Common Drug Review
Clinical Review Report

August 2015

Drug	alogliptin (Nesina)
Indications under review	1) in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycemic control 2) in combination with a sulfonylurea when diet and exercise plus a sulfonylurea alone do not provide adequate glycemic control
Listing request	As per indications under review
Manufacturer	Takeda Canada Inc.

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ABBREVIATIONS

A1C	glycated hemoglobin
ACS	acute coronary syndrome
AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
CDEC	Canadian Drug Expert Committee
CDR	**CADTH** Common Drug Review
CI	confidence interval
DPP-4	dipeptidyl peptidase-4
EMA	European Medicines Agency
FAS	full analysis set
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
LOCF	last observation carried forward
LSMD	least squares mean difference
MACE	major adverse cardiac events
MTD	maximum tolerated dose
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
PPS	per-protocol set
RCT	randomized controlled trial
SAE	serious adverse event
SGLT-2	sodium-glucose cotransporter-2
SU	sulfonylurea
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Diabetes is a chronic metabolic disease with significant health impacts on individuals and societies. The prevalence of diabetes in Canada was 6.8% (2.4 million Canadians) in 2009 and is expected to rise to 3.7 million people by 2019. Ninety per cent of people with diabetes have type 2 diabetes mellitus, which is characterized by increased hepatic glucose output, reduced insulin secretion, and insulin resistance. People with diabetes are at risk of microvascular complications such as diabetic nephropathy and retinopathy, macrovascular complications such as cardiovascular disease, and premature mortality. Improved glycemic control reduces the risk of microvascular complications and possibly of macrovascular complications. Current guideline recommendations specify a target for glycated hemoglobin (A1C) of 7% or less for most patients with type 2 diabetes.

There are currently 11 classes of antihyperglycemic drugs approved for use in Canada for type 2 diabetes: metformin, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 analogues, sodium-glucose cotransporter-2 inhibitors, basal insulins, bolus insulins, and biphasic insulins. Alogliptin is the fourth DPP-4 inhibitor to be introduced in Canada after sitagliptin, saxagliptin, and linagliptin. Upon submission, the manufacturer requested listing of alogliptin in a manner similar to other DPP-4 inhibitors in Canada. Based on consideration of listing criteria across Canada for existing DPP-4 inhibitors, and in consultation with the manufacturer, the following two of the six approved indications for alogliptin were reviewed by the CADTH Common Drug Review (CDR):

- in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycemic control
- in combination with a sulfonylurea when diet and exercise plus a sulfonylurea alone do not provide adequate glycemic control.

Upon review of the draft CDR clinical and pharmacoeconomic reports, the manufacturer asked that the requested listing criteria be modified to reflect the two indications under review.

Of note, the Canadian Drug Expert Committee recommendations for the existing DPP-4 inhibitors have recommended listing for patients with inadequate glycemic control on metformin and a sulfonylurea who are unable to use insulin. However, alogliptin is not approved for use in combination with metformin and a sulfonylurea.

Results and Interpretation

Included studies

Four randomized controlled trials (RCTs) met the criteria for inclusion in this review: Studies 007 (N = 500), 008 (N = 500), 305 (N = 2,639), and 302_MET (N = 784). Of these, Studies 007, 008, and 305 were considered pivotal trials by Health Canada. Studies 007, 008, and 302_MET were superiority studies of alogliptin 12.5 mg and 25 mg daily versus placebo, while Study 305 was a non-inferiority trial comparing alogliptin 12.5 mg and 25 mg daily with glipizide. Studies 007 and 008 were 26-week, double-blind, placebo-controlled, three-group, multi-centre RCTs of similar design; 007 compared dual therapies alogliptin + glyburide and placebo + glyburide, while 008 compared alogliptin + metformin and placebo + metformin. Enrolled patients had type 2 diabetes and inadequate glycemic control on sulfonylurea (007) or metformin (008) monotherapy. The primary outcome in both studies was change from baseline in A1C.

Study 305 was a 104-week, double-blind, active-controlled, three-group, multi-centre RCT. Patients had type 2 diabetes with inadequate glycemic control on previous metformin monotherapy. The study compared alogliptin 12.5 mg daily, alogliptin 25 mg daily, and glipizide up to 20 mg daily, all in combination with metformin > 1,500 mg daily or maximum tolerated dose. The primary outcome of this study was change from baseline A1C at 52 or 104 weeks, and the trial was powered to confirm non-inferiority of alogliptin versus glipizide, with a non-inferiority margin of 0.3%.

Study 302_MET was a 26-week, placebo-controlled, seven-group, multi-centre RCT. Patients had type 2 diabetes with inadequate glycemic control when treated with diet and exercise for at least two months before screening. Patients were randomized to one of seven treatment groups: alogliptin 12.5 mg twice daily + metformin 500 mg twice daily, alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily, alogliptin 12.5 mg twice daily, alogliptin 25 mg once daily, metformin 500 mg twice daily, metformin 1,000 mg twice daily, or placebo twice daily. The primary outcome of this study was change from baseline A1C at 26 weeks.

