacted]			
Baseline age: ≥ 65 years					
Baseline, N	[redacted]	[redacted]	[redacted]	[redacted]	
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	
52 weeks, N	[redacted]	[redacted]	[redacted]	[redacted]	

Outcome	AWARD-5				
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/Sitagliptin	Interaction Term *P* value
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	
52 weeks, LS mean difference — sitagliptin vs. dulaglutide (nominal 95% CI)	[redacted]	[redacted]			
Duration of diabetes at baseline: < 6 years					[redacted]
Baseline, N	[redacted]	[redacted]	[redacted]	[redacted]	
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	
52 weeks, N	[redacted]	[redacted]	[redacted]	[redacted]	
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	
52 weeks, LS mean difference – sitagliptin vs. dulaglutide (95% CI); *P* value	[redacted]	[redacted]			
Duration of diabetes at baseline: ≥ 6 years					
Baseline, N	[redacted]	[redacted]	[redacted]	[redacted]	
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	
52 weeks, N	[redacted]	[redacted]	[redacted]	[redacted]	
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	
52 weeks, LS mean difference — sitagliptin vs. dulaglutide (nominal 95% CI)	[redacted]	[redacted]			

A1C = glycated hemoglobin; CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error; vs. = versus.

[redacted]

Source: AWARD-5 Clinical Study Report.[13]

TABLE 29: ANALYSIS OF A1C BY SUBGROUPS IN AWARD-6

Subgroup	AWARD-6		
	Dulaglutide 1.5 mg	Liraglutide 1.8 mg	Interaction Term *P* Value
Baseline age: < 65 years			
Baseline, N			
Baseline, mean (SD)			
26 weeks, N			
26 weeks, change from baseline, LS mean (SE)			
26 weeks, LS mean difference (95% CI); *P* value			
Baseline age: ≥ 65 years			
Baseline, N			
Baseline, mean (SD)			
26 weeks, N			
26 weeks, change from baseline, LS mean (SE)			
26 weeks, LS mean difference (95% CI); *P* value			
Duration of diabetes at baseline: < 6 years			
Baseline, N			
Baseline, mean (SD)			
26 weeks, N			
26 weeks, change from baseline, LS mean (SE)			
26 weeks, LS mean difference (95% CI); *P* value			
Duration of diabetes at baseline: ≥ 6 years			
Baseline, N			
Baseline, mean (SD)			
26 weeks, N			
26 weeks, change from baseline, LS mean (SE)			
26 weeks, LS mean difference (95% CI); *P* value			
Baseline A1C: ≤ 8.5%			
Baseline, N			
Baseline, mean (SD)			
26 weeks, N			
26 weeks, change from baseline, LS mean (SE)			
26 weeks, LS mean difference (95% CI); *P* value			
Baseline A1C: > 8.5%			
Baseline, N			

Subgroup	AWARD-6		
	Dulaglutide 1.5 mg	Liraglutide 1.8 mg	Interaction Term *P* Value
Baseline, mean (SD)	[redacted]	[redacted]	
26 weeks, N	[redacted]	[redacted]	
26 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	
26 weeks, LS mean difference (95% CI); *P* value	[redacted]		

A1C = glycated hemoglobin; CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error.

[redacted]

Source: AWARD-6 Clinical Study Report.[14]

TABLE 30: ANALYSIS OF A1C BY SUBGROUPS IN AWARD-2

Outcome	AWARD-2			
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Insulin Glargine	Interaction Term *P* Value
Baseline age: < 65 years				[redacted]
Baseline, N	[redacted]	[redacted]	[redacted]	
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	
52 weeks, N	[redacted]	[redacted]	[redacted]	
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	
52 weeks, LS mean difference vs. insulin glargine (95% CI); *P* value	[redacted]	[redacted]		
Baseline age: ≥ 65 years				
Baseline, N	[redacted]	[redacted]	[redacted]	
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	
52 weeks, N	[redacted]	[redacted]	[redacted]	
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	
52 weeks, LS mean difference vs. insulin Glargine (95% CI); *P* value	[redacted]	[redacted]		
Duration of diabetes at baseline: < 8 years				[redacted]
Baseline, N	[redacted]	[redacted]	[redacted]	

Outcome	AWARD-2			
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Insulin Glargine	Interaction Term *P* Value
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	
52 weeks, N	[redacted]	[redacted]	[redacted]	
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	
52 weeks, LS mean difference vs. insulin glargine (95% CI); *P* value	[redacted]	[redacted]		
Duration of diabetes at baseline: ≥ 8 years				
Baseline, N	[redacted]	[redacted]	[redacted]	
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	
52 weeks, N	[redacted]	[redacted]	[redacted]	
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]	
52 weeks, LS mean difference vs. insulin glargine (95% CI); *P* value	[redacted]	[redacted]		
Baseline A1C				
In a subgroup analysis split into baseline ≤ 8.5% and > 8.5%, there was no interaction between subgroup and treatment arm (*P* = 0.698). Data were not provided for this analysis.				

CI = confidence interval; A1C = glycated hemoglobin; LS = least squares; NR = not reported; SD = standard deviation; SE = standard error.

[redacted]

Source: AWARD-2 Clinical Study Report.[22]

TABLE 31: HEALTH-RELATED QUALITY OF LIFE DATA (ADD-ON TO METFORMIN)

Outcome	AWARD-5				AWARD-6	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/Sitagliptin	Dulaglutide 1.5 mg	Liraglutide 1.8 mg
EQ-5D, VAS						
Baseline, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26 weeks, N					[redacted]	[redacted]
26 weeks, change from baseline, LSM (SE)					[redacted]	[redacted]
26 weeks, vs. liraglutide; *P* value					[redacted]	

Outcome	AWARD-5				AWARD-6	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin	Placebo/Sitagliptin	Dulaglutide 1.5 mg	Liraglutide 1.8 mg
52 weeks, N						
52 weeks, mean (SD)						
EQ-5D US Population-Based Index Score						
Baseline, N						
Baseline, mean (SD)						
52 weeks, N						
52 weeks, mean (SD)						
EQ-5D UK Population-Based Index Score						
Baseline, N						
Baseline, mean (SD)						
26 weeks, N						
26 weeks, change from baseline, LSM (SE)						
26 weeks, vs. liraglutide; *P* value						
52 weeks, N						
52 weeks, mean (SD)						
IWQOL, Total Score						
Baseline, N						
Baseline, mean (SD)						
52 weeks, N						
52 weeks, mean (SD)						

EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; IWQOL= Impact of Weight on Quality of Life–Lite questionnaire; LSM = least squares mean; SD = standard deviation; SE = standard error; VAS = visual analogue scale; vs. = versus.
Source: AWARD-5 Clinical Study Report (CSR),[13] AWARD-6 CSR.[14]

TABLE 32: HEALTH-RELATED QUALITY-OF-LIFE DATA (ADD-ON TO METFORMIN AND A SULFONYLUREA)

Outcome	AWARD-2		
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Insulin Glargine
EQ-5D, VAS			
Baseline, N	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
52 weeks, N	[redacted]	[redacted]	[redacted]
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]
Overall *P* value	[redacted]		
EQ-5D US Population-Based Index Score			
Baseline, N	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
52 weeks, N	[redacted]	[redacted]	[redacted]
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]
52 weeks, vs. insulin glargine; *P* value	[redacted]	[redacted]	
EQ-5D UK Population-Based Index Score			
Baseline, N	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
52 weeks, N	[redacted]	[redacted]	[redacted]
52 weeks, change from baseline, LS mean (SE)	[redacted]	[redacted]	[redacted]
52 weeks, vs. insulin glargine; *P* value	[redacted]	[redacted]	

EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; LS = least squares; SD = standard deviation; SE = standard error; VAS = visual analogue scale.
Source: AWARD-2 Clinical Study Report.[22]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D)
- Impact of Weight on Quality of Life Questionnaire – Lite (IWQOL-Lite).

Findings

TABLE 33: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Evidence of Validity	MCID	References
EQ-5D	EQ-5D is a generic, non–disease-specific health-related quality-of-life questionnaire.	Yes	Diabetes: Unknown General use: Index score 0.033 to 0.074.[58,59]	EuroQol Group[60]
IWQOL-Lite	IWQOL-Lite is a self-report instrument specifically developed to assess the effect of obesity on quality of life.	Yes	Diabetes: Unknown General use: Total score 7 to 12[61]	Kolotkin et al. 2001[62]

EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; IWQOL-Lite = Impact of Weight on Quality of Life–Lite Questionnaire — short form; MCID = minimal clinically important difference.