While the included trials demonstrated a number of methodological strengths, some limitations were also identified. In Study 305, glipizide appeared to be titrated in a relatively conservative fashion, and the mean doses achieved (5.2 mg daily) were relatively low. This could have biased results in favour of a finding of non-inferiority between alogliptin and glipizide. As well, a large proportion of patients (44% to 51%) withdrew prematurely from this study either because of hyperglycemic rescue or premature discontinuation, which may have introduced biases arising from potential imbalances between treatment groups over the course of the study.

Efficacy
None of the included studies evaluated outcomes related to macrovascular or microvascular complications of type 2 diabetes, or related to quality of life. The latter was identified as an important outcome in patient group input received by CADTH for this submission.

Sulfonylurea combination therapy: In Study 007, alogliptin 12.5 mg and 25 mg daily, both in combination with glyburide, demonstrated superiority in terms of A1C level achieved at 26 weeks compared with placebo + glyburide in the full analysis set (FAS) analysis (least squares mean differences [LSMD] were –0.4%; 95% confidence interval [CI], –0.6% to –0.2% for alogliptin 12.5 mg versus placebo and –0.5%; 95% CI, –0.7% to –0.3% for alogliptin 25 mg versus placebo). However, alogliptin 12.5 mg and alogliptin 25 mg did not demonstrate statistically significantly greater decreases in fasting plasma glucose (FPG) compared with placebo.

Patient group input submitted to CADTH for this submission indicated that increases in body weight represented an important limitation of some antihyperglycemic therapies. In Study 007, adjusted mean changes from baseline at 26 weeks were 0.6 kg, 0.7 kg, and 0.2 kg for the alogliptin 12.5 mg, alogliptin 25 mg, and placebo groups, respectively. Mean differences between alogliptin 12.5 mg and 25 mg and placebo were statistically significant (LSMD = 0.8 kg; 95% CI, 0.14 kg to 1.46 kg and LSMD = 0.9 kg; 95% CI, 0.21 kg to 1.54 kg, respectively).

Metformin combination therapy: In Study 008, alogliptin 12.5 mg and 25 mg daily, both in combination with metformin, demonstrated superiority to placebo in terms of A1C level achieved at 26 weeks in the FAS analysis (LSMD = –0.4%; 95% CI, –0.6% to –0.2% and LSMD = –0.5%; 95% CI, –0.7% to –0.3%, respectively). Alogliptin 12.5 mg and 25 mg also demonstrated statistically significantly greater decreases in FPG when compared with placebo (LSMD = –1.04 mmol/L; 95% CI, –1.51 mmol/L to –0.57 mmol/L and LSMD = –0.97; 95% CI, –1.44 mmol/L to –0.49 mmol/L, respectively). Adjusted mean changes from baseline body weight at 26 weeks were –0.4 kg, –0.7 kg, and –0.4 kg for the alogliptin 12.5 mg, alogliptin 25 mg, and placebo groups, respectively. There were no statistically significant differences in body weight change between alogliptin 12.5 mg and placebo (LSMD = 0.0 kg; 95% CI, –0.7 kg to 0.7 kg), and alogliptin 25 mg and placebo (LSMD = –0.3 kg; 95% CI, –0.9 kg to 0.4 kg).

In Study 305, alogliptin 12.5 mg and 25 mg daily, both in combination with metformin, demonstrated non-inferiority in terms of A1C level achieved at 52 weeks compared with glipizide + metformin based on the PPS analysis (LSMD = –0.09%; one-sided 98.75% CI, 0.03% and LSMD = –0.03%; one-sided 95% CI, 0.06%, respectively). Similarly, at 104 weeks, alogliptin 12.5 mg and 25 mg daily demonstrated non-inferiority to glipizide (LSMD = –0.09%; one-sided 98.75% CI, 0.04% and LSMD = –0.13%; one-sided 98.75% CI, –0.01%, respectively). At both 52 and 104 weeks, alogliptin 12.5 mg and 25 mg daily demonstrated statistically significantly greater reductions in FPG than placebo. Adjusted mean changes from baseline body weight at 52 weeks were –0.65 kg, –0.71 kg, and 0.86 kg for the alogliptin 12.5 mg, alogliptin 25 mg, and glipizide groups, respectively. Adjusted mean differences between alogliptin 12.5 mg and 25 mg versus glipizide were statistically significant (LSMD = –1.51 kg; 95% CI, –1.79 kg to –1.231 kg and LSMD = –1.58 kg; 95% CI, –1.86 kg to –1.30 kg, respectively). Results were similar at week 104.

In Study 302_MET, both alogliptin 12.5 mg twice daily + metformin 500 mg twice daily and alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily were associated with statistically significantly greater reductions in A1C from baseline at 26 weeks versus the respective doses of metformin monotherapy (LSMD = –0.6%; 95% CI, –0.9% to –0.3% and LSMD = –0.4%; 95% CI, –0.7% to –0.2%, respectively). Both dual-therapy regimens were also associated with statistically significant reductions in FPG compared with the respective metformin monotherapy regimens. Adjusted mean differences between alogliptin 12.5 mg twice daily + metformin 500 mg twice daily and alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily versus the respective metformin monotherapy doses were not statistically significant.

Harms

Sulfonylurea combination therapy: In Study 007, 11 patients in both the alogliptin 12.5 mg (5.4%) and 25 mg (5.6%) groups experienced a serious adverse event (SAE), compared with two patients in the placebo group (2.0%). There were no deaths in Study 007. Hypoglycemia was identified as a significant barrier to achieving glycemic control in the patient group input received by CDR. Thirty-two patients (15.8%) in the alogliptin 12.5 mg group, 19 patients (9.6%) in the alogliptin 25 mg group, and 11 patients (11.1%) in the placebo group experienced at least one episode of hypoglycemia.

Metformin combination therapy: In Study 008, eight patients (3.9%) in the alogliptin 12.5 mg group, six patients (2.8%) in the alogliptin 25 mg group, and four patients (3.8%) in the placebo group experienced an SAE. There was one death in Study 008, in the alogliptin 12.5 mg group. In Study 008, two patients (0.9%) in the alogliptin 12.5 mg group, no patients in the alogliptin 25 mg group, and three patients (2.9%) in the placebo group experienced at least one episode of hypoglycemia.

In Study 305, 11% of patients in the alogliptin 25 mg group, 9.9% in the alogliptin 12.5 mg group, and 9.3% in the glipizide group experienced an SAE. There were 11 deaths in Study 305, three (0.3%) in the alogliptin 12.5 group, three (0.3%) in the alogliptin 25 mg group, and five (0.6%) in the glipizide group. Twenty-two patients (2.5%) in the alogliptin 12.5 mg group, 12 patients (1.4%) in the alogliptin 25 mg group, and 202 patients (23.2%) in the glipizide group experienced at least one episode of hypoglycemia.

In Study 302_MET, the percentages of patients with an SAE were similar among the dual-therapy and metformin monotherapy groups. Two patients (1.9%) in the alogliptin 12.5 mg twice daily + metformin 500 mg twice daily group, two patients (1.8%) in the alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily group, two patients (1.8%) in the metformin 500 mg group, two patients (1.8%) in the metformin 1,000 mg group, and three patients (2.8%) in the placebo group experienced an SAE. There were no deaths in this study. Alogliptin + metformin dual therapy tended to be associated with more WDAEs than metformin alone: the percentages were 4.7% in the alogliptin 12.5 mg twice daily + metformin 500 mg twice daily group and 9.6% in the alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily group, compared with 2.8% and 1.8% in the respective metformin monotherapy groups. Hypoglycemia occurred in two (1.9%), six (5.3%), seven (6.3%), two (1.8%), and one (1.8%) in the alogliptin 12.5 mg twice daily + metformin 500 mg twice daily, alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily, metformin 1,000 mg twice daily, metformin 500 mg twice daily, and placebo groups, respectively.

All of the DPP-4 inhibitors approved for use in Canada carry a warning regarding the risk of pancreatitis in their respective product monographs. There were no cases of pancreatitis reported in Studies 007 and 008 and isolated cases in the other two studies with no apparent association with alogliptin. Recent comprehensive assessments from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) concluded that the currently available data did not support a causal association between incretin-based drugs and pancreatitis or pancreatic cancer.

Other considerations

Comparative efficacy and safety of alogliptin and other DPP-4 inhibitors

There were no trials comparing alogliptin with other DPP-4 inhibitors available in Canada; however, the manufacturer submitted a network meta-analysis (NMA) to assess comparative efficacy and safety among DPP-4 inhibitors in monotherapy, dual-therapy (with metformin or sulfonylurea), and triple-therapy (with metformin and a sulfonylurea) regimens. The NMA did not show evidence of differences in glycemic control, weight gain, or hypoglycemia risk between alogliptin and the other DPP-4 inhibitors in dual-therapy regimens; however, the analysis did not allow for a conclusion of non-inferiority or similarity among drugs. A second NMA submitted by the manufacturer assessed the relative efficacy and safety of alogliptin versus other DPP-4 inhibitors for dual therapy (i.e., in combination with metformin when a sulfonylurea is not appropriate, or in combination with a sulfonylurea when metformin is not appropriate). The results were similar to the original analysis, showing no significant differences in A1C change from baseline. However, this analysis went further to show that there was a high probability (ranging from 64% to 100%, depending upon the comparison and whether a fixed- or random-effects model was used) that alogliptin has effects on A1C similar to those of the other DPP-4 inhibitors, within a margin of 0.3%. Alogliptin + metformin dual therapy also demonstrated favourable results with respect to weight gain compared with saxagliptin, and with respect to hypoglycemia compared with sitagliptin and saxagliptin, but all other comparisons of alogliptin with other DPP-4 inhibitors on these outcomes were statistically non-significant.

Cardiovascular safety: The Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE) study (N = 5,380) compared alogliptin with placebo in combination with standard of care among individuals with type 2 diabetes mellitus and acute coronary syndrome. The primary objective of this study was to demonstrate non-inferiority of alogliptin to placebo with respect to a composite of major adverse cardiac events (MACE) in high-risk type 2 diabetes patients. The hazard ratio for the primary MACE composite outcome (0.96; one-sided 95% CI, 1.16) confirmed the non-inferiority hypothesis. The LSMD in change from baseline A1C between the alogliptin and placebo groups was –0.4% (95% CI, –0.4% to –0.3%). The overall safety profile of alogliptin was similar to placebo over the course of the study, and there were no apparent differences in the rates of SAEs between the two groups.