EQ-5D Questionnaire

The EQ-5D is a generic quality-of-life instrument that may be applied to a wide range of health conditions and treatments.[60] The first of two parts of the EQ-5D comprise 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 the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[60] The second part is a 20 cm visual analog scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

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

The EQ-5D 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 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. [60]

Evidence of the measurement properties of the EQ-5D in patients with type 2 diabetes mellitus (T2DM) was summarized in the systematic review by Janssen et al. 2011.[63] The authors concluded that construct, convergent, and discriminant validity of the EQ-5D was generally supported, based on data from 39 papers.[63] Test–retest reliability was found to be good to excellent and responsiveness was acceptable.[63] Several studies reported ceiling effects.[63,64] A qualitative study suggested that EQ-5D had content validity in diabetes; however, it was missing some important factors that have an impact on 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.[65]

A minimal clinically important difference (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.[58,59]

Impact of Weight on Quality of Life Questionnaire – Lite

The Impact of Weight on Quality of Life–Lite (IWQOL-Lite) is a self-administered, condition-specific instrument that assesses quality of life in obesity.[62] It is a variant of the original Impact of Weight on Quality of Life (IWQOL) (74 items) questionnaire developed by Kolotkin et al., which was designed to alleviate the response burden. The IWQOL-Lite is composed of five domains: physical function (11 items), self-esteem (seven items), sexual life (four items), public distress (five items), and work (four items) for a total of 31 items, which create the IWQOL-Lite score. There are five levels upon which to rate each item ranging from "always true" to "never true." Each level is assigned a score from 1 to 5, where "always true" is given a score of 5 and "never true" is given a score of 1.[62] The sum of scores for each item in its respective domain provides the domain score, and the sum of scores for each domain provides the total score, with higher scores associated with a poorer quality of life.[62] Domain and total scores may also be transformed to a 0 to 100 range, with lower scores indicating greater impairment.[61,66]

A study by Kolotkin et al. assessed weight-related quality of life in obese persons with T2DM using IWQOL-Lite.[66] The study involved (n = 1,197) obese people (of whom n = 225 had T2DM) seeking weight loss treatment in a clinical trial comparing an obesity medication with gastric bypass surgery.[66] The IWQOL-Lite demonstrated excellent internal consistency reliability, based on Cronbach's alpha, which was 0.981 and 0.980 for the total IWQOL-Lite score in diabetic and non-diabetic patients with obesity, respectively.[66] Moderately strong correlations were identified between the IWQOL-Lite and BMI, and were comparable in both diabetic and non-diabetic patients suffering from obesity, suggesting concurrent validity of the IWQOL-Lite.[66] Construct validity of the instrument was also assessed using confirmatory factor analysis; the factor structure between diabetic and non-diabetic patients was comparable, providing support of the scale structure, as well as the presence of a higher order factor (weight-related quality of life).[66]

An MCID for the IWQOL-Lite total score in patients with T2DM was not identified; however, in other conditions, values from 7 to 12 have been reported in the literature.[61]

Conclusion

The EQ-5D is a widely-used generic health status measure consisting of five self-reported health domains with three levels per domain. This questionnaire has demonstrated construct, convergent, and

discriminant validity in patients with diabetes; however, its responsiveness may be limited by a ceiling effect. The IWQOL-Lite is an obesity-specific quality-of-life measure composed of five domains and a total of 31 items. This instrument was demonstrated to be reliable and valid in obese persons with T2DM. The MCIDs for patients with T2DM were not identified for the EQ-5D or the IWQOL-Lite.

APPENDIX 6: SUMMARY OF INDIRECT COMPARISONS

Aim

The aim of this section is to review the indirect evidence on the efficacy and safety of dulaglutide compared with other antidiabetic drugs used in adult patients with type 2 diabetes mellitus (T2DM) who have experienced inadequate glycemic control on diet and exercise plus therapy with metformin alone or with metformin and a sulfonylurea. Although direct evidence is available comparing dulaglutide to sitagliptin, liraglutide, and insulin glargine, evidence is lacking for other comparators of interest.

Methods to Identify Indirect Comparisons

Two network meta-analyses (NMAs) submitted by the manufacturer were reviewed.[15] In addition, a literature search was undertaken to identify any other published indirect treatment comparisons: one other relevant NMA was found.[1]

Description of Indirect Comparisons

The manufacturer submitted two NMAs that evaluated the safety and efficacy of dulaglutide and other antidiabetic treatments in patients with T2DM who have experienced inadequate glycemic control on diet and exercise plus metformin alone (i.e., second-line therapy); or withmetformin and a sulfonylurea (i.e., third-line therapy).

A third NMA (Kayaniyil et al. 2016[1]) compared once-weekly exenatide to other GLP-1 agonists in patients with T2DM who failed to achieve glycemic control on metformin (i.e., second-line therapy).

Both NMAs submitted by the manufacturer used similar methods to conduct the systematic review and data analyses; therefore, the methods will be described together in “Summary of Manufacturer-Submitted Network Meta-Analyses,” followed by separate sections for the results of the second-line (”Results of Manufacturer-Submitted Network Meta-Analysis of Second-Line Therapies”) and third-line therapies (”Results of Manufacturer-Submitted Network Meta-Analysis for Third-Line Therapies”). The NMA by Kayaniyil et al. (2016)[1] will be described separately (“Summary of Kayaniyil et al. 2016” and “Results of Kayaniyil 2016”).

Summary of Manufacturer-Submitted Network Meta-Analyses

Systematic Review Methods

Both NMAs were based on a systematic review of the literature. The 2013 CADTH Optimal Use reports on Second- and Third-line Therapy for Patients With Diabetes were used as the basis for the systematic reviews,[67,68] and were supplemented by updated literature searches. Literature searches of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were conducted (date limits for second-line: January 2010 to December 2014; for third-line: January 2010 to July 2014), and restricted to English-language articles. Studies were eligible for inclusion if they met the criteria listed in Table 34. Abstracts and potentially relevant full-text articles were screened independently by two researchers, with disagreements resolved through discussion or by a third adjudicator.

The reviews included antidiabetic drugs at doses approved for use in Canada, the US, or Europe (Table 34). Outcomes of interest included change from baseline in glycated hemoglobin (A1C), weight and body mass index (BMI), the risk or rate of hypoglycemia or severe hypoglycemia, and the risk of serious adverse events. No criteria were listed to define hypoglycemia or severe hypoglycemia events. Any randomized controlled trials (RCTs) in which participants were randomized to receive treatment for at

least six months that reported any of the stated outcomes at six and or 12 months were eligible for inclusion. Outcomes of interest that were reported within four weeks of the six- or 12-month time points were included.

Key trial and patient characteristics, treatment, and outcome data were extracted independently by two researchers and verified by a third. Methods to impute missing study data (such as variance, or BMI) were described by the reviews' authors. A summary of patients' baseline characteristics and key outcome data from the individual RCTs were included in the reports. Limited information on study characteristics was provided.

The validity of RCTs was assessed using the Cochrane risk of bias instrument and a summary was provided in the reports.

TABLE 34: SELECTION CRITERIA FOR RANDOMIZED CONTROLLED TRIALS IN THE MANUFACTURER-SUBMITTED NETWORK META-ANALYSES

Criteria	Second-Line	Third-Line
Population	Adult patients diagnosed with T2DM experiencing inadequate control despite a diet and exercise program and a stable regimen of metformin[a]	Adult patients diagnosed with T2DM and inadequately controlled with metformin and sulfonylurea combination therapy[a]
Intervention[b]	GLP-1 agonists: • Albiglutide 30 mg and 50 mg • Exenatide 20 mcg daily • Lixisenatide 20 mcg[c] • Liraglutide 1.2 mg and 1.8 mg • Dulaglutide 0.75 mg and 1.5 mg SGLT2 inhibitors: • Canagliflozin 100 mg to 300 mg • Dapagliflozin 5 mg to 10 mg • *Empagliflozin 10 mg to 25 mg* DPP-4 inhibitors: • Alogliptin 25 mg • Sitagliptin 100 mg • Saxagliptin 5 mg • Linagliptin 5 mg • Vildagliptin 100 mg[c] Thiazolidinediones: • Pioglitazone 15 mg to 45 mg • Rosiglitazone 4 mg to 8 mg Meglitinides: • Nateglinide *60 mg to 120 mg*[c] • Repaglinide 0.5 mg to 16 mg Alpha-glucosidase inhibitors: • Acarbose 150 mg to 300 mg • *Miglitol 75 mg to 300 mg*[c]	Interventions and doses approved in Canada, the US, or the European Union: GLP-1 agonists: • Exenatide 10 mcg and *20 mcg b.i.d., and 2 mg q.w.* • Liraglutide 1.2 mg and 1.8 mg q.d. • Dulaglutide 0.75 mg and 1.5 mg q.w. • Albiglutide 30 mg or 50 mg q.w. • Lixisenatide 20 mcg (10 mcg initial dose and then up titrated to 20 mcg) q.d.[c] SGLT2 inhibitors: • Canagliflozin 100 mg to 300 mg q.d. • Dapagliflozin 5 mg to 10 mg q.d. DPP-4 inhibitors: • Sitagliptin 100 mg q.d. • Saxagliptin 5 mg q.d. • Linagliptin 5 mg q.d. • Vildagliptin 100 mg (50 mg b.i.d.)[c] • Alogliptin 25 mg q.d. Thiazolidinediones: • Pioglitazone 15 mg to 45 mg q.d. • Rosiglitazone 4 mg to 8 mg q.d. Meglitinides: • Nateglinide *180 mg to 360 mg*[c] • Repaglinide 0.5 mg to 16 mg

Criteria	Second-Line	Third-Line
	Sulfonylureas: • Gliclazide • Glimepiride • Glyburide • Chlorpropamide Basal insulin: • Insulin NPH[d] • Insulin detemir[d] • Insulin glargine[d] • Insulin degludec[c] Biphasic insulin:[d] • Premixed regular NPH • Biphasic insulin aspart • Biphasic insulin lispro Bolus insulin: • Aspart • Lispro • Glulisine	Alpha-glucosidase inhibitors: • Acarbose 150 mg to 300 mg (t.i.d.) Basal insulin:[d] • Insulin NPH • Insulin detemir • Insulin glargine • Insulin degludec[c] Biphasic insulin: • Premixed regular NPH[d] • Biphasic insulin aspart[d] • Biphasic insulin lispro[d] • *Degludec/aspart (iDeg plus)* [c] Bolus insulin
Comparators	Continuation of metformin (with or without placebo) or any of the interventions listed above	Continuation of metformin plus a sulfonylurea (with or without placebo) or any of the interventions listed above
Outcome	• Change in A1C • Change in body weight • Change in BMI • Risk of overall hypoglycemia • Risk of severe hypoglycemia • Rate of overall hypoglycemia • Rate of severe hypoglycemia • Serious adverse events	
Study design	RCTs with randomized treatment duration of at least 6 months treatments reporting any of the stated outcomes at 6 and or 12 months. Note: outcomes reported ± 4 weeks of the time point of interest were considered.	RCTs reporting results at 26 weeks (± 4 weeks) and/or at 52 weeks (± 4 weeks)

A1C = glycated hemoglobin; b.i.d. = twice daily; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; q.d. = once daily; q.w. = once weekly; RCT = randomized controlled trial; SGLT2 = sodium/glucose cotransporter 2; T2DM = type 2 diabetes mellitus; t.i.d. = three times daily.