Alogliptin triple therapy with metformin and sulfonylurea

In the absence of a specific trial of alogliptin as triple therapy with metformin and sulfonylurea, the manufacturer provided a post hoc exploratory subgroup analysis of patients treated with triple therapy in the EXAMINE trial. In the subgroup of patients receiving metformin and sulfonylurea at baseline, the adjusted mean difference on A1C between alogliptin and placebo [redacted] was [redacted]. The alogliptin and placebo groups did not differ significantly with respect to the incidence of overall adverse events [redacted] in the metformin + sulfonylurea subgroup. The incidence of hypoglycemia was [redacted]. These findings should be interpreted with caution given the post hoc nature of the analysis.

Conclusions

Four double-blind, placebo- or active-controlled RCTs were included in this review of alogliptin add-on therapy to metformin or a sulfonylurea. In all trials, the addition of alogliptin was associated with modest but clinically relevant improvements in A1C, ranging from 0.4% to 0.6%. In the only active-controlled trial in dual-therapy regimens, alogliptin + metformin dual therapy was demonstrated to be non-inferior to glipizide + metformin, although there was some concern that the conservative titration algorithm and relatively low mean doses of glipizide in this study may have biased results toward a finding of non-inferiority. There were no data available from the included trials regarding the long-term complications of diabetes or quality of life. Alogliptin add-on therapy resulted in modest weight gain compared with placebo when added to a sulfonylurea, was weight-neutral versus placebo when added to metformin, and was associated with lower weight gain than sulfonylurea when either was added to metformin. Alogliptin was not associated with a higher risk of hypoglycemia than placebo when added to either metformin or a sulfonylurea, but was associated with lower risk of hypoglycemia versus a sulfonylurea in dual therapy with metformin. There were no apparent associations between alogliptin and other adverse effects. The EXAMINE trial, which was designed to confirm the cardiovascular safety of alogliptin added to various existing antidiabetes therapies, reported that alogliptin was non-inferior to placebo on MACE.

There was no direct comparative evidence for alogliptin versus other DPP-4 inhibitors available in Canada in the context of metformin or sulfonylurea dual therapy. The manufacturer-submitted NMAs suggested that there are no differences among DPP-4 inhibitors in relation to A1C, body weight, and hypoglycemia, and that alogliptin as dual therapy with either metformin or sulfonylurea has a high probability of producing reductions in A1C (within a margin of 0.3%) similar to those of other DPP-4 inhibitors available in Canada.

TABLE 1: SUMMARY OF EFFICACY RESULTS

Parameter	Study 007			Study 008		
	ALO 12.5 mg + GLY (N = 203)	ALO 25 mg q.d. + GLY (N = 198)	PL + GLY (N = 99)	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
Change from baseline A1C (%), LSMD (95% CI) versus PL	–0.4[a] (–0.6 to –0.2)	–0.5[a] (–0.7 to –0.3)	NA	–0.5[a] (–0.7 to –0.3)	–0.5[a] (–0.7 to –0.3)	NA
Change from baseline FPG (mmol/L), LSMD (95% CI) versus PL	–0.38 (–1.02 to 0.26)	–0.58 (–1.22 to 0.05)	NA	–1.04[a] (–1.51 to –0.57)	–0.97[a] (–1.44 to –0.49)	NA
Change from baseline body weight (kg), LSMD (95% CI) versus PL	0.8[b] (0.14 to 1.46)	0.9[b] (0.21 to 1.54)	NA	0.0 (–0.7 to 0.7)	–0.3 (–0.9 to 0.4)	NA

Study 305			
	MET + ALO 12.5 mg (N = 867)	**MET + ALO 25 mg (N = 867)**	**MET + GLZ (N = 859)**
Week 52 change from baseline A1C, LSMD versus GLZc (1-sided 98.75% CI)	–0.1[d] (0.00)	–0.03[d] (0.06)	NA
Week 104 change from baseline A1C, LSMD versus GLZc (1-sided 98.75% CI)	–0.1[d] (0.04)	–0.1[d] (–0.01)	NA
Week 52 change from baseline FPG, LSMD versus GLZ (95% CI)	–0.33 (–0.52 to –0.14)	–0.02 (–0.03 to –0.01)	NA
Week 104 change from baseline FPG, LSMD versus GLZ (95% CI)	–0.35[a] (–0.55 to –0.15)	–0.02[a] (–0.03 to –0.01)	NA
Week 52 change from baseline body weight, LSMD (95% CI) versus MET + GLZ	–1.52[a] (–1.846 to –1.198)	–1.80[a] (–2.122 to –1.473)	NA
Week 104 change from baseline, LSMD (95% CI)	NR	NR	NR

Study 302_MET					
	MET 500 mg b.i.d. (N = 114)	**MET 1,000 mg b.i.d. (N = 111)**	**ALO 12.5 mg + MET 500 mg b.i.d. (N = 111)**	**ALO 12.5 mg + MET 1,000 mg b.i.d. (N = 114)**	**PL (N = 109)**
Change from baseline A1C, LSMD (97.5% CI) versus MET 500 mg	NA	NA	–0.6[a] (–0.9 to –0.3)	NA	NA

	Study 302_MET				
Change from baseline A1C, LSMD (95% CI) versus MET 1,000 mg	NA	NA	–0.4[a] (–0.7 to –0.2)	NA	NA
Change from baseline FPG, LSMD (97.5% CI) versus MET 500 mg	NA	NA	–1.12[e] (–1.81 to –0.43)	NA	NA
Change from baseline FPG, LSMD (97.5% CI) versus MET 1,000 mg	NA	NA	NA	–0.78[b] (–1.45 to –0.10)	NA
Change from baseline, LSMD (95% CI) versus MET 500 mg	NA	NA	NA	0.1 (–0.7 to 0.8)	NA
Change from baseline, LSMD (95% CI) versus MET 1,000 mg	NA	NA	0.3 (–0.5 to 1.1)	–0.3 (–1.1 to 0.5)	NA

A1C = glycated hemoglobin; ALO = alogliptin; b.i.d. = twice daily; CI = confidence interval; FPG = fasting plasma glucose; GLZ = glipizide; GLY = glyburide; LSMD = least squares mean difference; MET = metformin; NA = not applicable; PL = placebo; q.d. = once daily.

[a] $P < 0.001$.

[b] $P < 0.05$.

[a] In Study 305, a non-inferiority margin of 0.3% was tested with a one-sided significance level of 0.0125.

[b] Non-inferiority was established.

[e] $P < 0.01$.

TABLE 2: SUMMARY OF HARMS

Parameter	Study 007			Study 008		
	ALO 12.5 mg + GLY (N = 203)	ALO 25 q.d. mg + GLY (N = 198)	PL + GLY (N = 99)	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
SAEs	11 (5.4)	11 (5.6)	2 (2.0)	6 (2.8)	8 (3.9)	4 (3.8)
WDAEs	5 (2.5)	4 (2.0)	2 (2.0)	7 (3.3)	4 (1.9)	1 (1.0)
Deaths	0	0	0	1 (0.5)	0	0
Hypoglycemia	1 (0.5)	1 (0.5)	0	2 (0.9)	0	3 (2.9)

	Study 305		
	MET + ALO 12.5 mg (N = 867)	**MET + ALO 25 mg (N = 867)**	**MET + GLZ (N = 859)**
SAEs	86 (9.9)	97 (11.0)	81 (9.3)
WDAEs	59 (6.8)	74 (8.4)	82 (9.4)
Deaths	3 (0.3)	3 (0.3)	5 (0.6)
Hypoglycemia	18 (2.1)	6 (0.7)	91 (10.5)

	Study 302_MET				
	MET 500 mg b.i.d. (N = 114)	**MET 1,000 mg b.i.d. (N = 111)**	**ALO 12.5 mg + MET 500 mg b.i.d. (N = 111)**	**ALO 12.5 mg + MET 1,000 mg b.i.d. (N = 114)**	**PL (N = 109)**
SAEs	2 (1.8)	2 (1.8)	2 (1.9)	2 (1.8)	3 (2.8)
WDAEs[a]	3 (2.8)	2 (1.8)	5 (4.7)	11 (9.6)	5 (4.7)
Deaths	0	0	0	0	0
Hypoglycemia	2 (1.8%)	7 (6.3%)	2 (1.9%)	6 (5.3%)	1 (0.9%)

AEs = adverse event; ALO = alogliptin; b.i.d. = twice daily; GLZ = glipizide; GLY = glyburide; MET = metformin; PL = placebo; q.d. = once daily; SAE = serious adverse event; WDAEs = withdrawal due to adverse events.

[a] The number of patients who discontinued because of an AE in the placebo group differ between this table (n = 5) and the disposition data (n = 4), as one patient discontinued at the discretion of the principal investigator (as a result of hyperglycemia).

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Diabetes is a chronic metabolic disease with significant health impacts on individuals and societies. The incidence of diabetes is increasing at a dramatic rate around the world. The International Diabetes Federation estimated that 371 million people worldwide had diabetes in 2012, and projected that this number would increase to 552 million by 2030.[1] The prevalence of diabetes in Canada was 6.8% (2.4 million Canadians) in 2009 and is expected to rise to 3.7 million people by 2019.[2] 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.[3]

Ninety per cent of people with diabetes have type 2 diabetes mellitus,[4] which is characterized by increased hepatic glucose output, reduced insulin secretion, and insulin resistance. It is generally diagnosed in adults older than 40 years of age, although it is increasingly being detected in adolescents and children. Diagnosis is based on a fasting plasma glucose (FPG) level of ≥ 7.0 mmol/L, a two-hour plasma glucose level following a 75 g oral glucose tolerance test of ≥ 11.1 mmol/L, or a glycated hemoglobin (A1C) level of 6.5% or greater.[1]

These thresholds for diagnosis were established because they predict the development of retinopathy, which is one of the common microvascular complications of diabetes.[1] Other microvascular complications are nephropathy (which may progress to end-stage renal disease) and neuropathy (which may cause pain, tingling, gastroparesis, erectile dysfunction, or lower extremity peripheral vascular disease, often resulting in the need for amputation). Diabetes is the primary cause of blindness, end-stage renal disease, and non-traumatic amputation in Canadian adults.[1] Cardiovascular disease (i.e., heart disease, stroke, and peripheral vascular disease) is a major macrovascular complication and is the leading cause of death in people with type 2 diabetes.[2]