[a] Inadequately controlled defined as A1C > 6.5%, fasting plasma glucose > 7 mmol/L or two-hour post-prandial glucose > 10 mmol/L.

[b] Differences between interventions included in the second-line and third-line systematic reviews are in italics.

[c] Not available in Canada.

[d] Doses for all insulin treatments are individualized, but with a defined daily dose of 40 units.

Source: CADTH Common Drug Review submission.[15]

Network Meta-Analysis Methods

Bayesian NMAs were run using OpenBUGS software (version 3.2.3) for the outcomes of interest. The authors reported that the models were standard NMA practice models described by the National Institute for Health and Care Excellence (NICE) Decision Support Unit's Technical Support Document no. 2.[69] All doses and drugs within a drug class were analyzed as one treatment node, except for dulaglutide 0.75 mg and 1.5 mg, which were analyzed as separate nodes and were not pooled with other GLP-1 agonists. Both random- and fixed-effects models were run and model fit (based on the deviance information criterion [DIC]) was used to select the model. Markov chain Monte Carlo methods were used to estimate posterior densities for unknown parameters. Three chains were run for each model and convergence was confirmed by the Gelman–Rubin statistic. The first iterations from the model were discarded as burn-in; however, the number of iterations run and the number in the burn-in were not reported. Inconsistency was assessed for closed loops using the Bucher test for inconsistency. The authors did not report how multi-arm trials were handled in the model or the priors used (except for priors for between-trial heterogeneity specified in Table 35). Descriptions of the models are listed in Table 35.

Prior to conducting the NMA, a feasibility assessment was conducted to qualitatively examine the distribution of patient characteristics, which were potential effect-modifiers, across the included studies. Due to variations in key patient characteristics, a decision was made to run meta-regression analyses that included baseline weight, BMI, A1C and duration of diabetes as covariates for both the second- and third-line patient populations. Because some studies that exclusively enrolled Asian populations have shown differences in treatment effects compared with studies in predominantly non-Asian diabetic populations, the NMA of second-line therapies excluded studies that enrolled 100% Asian patients from the primary analysis, but included them in a sensitivity analysis. In the third-line NMA, Asian studies were included in the primary analyses and excluded in the sensitivity analyses. For the second- and third-line evidence networks, the majority of studies reported outcomes at 26 weeks (± 4 weeks), whereas data at 52 weeks were available from few trials. Thus, the authors decided that data reported at 26 weeks would be used for the primary analysis, but a sensitivity analysis would be run using the last time point available (i.e., 52-week data if available; otherwise, 26-weeks data were included). Rosiglitazone trials were included in the primary analysis of second-line therapies but were removed in a secondary analysis (due to concerns regarding cardiovascular adverse events with this drug and its delisting and removal from reimbursement in some regions). Rosiglitazone trials were included in all NMAs for third-line therapies.

TABLE 35: DESCRIPTION OF NETWORK META-ANALYSIS MODELS

	Continuous	Binary	Count (rate)
Model	Linear regression with identity link and normal likelihood	Logistic regression model with logit link and binomial likelihood	Poisson regression model with log link and Poisson likelihood
Prior for between-trial heterogeneity of random-effects model	Uniform distribution with minimum 0 and maximum 5 times the average mean difference standard error	Second-line: Uniform distribution 0 to 2 Third-line: Moderately informative prior based on Turner et al. 2012[70]	Uniform distribution 0 to 5
Outcome reported	Mean difference (95% credible interval)	Relative risks (95% credible interval)	Rate ratio (95% credible interval)

Source: CADTH Common Drug Review submission.[15]

For binary outcomes analyzed in the third-line NMA, the conversion of odds ratios to relative risks was based on the modelled average control group risk. In the second-line NMA, the methods used to model the relative risks were not described.

Results of Manufacturer-Submitted Network Meta-Analysis of Second-Line Therapies

Evidence Network

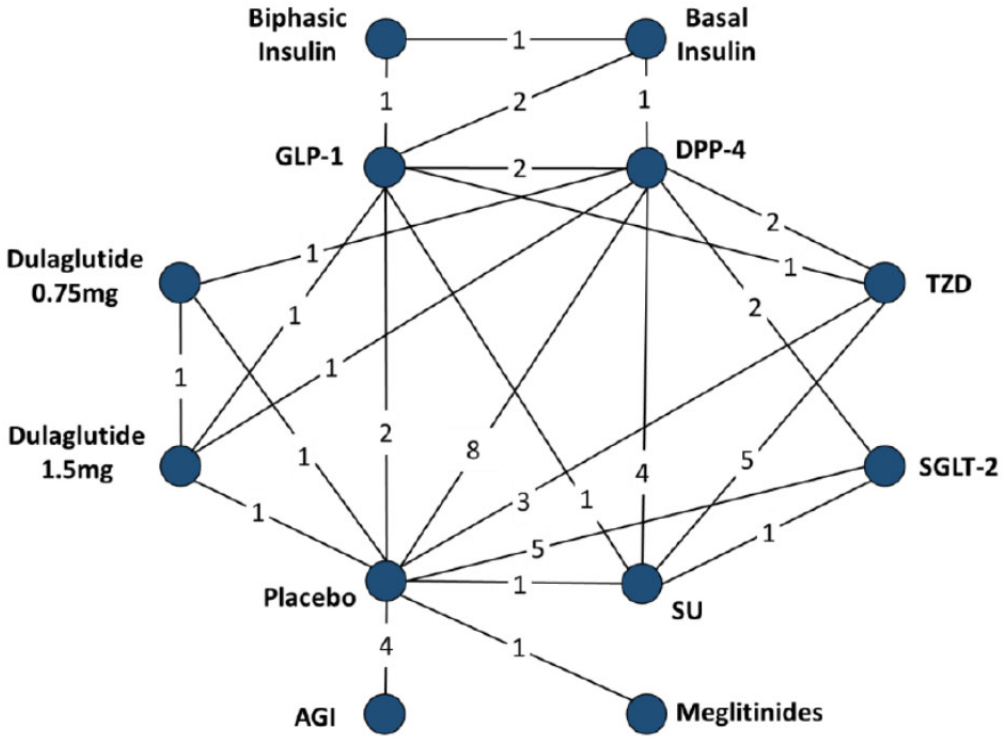
A total of 51 RCTs were included in the review. These trials included 27 different treatments that were grouped in 12 drug classes or nodes. An example of the evidence network is provided in Figure 9. Of the 51 trials included in the manufacturer-submitted NMA, 39 were also included in the CADTH therapeutic review, and 12 were newly identified trials. Eighteen trials that had been included in the CADTH report were excluded because they reported short-term outcomes after one to five months, and therefore did not meet the inclusion criteria. The dulaglutide trials, AWARD-5 and AWARD-6, were included in the NMAs.

Overall, 65% of trials had an unclear risk of bias on two to five of the seven domains of the risk of bias tool, including sequence generation, allocation concealment, and blinding of participants or outcome assessors. One study had a high risk of bias for random sequence generation, and 45% and 35% had a low risk of bias for random sequence generation and allocation concealment, respectively. The majority of trials had a low risk of bias for other domains.

The patients enrolled in the RCTs had the following characteristics:

- Mean age range 52 to 63 years
- Proportion males range 21% to 71%
- Median baseline mean weight 87.7 kg (range 68.4 to 100.3 kg)
- Median baseline mean A1C 8.1 (range 7.1 to 9.7)
- Median baseline mean disease duration 6.2 years (range 4.4 to 10.3 years)
- Median proportion of Asian patients 8.4% (three trials that enrolled 100% Asian population were excluded from the primary analysis and included in a sensitivity analysis).

FIGURE 9: NETWORK DIAGRAM FOR A1C — ADD-ON TO METFORMIN



Note: Nodes represent a treatment. Labels represent included RCTs with direct comparisons for the corresponding edge.

A1C = glycated hemoglobin; AGI = alpha-glucosidase inhibitor; DPP-4 = dipeptidyl peptidase -4 inhibitors; GLP-1 = glucagon-like peptide-1 agonists; RCT = randomized controlled trial; SGLT-2 = sodium/glucose cotransporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione.
Source: CADTH Common Drug Review submission.[15]

Results

A summary of the results of the NMA for A1C, weight, hypoglycemia, severe hypoglycemia, and serious adverse events are presented in the sections below. The number of trials included in the NMA for each outcome is listed in Table 36.

Based on DIC values, the random-effects model was chosen as the best fit over fixed-effect or meta-regression models for A1C, weight, risk and rate of hypoglycemia. A fixed-effects model was reported as the primary analysis of serious adverse events.

Inconsistency was detected in one or more closed loops in the analysis of A1C, weight, risk, and rate of hypoglycemia. When Asian trials were excluded, statistical inconsistency was no longer detected for A1C and weight.

TABLE 36: STUDIES INCLUDED IN THE NETWORK META-ANALYSIS FOR SECOND-LINE TREATMENTS

Outcome	RCTs	Treatment Groups	Nodes	Patients
A1C	42	100	12	20,379
Weight	33	81	12	14,710
Risk of overall hypoglycemia	33	82	12	15,424
Rate of overall hypoglycemia	10	24	9	6,604
Risk of severe hypoglycemia	17	Unable to run NMA		
Rate of severe hypoglycemia	15	Unable to run NMA		
Risk of serious adverse events	23	54	11	10,346

A1C = glycated hemoglobin; BMI = body mass index; NMA = network meta-analysis; RCTs = randomized controlled trials.
Source: CADTH Common Drug Review submission.[15]

A1C: All treatments were associated with statistically significant reductions in A1C from baseline to week 26, compared with placebo [redacted] (Table 37). No statistically significant differences in A1C were detected between dulaglutide and sulfonylureas, other GLP-1 agonists, and basal or biphasic insulin. Dulaglutide 0.75 mg and 1.5 mg doses showed statistically significantly greater reductions from baseline A1C compared with DPP-4 inhibitors, sodium/glucose cotransporter 2 (SGLT2) inhibitors, acarbose and meglitinides [redacted], and dulaglutide 1.5 mg showed statistically significantly greater reductions from baseline A1C than thiazolidinediones [redacted].