1.2 Standards of Therapy

The Canadian Diabetes Association 2013 clinical practice guidelines recommend a target A1C of 7% for most patients with type 2 diabetes, a target FPG of 4 mmol/L to 7 mmol/L, and a two-hour postprandial glucose target of 5 mmol/L to 10 mmol/L.[1] There are currently 11 classes of antihyperglycemic drugs approved for use in Canada: biguanides (i.e., metformin), sulfonylureas (SUs), meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, sodium-glucose cotransporter-2 inhibitors, basal insulins, bolus insulins, and biphasic insulins. Metformin is recommended as the first-line oral antidiabetes drug for most patients with type 2 diabetes when glycemic control cannot be achieved by dietary and lifestyle interventions alone.[1] Because of the progressive nature of type 2 diabetes, patients treated with metformin may require additional therapies over time to maintain glycemic control. Recommendations regarding which drugs should be added to metformin vary, with some guidelines providing considerations for choosing between the available drug classes based on patient factors rather than recommending one drug class over another.[1] In 2013, CADTH published an updated Therapeutic Review assessing the comparative safety, efficacy, and cost-effectiveness of all available classes of antihyperglycemic therapies in the following clinical situations: (1) patients with type 2 diabetes with inadequate glycemic control on metformin monotherapy;[5] and (2) patients with type 2 diabetes with inadequate glycemic control on metformin and an SU.[6]

Based on this evidence, the Canadian Drug Expert Committee (CDEC) recommended the following:[7]

- An SU should be added to metformin for most adults with type 2 diabetes who are inadequately controlled on metformin alone.
- Neutral protamine Hagedorn (NPH) insulin should be added for most adults with type 2 diabetes inadequately controlled on metformin and an SU.
- A DPP-4 inhibitor may be added to metformin and SU therapy in circumstances where patients with type 2 diabetes are unable to use insulin as a third-line option.

CDEC recommendations for DPP-4 inhibitors submitted to date to the CADTH Common Drug Review (CDR) have aligned with the above recommendations.[8-10]

1.3 Drug

GLP-1 and glucose-dependent insulinotropic polypeptide (also known as gastric inhibitory peptide) belong to the incretin class of gastrointestinal hormones. Incretins stimulate a decrease in blood glucose levels by causing increased postprandial insulin release from the beta cells of the pancreas. GLP-1 also suppresses glucagon secretion and exhibits other glucoregulatory actions after secretion in the gut.[11] DPP-4 is an enzyme that rapidly degrades, and thereby inactivates, both GLP-1 and gastric inhibitory peptide. DPP-4 inhibitors prolong the endogenous plasma levels and hence the activity of both of these key hormones.[12] Alogliptin, a potent and highly selective DPP-4 inhibitor, is the fourth DPP-4 inhibitor to be introduced in Canada, following the approval of sitagliptin, saxagliptin, and linagliptin.

Alogliptin is indicated to improve glycemic control in adult patients with type 2 diabetes mellitus as follows:

- as monotherapy as an adjunct to diet and exercise in patients for whom metformin is inappropriate due to contraindications or intolerance
- in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycemic control
- in combination with an SU when diet and exercise plus an SU alone do not provide adequate glycemic control
- in combination with pioglitazone when diet and exercise plus pioglitazone alone do not provide adequate glycemic control
- in combination with pioglitazone and metformin when diet and exercise plus dual therapy with these drugs do not provide adequate glycemic control
- in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin (with or without metformin) do not provide adequate glycemic control.

Unlike other DPP-4 inhibitors available in Canada, alogliptin is not approved for use in combination with metformin and an SU.

Upon submission, the manufacturer requested listing of alogliptin in a manner similar to other DPP-4 inhibitors in Canada. While listing criteria for DPP-4 inhibitors vary somewhat across Canada, the two indications listed in the table were determined, in consultation with the manufacturer, to be of greatest relevance for listing decisions and are the focus of this review. Upon review of the draft CDR clinical and pharmacoeconomic reports, the manufacturer asked that the requested listing criteria be modified to reflect the two indications under review.

Indications under review
• In combination with metformin when diet and exercise plus metformin alone do not provide adequate glycemic control • In combination with a sulfonylurea (SU) when diet and exercise plus an SU alone do not provide adequate glycemic control
Listing criteria requested by sponsor
As per indications under review

TABLE 3: KEY CHARACTERISTICS OF DPP-4 INHIBITORS AVAILABLE IN CANADA

	Alogliptin[13]	Saxagliptin[14]	Linagliptin[15]	Sitagliptin[16]
Mechanism of action	Inhibition of DPP-4			
Indications[a]	As monotherapy or in combination with MET, SU, INS, PIO, PIO + MET, or INS + MET	In combination with the following: MET, an SU, premixed or long- or intermediate-acting insulin (with or without MET), or MET and an SU	• As monotherapy • In combination with the following: MET, an SU, premixed or long- or intermediate-acting insulin (with or without MET), PIO, or MET and PIO	• As monotherapy • In combination with MET, an SU, or MET and an SU
Route of administration	Oral	Oral	Oral	Oral
Recommended dose	25 mg q.d.	5 mg q.d.	5 mg q.d.	100 mg q.d.
Dosage adjustment for renal impairment	No dosage adjustment is required in patients with mild renal impairment Alogliptin 12.5 mg q.d. for patients with moderate renal impairment Alogliptin 6.25 mg q.d. for patients with severe renal impairment or end-stage renal disease requiring hemodialysis	• 2.5 mg q.d. (moderate or severe renal impairment)	• No dose adjustment	50 mg q.d. (moderate renal impairment) 25 mg q.d. (severe renal impairment or end-stage renal disease)

	Alogliptin[13]	Saxagliptin[14]	Linagliptin[15]	Sitagliptin[16]
Warnings and precautions	Use with caution in patients with CHF of NYHA functional class III or IV. Alogliptin should be used with caution in patients with severe renal impairment or end-stage renal disease requiring dialysis. Reports of acute pancreatitis	• Reports of acute pancreatitis • Not recommended for patients with CHF	• Reports of acute pancreatitis • Not recommended for patients with CHF	• Reports of acute pancreatitis • Not recommended for patients with CHF

CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4; INS = insulin; MET = metformin; NYHA = New York Heart Association; PIO = pioglitazone; q.d. = once daily; SU = sulfonylurea.
[a] Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of alogliptin 6.25 mg, 12.5 mg, or 25 mg once daily, combined with metformin or an SU, for the treatment of adults with type 2 diabetes who have experienced inadequate glycemic control with diet, exercise, and metformin or an SU alone.

2.2 Methods

All studies identified by Health Canada as pivotal trials relevant to the two indications under review were included. Other studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

	Indication 1: Combination with Metformin	**Indication 2: Combination with Sulfonylurea**
Patient population	Adults with type 2 diabetes who have experienced inadequate glycemic control with diet and exercise plus metformin	Adults with type 2 diabetes who have experienced inadequate glycemic control with diet and exercise plus sulfonylurea
Intervention	Alogliptin (6.25 mg daily, 12.5 mg daily, or 25 mg daily) in combination with metformin	Alogliptin (6.25 mg daily, 12.5 mg daily, or 25 mg daily) in combination with a sulfonylurea
Comparators	• Metformin monotherapy or metformin plus placebo • Metformin plus one other antidiabetes drug available in Canada (i.e., another DPP-4 inhibitor, sulfonylurea, thiazolidinedione, insulin/insulin analogue, SGLT-2 inhibitor, GLP-1 analogue)	• Sulfonylurea monotherapy or sulfonylurea plus placebo • Sulfonylurea plus one other antidiabetes drug available in Canada (i.e., another DPP-4 inhibitor, metformin, thiazolidinedione, insulin/insulin analogue, SGLT-2 inhibitor, GLP-1 analogue)
Outcomes	**Key efficacy outcomes:** • Mortality • Diabetes-related morbidity (macrovascular, microvascular) • Glycemic control (A1C, FPG) • Health-related quality of life (measured by any validated scale) • Changes in body weight **Harms outcomes:** • Serious adverse events • Hypoglycemia • Withdrawal due to adverse events • Total adverse events **Other outcomes:** • Health care resource utilization	
Study design	Published and unpublished RCTs excluding phase 1 and 2	

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium-glucose cotransporter-2; RCT = randomized controlled trial.

Supplemental issues

- Critical appraisal of the manufacturer's network meta-analysis
- Summary of the EXAMINE Study (Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care in patients with type 2 diabetes and acute coronary syndrome)

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 through Ovid; Embase (1974–) through 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 alogliptin, Nesina, and Kazano.

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.

The initial search was completed on August 15, 2014. Regular alerts were established to update the search until the meeting of CDEC on December 10, 2014. 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 CADTH Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials and databases (free). Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5; excluded studies (with reasons) are presented in APPENDIX 4: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 4: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

QUOROM = Quality of Reporting of Meta-analyses.