The meta-regression analyses that included baseline A1C, weight, BMI, or disease duration as covariates showed similar results to the primary analysis. The coefficients for baseline A1C and duration of diabetes were both statistically significantly lower than 0, suggesting possible effect modification. Patients with higher baseline values of A1C or longer disease duration showed a larger reduction in A1C. The sensitivity analyses (excluding trials that enrolled 100% Asian patients or that evaluated rosiglitazone, or analyses using the last available outcome data) showed similar findings and the primary analysis.

TABLE 37: NETWORK META-ANALYSIS RESULTS FOR CHANGE FROM BASELINE IN A1C — ADD-ON TO METFORMIN

Treatment	Mean Difference (95% CrI) for Change From Baseline to Week 26 in A1C (%)[a]		
	Versus Placebo	Versus Dulaglutide 0.75 mg	Versus Dulaglutide 1.5 mg
Sulfonylurea	[redacted]	[redacted]	[redacted]
Dulaglutide 0.75 mg	[redacted]	[redacted]	[redacted]
Dulaglutide 1.5 mg	[redacted]	[redacted]	[redacted]
GLP-1 agonist	[redacted]	[redacted]	[redacted]
DPP-4 inhibitor	[redacted]	[redacted]	[redacted]
SGLT2 inhibitor	[redacted]	[redacted]	[redacted]
Thiazolidinedione	[redacted]	[redacted]	[redacted]
Acarbose	[redacted]	[redacted]	[redacted]
Meglitinides	[redacted]	[redacted]	[redacted]
Basal insulin	[redacted]	[redacted]	[redacted]
Biphasic insulin	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium/glucose cotransporter-2.
[a] Random-effect model. Negative values favor the treatment versus control (placebo or dulaglutide). Data in bold are statistically significant.
Source: CADTH Common Drug Review submission.[15]

Weight: Relative to placebo, dulaglutide 1.5 mg, other GLP-1 agonists, SGLT2 inhibitors, and acarbose were associated with statistically significant decreases in weight over baseline [redacted]. Conversely, sulfonylureas, thiazolidinediones, and insulin were associated with increases in weight over baseline, compared with placebo, with the mean difference in change in weight from baseline ranging from [redacted]. The differences between other drugs and placebo were not statistically significant.

When compared with dulaglutide (0.75 mg and 1.5 mg), the sulfonylureas, DDP-4 inhibitors, thiazolidinediones, meglitinides, and insulin were all associated with statistically significant increases in weight over baseline [redacted](Table 38). The differences between other GLP-1 agonists and acarbose versus dulaglutide were not statistically significantly different. The mean difference in the change in weight was statistically significant, favouring the SGLT2 inhibitors versus dulaglutide 0.75 mg, but not for the dulaglutide 1.5 mg dose. The meta-regression analyses and sensitivity analyses showed similar results to the primary analysis.

TABLE 38: NETWORK META-ANALYSIS RESULTS FOR CHANGE FROM BASELINE IN WEIGHT — ADD-ON TO METFORMIN

Treatment	Mean Difference (95% CrI) for Change From Baseline to Week 26 in Weight (kg)[a]		
	Versus Placebo	Versus Dulaglutide 0.75 mg	Versus Dulaglutide 1.5 mg
Sulfonylurea	[redacted]	[redacted]	[redacted]
Dulaglutide 0.75 mg	[redacted]	[redacted]	[redacted]
Dulaglutide 1.5 mg	[redacted]	[redacted]	
GLP-1 agonist	[redacted]	[redacted]	[redacted]
DPP-4 inhibitor	[redacted]	[redacted]	[redacted]
SGLT-2 inhibitor	[redacted]	[redacted]	[redacted]
Thiazolidinedione	[redacted]	[redacted]	[redacted]
Acarbose	[redacted]	[redacted]	[redacted]
Meglitinides	[redacted]	[redacted]	[redacted]
Basal insulin	[redacted]	[redacted]	[redacted]
Biphasic insulin	[redacted]	[redacted]	[redacted]

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium/glucose cotransporter 2.
[a] Random-effect model. Negative values favour the treatment versus control (placebo or dulaglutide). Data in bold are statistically significant.
Source: CADTH Common Drug Review submission.[15]

Hypoglycemia: Thirty-three RCTs reported the percentage of patients with hypoglycemia, and among the 20 trials that included a placebo group, the percentage with hypoglycemia ranged from 0% to 5.3%.

Compared with placebo, the risk of hypoglycemia was statistically greater for dulaglutide 1.5 mg, sulfonylureas, SGLT-2 inhibitors, and biphasic insulin [redacted]. Sulfonylureas were associated with an increased risk of hypoglycemia compared with [redacted]. Compared with dulaglutide 1.5 mg, the risk of hypoglycemia was statistically lower for other [redacted] The differences between dulaglutide and other drug classes were not statistically significant. The results of the meta-regression and sensitivity analyses showed similar findings to the primary analysis.

TABLE 39: NETWORK META-ANALYSIS RESULTS FOR RISK OF HYPOGLYCEMIA — ADD-ON TO METFORMIN

Treatment	Relative Risk (95% CrI) for Hypoglycemia[a]		
	Versus Placebo	Versus Dulaglutide 0.75 mg	Versus Dulaglutide 1.5 mg
Sulfonylurea	[redacted]	[redacted]	[redacted]
Dulaglutide 0.75 mg	[redacted]	[redacted]	[redacted]
Dulaglutide 1.5 mg	[redacted]	[redacted]	[redacted]
GLP-1 agonist	[redacted]	[redacted]	[redacted]
DPP-4 inhibitor	[redacted]	[redacted]	[redacted]
SGLT2 inhibitor	[redacted]	[redacted]	[redacted]
Thiazolidinedione	[redacted]	[redacted]	[redacted]
Acarbose	[redacted]	[redacted]	[redacted]
Meglitinides	[redacted]	[redacted]	[redacted]
Basal insulin	[redacted]	[redacted]	[redacted]
Biphasic insulin	[redacted]	[redacted]	[redacted]

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium/glucose cotransporter 2.
[a] Random-effect model. Values less than 1 favour the treatment versus control (placebo or dulaglutide). Data in bold are statistically significant.
Source: CADTH Common Drug Review submission.[15]

Data were limited for the rate of hypoglycemia events, with 10 RCTs reporting this outcome at 26 weeks. Although the random-effects model was chosen as the best fit based on the DIC values, the authors commented that neither the random- nor the fixed-effect models fit well. As a result, there was uncertainty in the model estimates, as reflected in the wide 95% credible intervals observed for some comparisons. Due to this uncertainty, the results have not been summarized in this report.

Serious hypoglycemia: Fifteen RCTs reported the rate of severe hypoglycemia and 17 RCTs reported the risk of severe hypoglycemia; however, due to the high proportion of zero events among the studies, the authors were unable to run the NMA models.

Serious adverse events: The proportion of patients who experienced a serious adverse event was reported in 23 RCTs, and among placebo treatment groups, 0% to 5.3% of patients reported an event. No statistically significant differences in the risk of serious adverse events were detected for dulaglutide, other GLP-1 agonists, SGLT2 inhibitors, DPP-4 inhibitors, thiazolidinediones, acarbose, and insulin compared with placebo, or between dulaglutide and other active drugs (Table 40). The results of the meta-regression analyses and the sensitivity analyses showed similar findings as in the primary analysis.

TABLE 40: NETWORK META-ANALYSIS RESULTS FOR RISK OF SERIOUS ADVERSE EVENTS — ADD-ON TO METFORMIN

Treatment	Relative Risk (95% CrI) for Serious Adverse Events[a]		
	Versus Placebo	Versus Dulaglutide 0.75 mg	Versus Dulaglutide 1.5 mg
Sulfonylurea	[redacted]	[redacted]	[redacted]
Dulaglutide 0.75 mg	[redacted]	[redacted]	[redacted]
Dulaglutide 1.5 mg	[redacted]	[redacted]	[redacted]
GLP-1 agonist	[redacted]	[redacted]	[redacted]
DPP-4 inhibitor	[redacted]	[redacted]	[redacted]
SGLT2 inhibitor	[redacted]	[redacted]	[redacted]
Thiazolidinedione	[redacted]	[redacted]	[redacted]
Acarbose	[redacted]	[redacted]	[redacted]
Basal insulin	[redacted]	[redacted]	[redacted]
Biphasic insulin	[redacted]	[redacted]	[redacted]

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium/glucose cotransporter 2.
[a] Fixed-effect model. Values less than 1 favour the treatment versus control (placebo or dulaglutide). Data in bold are statistically significant.
Source: CADTH Common Drug Review submission.[15]

Results of Manufacturer-Submitted Network Meta-Analysis for Third-Line Therapies

Evidence Network

Overall, 29 RCTs met the inclusion criteria and contributed to the NMAs of third-line therapies for T2DM. Of these, 23 were included in the previous CADTH report,[68] and six were new studies. The manufacturer-submitted NMA excluded five RCTs that were included in the CADTH report[68] because of their short duration (one to five months); the reasons for exclusion of other studies were not reported. AWARD-2 was the only dulaglutide trial that met the inclusion criteria.

The risk of bias was reported for all 29 included studies. Eight RCTs were rated as a high risk of bias on one or more domains of the Cochrane risk of bias tool (random sequence generation [two RCTs], allocation concealment [six], blinding [four]). Two trials were rated as low risk of bias on all domains of the Cochrane risk of bias tool and the remaining 19 had a mix of low or unclear risk of bias on various domains, including 17 with an unclear risk of bias on allocation concealment.

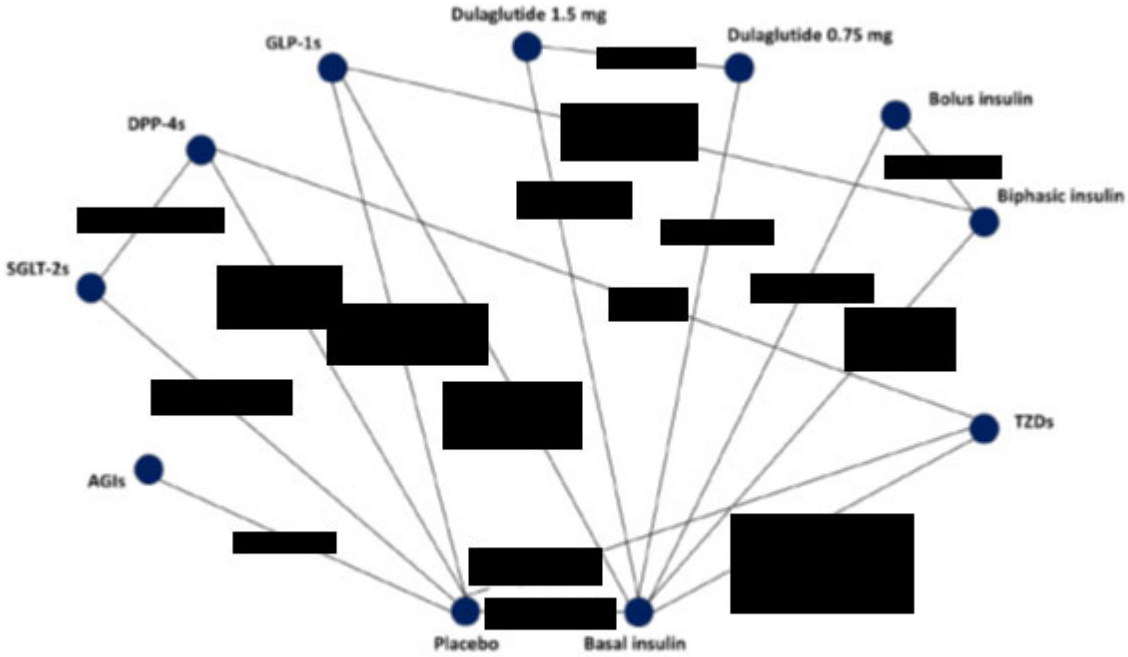
The patients enrolled in the RCTs had the following characteristics:

- Mean age range 47 to 62 years
- Proportion of males 31% to 73%
- Four RCTs enrolled 100% Asian population (these trials excluded in a sensitivity analysis)
- Median baseline mean weight 84 kg (range 65 to 99 kg).
- Median baseline mean A1C 8.6 (range 8.1 to 10.3)
- Median baseline mean disease duration 9.5 years (range 7.2 to 13.6 years).

Five insulin RCTs did not administer metformin and a sulfonylurea concomitantly in one or more of the insulin treatment groups. The authors of the NMA decided that differences in background therapy were likely an effect modifier and excluded these trials from the primary analysis. Frequentist meta-analysis of insulin trials showed differences in treatment effects across subgroups based on background therapy

($P < 0.0001$); thus, no sensitivity analyses were conducted that included these five RCTs. The network diagram for the A1C outcome is provided in Figure 10. Of note, no data for the meglitinide drug class were available.

FIGURE 10: NETWORK DIAGRAM FOR A1C — ADD-ON TO METFORMIN PLUS A SULFONYLUREA



Note: Nodes represent a treatment. Labels represent included RCTs with direct comparisons for the corresponding edge.

A1C = glycated hemoglobin; AGI = alpha-glucosidase inhibitor; DPP-4 = dipeptidyl peptidase -4 inhibitors; GLP-1 = glucagon-like peptide-1 agonists; SGLT2 = sodium/glucose cotransporter 2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione.
Source: CADTH Common Drug Review submission.[15]

Results

A summary of the results of the NMA for A1C, weight, hypoglycemia, severe hypoglycemia, and serious adverse events are presented in the section below. The number of trials included in the NMA for each outcome is listed in Table 41.

Based on DIC values, the random-effects model was chosen as the best fit over fixed-effect or meta-regression models for A1C, weight, risk of hypoglycemia, risk of severe hypoglycemia, and risk of serious adverse events. A fixed-effects model was reported as the primary analysis for the rate of hypoglycemia.

Inconsistency was detected in one or more closed loops in the analysis of A1C, weight, and risk of hypoglycemia. When Asian trials were excluded, statistical inconsistency was no longer detected for A1C and weight analyses.

TABLE 41: STUDIES INCLUDED IN THE NETWORK META-ANALYSIS FOR THIRD-LINE TREATMENTS

Outcome	RCTs	Treatment groups	Nodes	Patients
A1C	24	54	11	9,415
Weight	22	50	11	9,273
Rate of overall hypoglycemia	4	9	5	2,346
Risk of overall hypoglycemia	17	38	10	6,535
Risk of severe hypoglycemia	18	40	9	7,051
Rate of severe hypoglycemia	7	Model did not converge		
Risk of serious adverse events	16	37	9	7,160

A1C = glycated hemoglobin; BMI = body mass index; NMA = network meta-analysis; RCT = randomized controlled trial.
Source: CADTH Common Drug Review submission.[15]

A1C: All treatments, except acarbose, were associated with statistically significant reductions in A1C from baseline to week 26, compared with placebo [redacted](Table 42). No statistically significant differences were detected between dulaglutide 0.75 mg or 1.5 mg doses and other GLP-1 agonists, SGLT2 inhibitors, or insulin. Dulaglutide 0.75 mg [redacted], and dulaglutide 1.5 mg [redacted] showed statistically significantly greater reductions from baseline in A1C levels compared with DDP-4 inhibitors. Dulaglutide 1.5 mg also showed statistically significantly greater reductions from baseline in A1C levels compared with thiazolidinediones [redacted]

Meta-regression models that included baseline A1C, weight, BMI, or disease duration showed results that were generally consistent with the primary analysis for A1C. Of note, only 69% of RCTs reported baseline weight, thus limiting the number of trials available for the meta-regression that included weight as a covariate. Sensitivity analyses that excluded 100% Asian trials, or that used the last available data (26 weeks or 52 weeks), also showed results that were similar, in general, with the primary analysis, although some treatment comparisons showed changes in statistical significance.

TABLE 42: NETWORK META-ANALYSIS RESULTS FOR CHANGE FROM BASELINE IN A1C — ADD-ON TO METFORMIN PLUS A SULFONYLUREA

Treatment	Mean Difference (95% CrI) for Change From Baseline to Week 26 in A1C (%)[a]		
	Versus Placebo	Versus Dulaglutide 0.75 mg	Versus Dulaglutide 1.5 mg
Dulaglutide 0.75 mg	[redacted]	[redacted]	[redacted]
Dulaglutide 1.5 mg	[redacted]	[redacted]	[redacted]
GLP-1 agonists	[redacted]	[redacted]	[redacted]
SGLT2 inhibitors	[redacted]	[redacted]	[redacted]
DPP-4 inhibitors	[redacted]	[redacted]	[redacted]
Thiazolidinedione	[redacted]	[redacted]	[redacted]
Acarbose	[redacted]	[redacted]	[redacted]
Basal insulin	[redacted]	[redacted]	[redacted]
Biphasic insulin	[redacted]	[redacted]	[redacted]
Bolus insulin	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium/glucose cotransporter 2.
[a] Random-effect model. Negative values favour the treatment versus control (placebo or dulaglutide). Data in bold are statistically significant.
Source: CADTH Common Drug Review submission.[15]

Weight: No statistically significant differences were detected in the change from baseline in weight for dulaglutide (0.75 mg and 1.5 mg) and [redacted] were associated with statistically significant reductions from baseline in weight [redacted] were associated with statistically significant increases from baseline in weight [redacted].

Thiazolidinediones and insulin were associated with statistically significant weight gains (mean difference [MD] 2.5 to 3.8 kg) compared with dulaglutide (0.75 mg or 1.5 mg) (Table 43). The change from baseline in weight was lower than other GLP-1 agonists compared with dulaglutide 0.75 mg (MD –1.5 kg) and dulaglutide 1.5 mg (MD –1.1 kg); however, the differences were statistically significant for the dulaglutide 0.75 mg dose only. The differences between dulaglutide and [redacted] were not statistically significantly different.

Some changes in effect estimates were noted in the meta-regression analysis of weight that included baseline A1C as a covariate, particularly for acarbose and SGLT2 inhibitors. These classes were informed by one trial and thus should be interpreted with caution. The findings for meta-regression analyses including baseline weight, BMI, or disease duration, and the sensitivity analyses were generally consistent with the primary analysis.

TABLE 43: NETWORK META-ANALYSIS RESULTS FOR CHANGE FROM BASELINE IN WEIGHT — ADD-ON TO METFORMIN PLUS A SULFONYLUREA

Treatment	Mean Difference (95% CrI) for Change From Baseline to Week 26 in Weight (kg)[a]		
	Versus Placebo	Versus Dulaglutide 0.75 mg	Versus Dulaglutide 1.5 mg
Dulaglutide 0.75 mg	[redacted]	[redacted]	[redacted]
Dulaglutide 1.5 mg	[redacted]	[redacted]	[redacted]
GLP-1 agonists	[redacted]	[redacted]	[redacted]
SGLT2 inhibitors	[redacted]	[redacted]	[redacted]
DPP-4 inhibitors	[redacted]	[redacted]	[redacted]
Thiazolidinedione	[redacted]	[redacted]	[redacted]
Acarbose	[redacted]	[redacted]	[redacted]
Basal insulin	[redacted]	[redacted]	[redacted]
Biphasic insulin	[redacted]	[redacted]	[redacted]
Bolus insulin	[redacted]	[redacted]	[redacted]

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitors; GLP-1 = glucagon-like peptide-1 agonists; SGLT2 = sodium/glucose cotransporter 2 inhibitors.
[a] Random-effect model. Negative values favour the treatment versus control (placebo or dulaglutide). Data in bold are statistically significant.
Source: CADTH Common Drug Review submission.[15]

Hypoglycemia: The proportion of patients reporting hypoglycemia in the metformin plus sulfonylurea groups ranged from 0% to 25% (median 6.9%) among the 17 included trials.

The [redacted] were associated with an increased risk of hypoglycemia compared with placebo (Table 44). No statistically significant differences were detected in the risk of hypoglycemia for dulaglutide versus other active treatments. Meta-regression analyses and the sensitivity analysis (excluding Asian studies) were generally consistent with the primary analysis results.

TABLE 44: NETWORK META-ANALYSIS RESULTS FOR RISK OF HYPOGLYCEMIA — ADD-ON TO METFORMIN PLUS A SULFONYLUREA

Treatment	Relative Risk (95% CrI) of Hypoglycemia[a]		
	Versus Placebo	Versus Dulaglutide 0.75 mg	Versus Dulaglutide 1.5 mg
Dulaglutide 0.75 mg	[redacted]	[redacted]	[redacted]
Dulaglutide 1.5 mg	[redacted]	[redacted]	[redacted]
GLP-1 agonists	[redacted]	[redacted]	[redacted]
SGLT2 inhibitors	[redacted]	[redacted]	[redacted]
DPP-4 inhibitors	[redacted]	[redacted]	[redacted]
Thiazolidinedione	[redacted]	[redacted]	[redacted]
Acarbose	[redacted]	[redacted]	[redacted]
Basal insulin	[redacted]	[redacted]	[redacted]
Biphasic insulin	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium/glucose cotransporter 2.
[a] Random-effect model. Values less than 1 favour the treatment versus control (placebo or dulaglutide). Data in bold are statistically significant.
Source: CADTH Common Drug Review submission.[15]

The evidence network informing the analysis of the rate of hypoglycemia was sparse, with only four RCTs providing data. Based on these data, [redacted] were associated with a statistically significant increased rate of hypoglycemia compared with [redacted] (Table 45). Dulaglutide was associated with statistically significant lower rate of hypoglycemia compared with [redacted]. No data were available for other drug classes. The sensitivity analyses showed similar findings. No meta-regression analyses were conducted.

TABLE 45: NMA RESULTS FOR RATE OF HYPOGLYCEMIA — ADD-ON TO METFORMIN PLUS A SULFONYLUREA

Treatment	Rate Ratio (95% CrI) of Hypoglycemia[a]		
	Versus Basal Insulin	Versus Dulaglutide 0.75 mg	Versus Dulaglutide 1.5 mg
Dulaglutide 0.75 mg	[redacted]	[redacted]	[redacted]
Dulaglutide 1.5 mg	[redacted]	[redacted]	[redacted]
GLP-1 agonists	[redacted]	[redacted]	[redacted]
Biphasic insulin	[redacted]	[redacted]	[redacted]

A1C = glycated hemoglobin; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.
[a] Fixed-effect model. Values less than 1 favour the treatment versus control (basal insulin or dulaglutide). Data in bold are statistically significant.
Source: CADTH Common Drug Review submission.[15]

Severe hypoglycemia: The risk of severe hypoglycemia was reported in 18 RCTs; however, many of the trials had zero event data in one or more treatment groups. Given that trials with zero events across all groups do not contribute evidence to the network, the NMAs for this outcome were sparse, and there is considerable uncertainty in the treatment effects. Although no statistically significant differences were detected on the risk of severe hypoglycemia between dulaglutide and placebo or other drug classes, the credible intervals (CrIs) were wide, and these data should be interpreted with caution. For this reason, the results of the NMA have not been summarized in this report.

Seven RCTs reported on the rate of severe hypoglycemia; however, the Markov chain Monte Carlo simulation did not converge, due to the number of trials with zero events.

Serious adverse events: No statistically significant differences in the risk of serious adverse events were detected for dulaglutide, other GLP-1 agonists, SGLT2 inhibitors, DPP-4 inhibitors, thiazolidinediones and insulin compared with placebo, or between dulaglutide and other active agents (Table 46). The results of the meta-regression analyses and the sensitivity analysis excluding Asian studies showed similar findings to the primary analysis.

The percentage of patients in the placebo treatment groups who reported a serious adverse event ranged from 1.6% to 6.1%

TABLE 46: NETWORK META-ANALYSIS RESULTS FOR RISK OF SERIOUS ADVERSE EVENTS — ADD-ON TO METFORMIN PLUS A SULFONYLUREA

Treatment	Relative Risk (95% CrI) of Serious Adverse Events[a]		
	Versus Placebo	Versus Dulaglutide 0.75 mg	Versus Dulaglutide 1.5 mg
Dulaglutide 0.75 mg	[redacted]	[redacted]	[redacted]
Dulaglutide 1.5 mg	[redacted]	[redacted]	[redacted]
GLP-1 agonists	[redacted]	[redacted]	[redacted]
SGLT2 inhibitors	[redacted]	[redacted]	[redacted]
DPP-4 inhibitors	[redacted]	[redacted]	[redacted]
Thiazolidinedione	[redacted]	[redacted]	[redacted]
Basal insulin	[redacted]	[redacted]	[redacted]
Biphasic insulin	[redacted]	[redacted]	[redacted]

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium/glucose cotransporter 2.
[a] Random-effect model. Values less than 1 favour the treatment versus control (placebo or dulaglutide). Data in bold are statistically significant.
Source: CADTH Common Drug Review submission.[15]

Summary of Kayaniyil et al. 2016

The objective was to estimate the relative efficacy and tolerability of exenatide weekly to other GLP-1 agonists approved in the US or Europe, for the treatment of patients with T2DM who failed to achieve glycemic control on metformin monotherapy. The study was funded by AstraZeneca, the company that markets exenatide.

The authors conducted a systematic review and NMA. A literature search was conducted of Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials (from inception to October 2014), PubMed (August to October 2014), and conference abstracts, for English-language publications that met the inclusion criteria (Table 47). Two researchers independently screened articles and assessed the validity of trials using the Cochrane risk of bias tool. Data extraction was conducted by one reviewer and verified by a second. Discrepancies were resolved through discussion or by a third reviewer. The authors reported that missing variance data from the trials were imputed from other studies according to the methods in the *Cochrane Handbook for Systematic Reviews of Interventions*.

TABLE 47: SELECTION CRITERIA FOR RANDOMIZED CONTROLLED TRIALS IN KAYANIYIL ET AL. (2016)

Criteria	Second-Line
Population	Adult patients diagnosed with T2DM experiencing inadequate glycemic control despite metformin monotherapy[a]
Intervention	GLP-1 agonists (at approved doses in the US or Europe) as add-on therapy to metformin monotherapy:[a] • Albiglutide 30 mg and 50 mg weekly • Exenatide 5 mcg and 10 mcg twice daily, 2 mg weekly • Lixisenatide 20 mcg daily[b] • Liraglutide 1.2 mg and 1.8 mg daily • Dulaglutide 0.75 mg and 1.5 mg weekly
Comparator	Not specified
Outcome	Outcomes reported at 24 ± 6 weeks: • Change in A1C • Change in body weight • Change in systolic blood pressure • Proportion of patients who achieved glycemic targets (A1C < 7% and ≤ 7%) at 24 ± 6 weeks • Nausea • Treatment discontinuation due to adverse events
Study design	RCTs

A1C = glycated hemoglobin; GLP-1 = glucagon-like peptide-1; RCT = randomized controlled trial; T2DM = type 2 diabetes mellitus.
[a] At least 80% of the patients in each treatment group must have received metformin monotherapy as background therapy during the trial, and at least 80% received metformin monotherapy or diet and exercise as pre-trial diabetes management.
[b] Not available in Canada.
Source: Kayaniyil et al. 2016.[1]

The NMA models were fitted using Markov chain Monte Carlo methods in WinBUGS v. 1.4.3. and based on code from the NICE Decision Support Unit's Technical Support Document no. 2.[69] Non-informative priors were assigned treatment effects (normal 0, 0.0001) and between-studies standard deviation (uniform 0, 5). There was a 20,000 iteration burn-in, and 100,000 iterations for parameter estimation with a thin parameter of 10 (i.e., retaining every 10th parameter in each of the three Markov chains) to reduce autocorrelation. Convergence was checked using caterpillar and density plots. Although both fixed- and random-effects models were run, the random-effects model was chosen a priori as the preferred model. However, fixed-effect models could be selected as the preferred model based on model fit (DIC), and in cases where the model could not estimate the between-studies variance with reasonable precision (e.g., due to a sparse network). Meta-regression analyses were run to explore heterogeneity due to differences in baseline values, but the authors stated that these models were not robust, due to insufficient data points, and thus did not report the results of these analyses. The mean changes in A1C, weight, and blood pressure were reported as mean differences (95% CrI) and patients achieving glycemic control, and patients with nausea or discontinuing treatment due to adverse events were reported as odds ratio (95% CrI). Heterogeneity in patients' baseline characteristics were examined qualitatively using box plots.

Results of Kayaniyil et al. 2016

Evidence Network

A total of 14 RCTs, published between 2005 and 2014, met the inclusion criteria. The numbers of RCTs for each drug were as follows — dulaglutide 1.5 mg (1), albiglutide (1), exenatide weekly (1), exenatide daily (6), lixisenatide (4), and liraglutide (3). The NMA by Kayaniyil et al.[1] included the AWARD-6 trial but not the AWARD-5 trial (reason for exclusion not reported).

The authors reported that the overall quality of the included studies was good, although methods to generate randomization and conceal allocation were not always reported. Eight trials were open-label. No further information was provided on the possible risk of bias for the included studies.

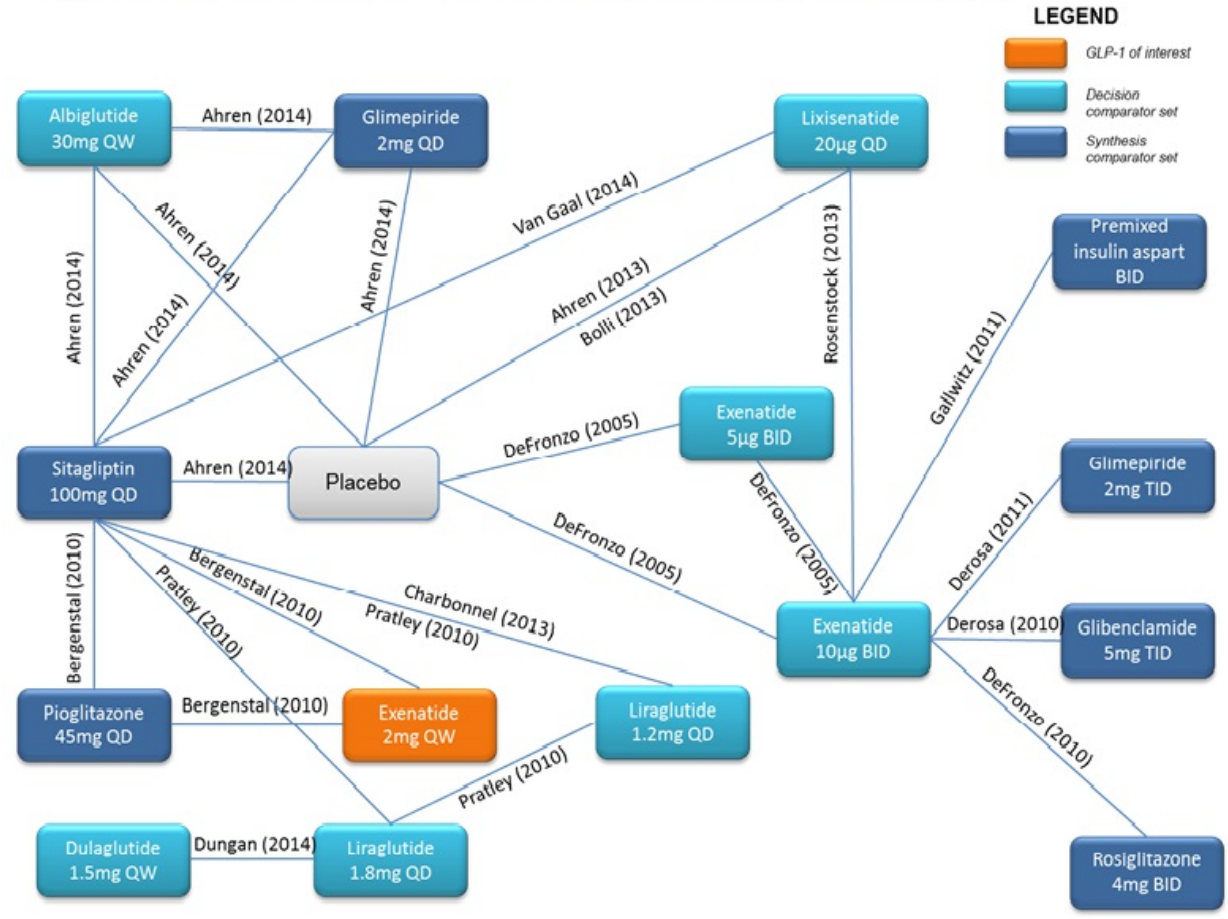
The mean baseline patient characteristics of the included trials were as follows:

- Age 42.7 to 58.2 years
- A1C 7.8% to 8.9%
- Weight 80.2 to 101 kg
- Duration of diabetes 4.4 to 8.2 years.

No substantial imbalances were apparent between treatment groups within studies based on the information provided.

Random-effects models were selected as the primary analysis for A1C, weight, proportion achieving glycemic target, and nausea. Fixed-effect models were selected for systolic blood pressure and treatment discontinuation due to adverse events. Between 10 and 14 trials were included in the analyses, except for systolic blood pressure, which was reported in only five RCTs. The authors reported there were no problems with convergence. Figure 11 shows the evidence network for A1C.

FIGURE 11: NETWORK DIAGRAM FOR A1C — ADD-ON TO METFORMIN (KAYANIYIL ET AL. 2016)



BID = twice-daily; GLP-1 = glucagon-like peptide-1; QD = once-daily; QW = once-weekly; TID = three times daily.
Source: Kayaniyil S, Lozano-Ortega G, Bennett HA, Johnsson K, Shaunik A, Grandy S, et al. Figure S3. Network diagram for mean change from baseline HbA1c (%) From: Kayaniyil S, Lozano-Ortega G, Bennett HA, Johnsson K, Shaunik A, Grandy S, et al. A Network Meta-analysis Comparing Exenatide Once Weekly with Other GLP-1 Receptor Agonists for the Treatment of Type 2 Diabetes Mellitus. Diabetes Ther. 2016 Feb 17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26886440?dopt=Citation

Results

The NMA results comparing GLP-1 agonists to placebo are presented in Table 48, and results for dulaglutide versus exenatide weekly are summarized in Table 49. No information was available for dulaglutide versus other GLP-1 agonists. There were no placebo-controlled trials in the NMA of systolic blood pressure.

The mean decrease from baseline in A1C was statistically significantly greater for all GLP-1 agonists (except exenatide 5 mcg twice daily), compared with placebo (MD –0.5 to –1.1) (Table 48). For the change from baseline in weight, only exenatide 10 mcg twice daily showed a statistically significant difference versus placebo (Table 48). No clinically or statistically significant differences were detected between dulaglutide 1.5 mg and exenatide 2 mg weekly doses for the change from baseline in A1C, weight, or systolic blood pressure (Table 49).

There was substantial uncertainty in the effect estimates for patients achieving glycemic control, risk of nausea, or treatment discontinuation due to adverse event outcomes, as reflected by the wide CrIs for some comparisons (Table 48 and Table 49). Thus, these findings should be interpreted with caution.

TABLE 48: NETWORK META-ANALYSIS RESULTS FOR GLP-1 AGONISTS VERSUS PLACEBO — ADD-ON TO METFORMIN (KAYANIYIL ET AL. 2016)

Treatment	NMA Results Versus Placebo (24 ± 6 weeks)[a]				
	Change from baseline in A1C (%) MD (95% CrI)	Proportion achieving glycemic target (A1C ≤ 7%) OR (95% CrI)	Change from baseline in weight (kg) MD (95% CrI)	Nausea OR (95% CrI)	Treatment discontinuation due to adverse events OR (95% CrI)
Model	Random-effect	Random-effect	Random-effect	Random-effect	Fixed-effect
Number of RCTs included	14	10	14	11	13
Dulaglutide 1.5 mg weekly	**–1.09 (–1.75 to –0.43)**	10.55 (0.68 to 174.34)	–1.34 (–4.17 to 1.37)	15.13 (0.09 to 2563.17)	**23.95 (3.41 to 178.57)**
Liraglutide 1.2 mg daily	**–0.71 (–1.16 to –1.26)**	5.76 (0.70 to 49.75)	–1.68 (–3.79 to 0.31)	9.89 (0.21 to 490.78)	**22.20 (3.94 to 134.29)**
Liraglutide 1.8 mg daily	**–1.03 (–1.55 to –0.51)**	**10.38 (1.06 to 108.20)**	–2.05 (–4.41 to 0.16)	12.96 (0.18 to 975.55)	**23.88 (3.87 to 157.59)**
Albiglutide 30 mg weekly	**–0.69 (–1.11 to –0.28)**	NR	–0.20 (–3.49 to 3.00)	NR	NR
Lixisenatide 20 mcg daily	**–0.50 (–0.75 to –0.25)**	**2.91 (1.12 to 7.83)**	–0.80 (–1.87 to 0.15)	4.45 (0.78 to 27.49)	**4.45 (2.07 to 10.79)**
Exenatide 5 mcg twice daily	–0.42 (–0.87 to 0.00)	2.45 (0.57 to 12.07)	–1.15 (–2.80 to 0.48)	2.53 (0.18 to 36.05)	2.90 (0.64 to 12.43)
Exenatide 10 mcg twice daily	**–0.75 (–1.11 to –0.43)**	**3.75 (1.19 to 13.71)**	**–2.05 (–3.48 to –0.83)**	4.69 (0.54 to 40.69)	**5.91 (2.51 to 15.36)**
Exenatide 2 mg weekly	**–1.09 (–1.65 to –0.53)**	7.92 (0.76 to 85.71)	–1.00 (–3.48 to 1.33)	4.37 (0.06 to 361.04)	**12.78 (1.82 to 97.03)**

A1C = glycated hemoglobin; CrI = credible interval; MD = mean difference; NR = not reported; OR = odds ratio; RCT = randomized controlled trial.
[a] Statistically significant differences in bold.
Source: Kayaniyil et al. 2016.[1]

TABLE 49: NETWORK META-ANALYSIS RESULTS FOR WEEKLY EXENATIDE VERSUS DULAGLUTIDE — ADD-ON TO METFORMIN (KAYANIYIL ET AL. 2016)

Outcome	Number of RCTs	Exenatide 2 mg Weekly Versus Dulaglutide 1.5 mg Weekly	
		Random-effects[a]	Fixed-effects[a]
Change from baseline to week 24 ± 6 weeks in:		**MD (95% CrI)**	**MD (95% CrI)**
A1C (%)	14	0.00 (–0.72 to 0.72)	0.00 (–0.33 to 0.33)
Weight (kg)	14	0.35 (–2.43 to 3.10)	0.37 (–0.92 to 1.65)
SBP (mm Hg)	5	NR	–2.40 (–6.41 to 1.62)
Proportion of patients at 24 ± 6 weeks		**OR (95% CrI)**	**OR (95% CrI)**
Achieving glycemic target (A1C ≤ 7%)	10	7.92 (0.76 to 85.71)	**7.68 (3.86 to 15.44)**
Nausea	11	0.29 (0.00 to 33.99)	**0.28 (0.11 to 0.73)**
Treatment discontinuation due to adverse events	13	0.52 (0.01 to 15.53)	0.53 (0.11 to 2.69)

A1C = glycated hemoglobin; CrI = credible interval; MD = mean difference; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; SBP = systolic blood pressure.

[a] Statistically significant differences in bold. Random-effects models were selected as the primary analysis for A1C, weight, proportion achieving glycemic target, and nausea. Fixed-effect models were selected for SBP and treatment discontinuation due to adverse events.

Source: Kayaniyil et al. 2016.[1]

Critical Appraisal

The three NMAs were based on updates to, or newly conducted, systematic reviews, and the authors appear to have used accepted methods to conduct the reviews, including searching multiple databases, duplicate screening, extraction, and assessment of study validity. No grey literature sources were searched and a number of gaps in reporting were noted. The list of studies excluded from the systematic reviews or NMAs and reasons for exclusion were incomplete in all three reports. Despite similar inclusion and exclusion criteria between Kayaniyil et al.[1] and the manufacturer-submitted NMA of second-line therapies, there were differences in the GLP-1 agonist trials included in each report. The manufacturer's NMA included 11 GLP-1 agonist RCTs and Kayaniyil et al.[1] included 14 RCTs; however, only five RCTs were included in both reports. Neither report supplied a complete list of excluded RCTs or the reasons for exclusion; thus, it was not possible to explore the reasons for the differences. A limited description of the study characteristics was provided in all three NMAs, and data such as blinding, withdrawal rate, insulin titration schedule, glycemic target, and definition of hypoglycemia were not summarized.

All NMAs included patient populations that were relevant to this formulary review. Sensitivity analyses excluding trials that enrolled a 100% Asian population, which may not be generalizable to Canadian patients with diabetes, were conducted in both the manufacturer-submitted NMAs. Comparators that were relevant to the Canadian context were included in NMAs. In Kayaniyil et al.; [1] however, the scope was limited to GLP-1 agonists, and due to the incomplete reporting of NMA results, there were limited data of interest to this review. In all three NMAs, no information was provided on the doses of background therapy (i.e., metformin or sulfonylurea) and limited data were available on the insulin doses used in the RCTs; thus, it is not possible to assess whether dosing was comparable across or within trials. The outcomes evaluated were pertinent to this review by the CADTH Common Drug Review (CDR); however, the manufacturer-submitted NMAs did not evaluate blood pressure or fasting plasma glucose, which were outcomes of interest. None of the NMAs evaluated health-related quality of life or longer-term outcomes of importance to patients, such as microvascular or macrovascular complications of diabetes.

All three reports included Bayesian NMAs and the authors reported that the methods used were guided by the NICE Decision Support Unit's Technical Support Document no. 2.[69] In the manufacturer-submitted NMAs, drugs were grouped and analyzed as a drug class, except for dulaglutide. This approach requires the important assumption that drugs within a particular drug class are similar enough to pool. The authors, however, did not present any evidence that the within-class treatment effects were similar. No pairwise meta-analyses were conducted, so it is not possible for the reader to compare the direct and indirect effect estimates, or to examine the drug classes for statistical heterogeneity. The authors also did not run any sensitivity analyses on the NMAs, analyzing drugs individually instead of as a drug class. Although the CADTH therapeutic review did not find substantial differences within drug class, the manufacturer's analyses added several new treatments and RCTs to the network, and a re-examination of within-class treatment effects was warranted. In addition, the authors did not run sensitivity analyses that pooled the two dulaglutide doses. It may not be a fair comparison to analyze high and low doses of dulaglutide as separate nodes versus pooled estimates of drugs with a known dose-response relationship. Although there was a degree of heterogeneity between studies in baseline A1C, weight, BMI, and disease duration, these did not appear to affect the findings of the manufacturer-submitted NMAs.

None of the NMAs conducted sensitivity analyses using different priors. In the networks that were sparse, the estimates of the between-study standard deviation in the random-effects model may not be robust and may be overly influenced by vague priors. This may have contributed to the wide CrIs observed in the analyses of nausea and patients achieving glycemic targets in Kayaniyil et al.[1]

Although all NMAs provided some information on the risk of bias of the included trials, it was not clear how this information was used. Eight of 29 RCTs (28%) in the NMA of third-line therapy had a high risk of bias on random sequence generation, allocation concealment, or blinding, and no sensitivity analyses were conducted to determine the impact of these high-risk studies on the NMA findings. Considering the high proportion of potentially biased trials, some caution may be warranted in the interpretation of the third-line therapy NMA's findings. The risk of bias in information provided in Kayaniyil et al.[1] was sparse and insufficient to assess the potential impact on the studies' findings.

Overall, the evidence for safety was sparse, with a high proportion of treatment groups reporting zero events (particularly for severe hypoglycemia) and some NMAs showing wide CrIs, reflecting the uncertainty in the findings. No information on the definition of hypoglycemia or severe hypoglycemia from individual trials was provided; thus, it is not possible to determine whether there are clinically important differences between studies. The CADTH therapeutic reviews[67,68] reported some degree of variability in the criteria to define hypoglycemia and glycemic targets, which may explain some of the differences in frequency noted between trials. There was substantial variation in the frequency of hypoglycemia in the placebo group in the NMA of third-line therapies (0% to 25%); thus, the transitivity assumption may not hold. Considering that the trials had short follow-up durations (six to 12 months) and were not powered for safety outcomes, the lack of substantial differences between treatments in the risk of adverse events cannot be interpreted as comparable safety.

In the NMAs, there was insufficient information presented on individual studies to fully assess the external validity. The findings were limited due to the short duration of follow-up (six to 12 months), limited sample sizes, use of surrogate end points (e.g., A1C) as opposed to more clinically meaningful end points (e.g., diabetes-related complications), and failure to report definitions for hypoglycemia. No information was provided on the dosing of background therapies (i.e., metformin with or without a sulfonylurea) and limited information was available on insulin dosing; thus, it is not possible to determine if patients received therapeutic doses. No information was provided on the location of the included studies, but the CADTH

therapeutic review, which was the foundation for the manufacturer-submitted NMAs, stated that many studies were conducted exclusively in countries where health care delivery and practice patterns may differ markedly from Canada.

Discussion

The three industry-sponsored NMAs showed dulaglutide was more effective in reducing A1C over the short term (six months) compared with placebo, in adults with T2DM who were inadequately controlled on metformin, or metformin plus a sulfonylurea. No statistically significant differences were detected in A1C between dulaglutide and exenatide weekly or other GLP-1 agonists, sulfonylureas or insulin (as add-on to metformin therapy), or compared with other GLP-1 agonists, SGLT-2 inhibitors or insulin (as add-on therapy to metformin plus a sulfonylurea). Dulaglutide showed modest, statistically significant reductions in A1C compared with DPP-4 inhibitors [redacted], acarbose [redacted] and meglitinides [redacted]. The differences between dulaglutide and thiazolidinediones were statistically significant favouring the dulaglutide 1.5 mg dose only in both the second- and third-line NMAs [redacted]. Dulaglutide showed statistically significantly lower A1C levels compared with SGLT-2 inhibitors in the second-line population only [redacted].

Sulfonylureas, thiazolidinediones, and insulin were associated with statistically significantly higher weight gain after six months compared with dulaglutide, when used as add-on therapy to metformin with or without a sulfonylurea [redacted]. No statistically significant differences in the change from baseline in weight were detected for dulaglutide compared with acarbose. The findings varied when the change in weight for dulaglutide was compared with other GLP-1 agonists, SGLT-2 inhibitors, DPP-4 inhibitors, and meglitinides, although the differences were generally small [redacted].

The risk of hypoglycemia was significantly elevated for sulfonylureas, dulaglutide 1.5 mg, SGLT2 inhibitors, and insulin, compared with placebo as add-on therapy to metformin, but the CrIs were wide for some comparisons, indicating there is considerable uncertainty in the results. Given the limitations in the analysis of the risk of hypoglycemia with third-line therapies (highly variable placebo rate, inclusion of high risk of bias trials) and uncertainty in the effect estimates, the data should be viewed with caution. Kayaniyil et al.[1] did not assess the risk of hypoglycemia.

Conclusion

The indirect evidence, based on three industry-sponsored NMAs, was generally consistent with the direct evidence from AWARD-2, -5, and -6. Dulaglutide was more effective in reducing A1C over the short term (six months) than placebo, in adults with T2DM who were inadequately controlled on metformin, or metformin plus a sulfonylurea. Dulaglutide was associated with greater reductions in A1C than the DPP-4 inhibitors, acarbose, and meglitinides, and no statistically significant differences compared with other GLP-1 agonists, insulin, or sulfonylureas. The indirect evidence suggests that dulaglutide may be associated with less weight gain than sulfonylureas, thiazolidinediones, and insulin.

The evidence for safety was sparse, with a high proportion of treatment groups reporting zero events (particularly for severe hypoglycemia) and some NMAs showing wide CrIs, reflecting the uncertainty in the findings. Additional longer-term comparative data are required to determine the relative risk of adverse events with dulaglutide.

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