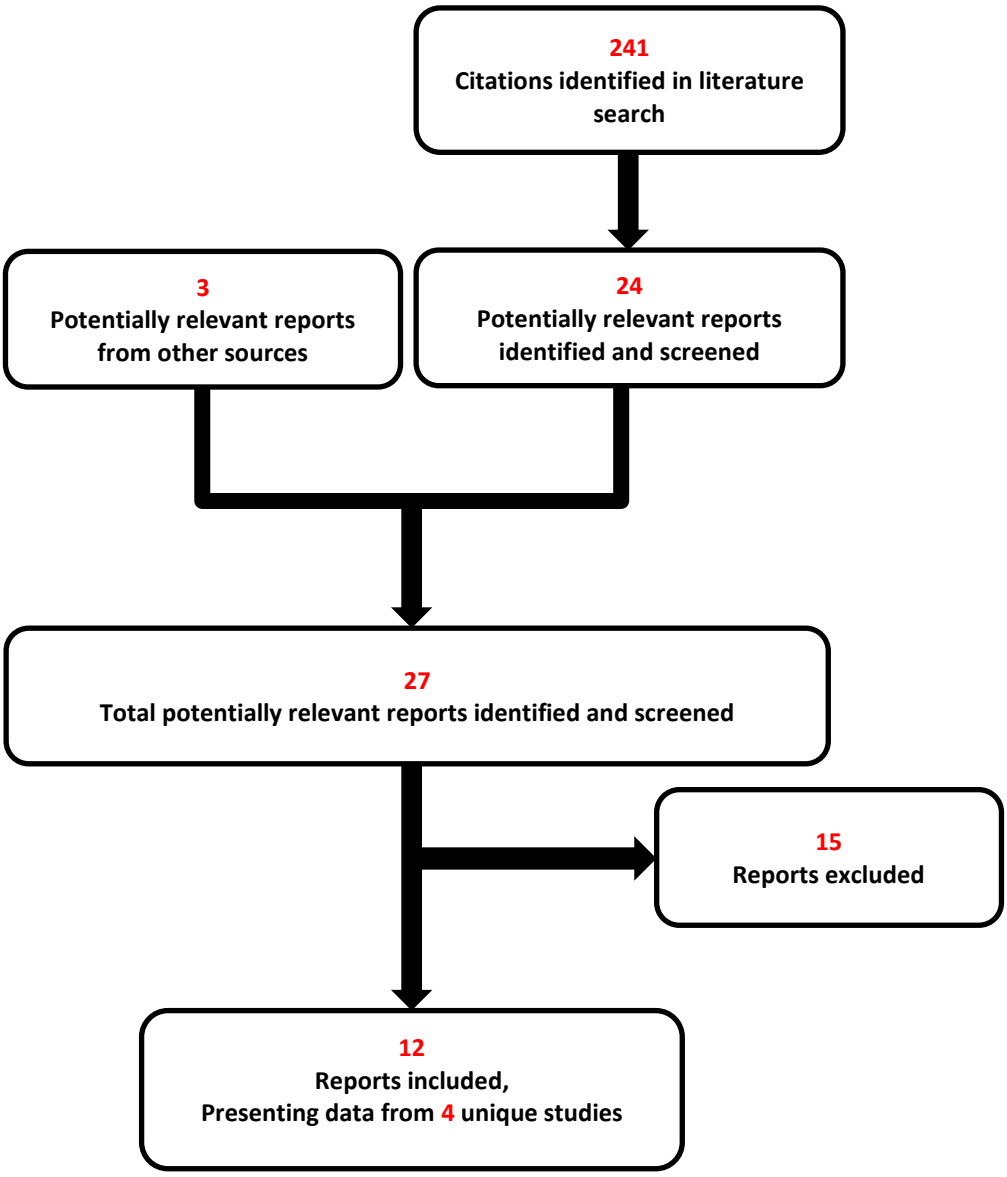


TABLE 5: DETAILS OF INCLUDED STUDIES

		Study 007	Study 008	Study 302_MET	Study 305
DESIGNS & POPULATIONS	**Study design**	DB, PC, MC, 3-group, RCT	DB, PC, MC, 3-group, RCT	DB, MC, PC, 7-group, RCT	DB, AC, MC, 3-group, RCT
	Locations	United States, Argentina, Brazil, Chile, Dominican Republic, Guatemala, Mexico, and Peru	United States, Brazil, Chile, Guatemala, and Mexico	United States, Czech Republic, Hungary, Israel, Lithuania, Poland, Romania, Russia, Slovakia, and Ukraine	United States, Canada, Brazil, Chile, Mexico, Peru, and Puerto Rico
	Randomized (N)	500	500	784	2,639
	Inclusion criteria	Aged 18 to 80 years with T2DM and inadequate glycemic control when treated with SU; A1C between 7.0% and 10.0%, inclusive; BMI ≥ 23 kg/m^2 and ≤ 45 kg/m^2; systolic blood pressure ≤ 180 mm Hg and diastolic pressure ≤ 110 mm Hg	Aged 18 to 80 years with T2DM and inadequate glycemic control when treated with MET; A1C between 7.0% and 10.0%; BMI ≥ 23 kg/m^2 and ≤ 45 kg/m^2; systolic blood pressure ≤ 180 mm Hg and diastolic pressure ≤ 110 mm Hg	Aged 18 to 80 years with diagnosis of T2DM and inadequate glycemic control when treated with diet and exercise; A1C 7.5% to 10.0% inclusive at screening; BMI ≥ 23 kg/m^2 and ≤ 45 kg/m^2	All patients were aged 18 to 80 years of age with T2DM; inadequate glycemic control when treated with MET; BMI ≥ 23 kg/m^2 and ≤ 45 kg/m^2 AND enrolled under Schedule A or B as follows **Schedule A:** Patients who experienced inadequate glycemic control (A1C 7.0% to 9.0%, inclusive) while on MET therapy (daily dose ≥ 1,500 mg or MTD) **Schedule B:** Patients who experienced inadequate glycemic control (A1C 7.5% to 10.0%, inclusive) while on MET therapy (daily dose

		Study 007	Study 008	Study 302_MET	Study 305
					< 1,500 mg without documented MTD)
	Exclusion criteria	Urine albumin/creatinine ratio > 1,000 mcg/mg; history of cancer (other than squamous cell or basal cell carcinoma of the skin); NYHA class III or IV heart failure		Hemoglobin ≤ 7.45 mmol/L for men and ≤ 6.21 mmol/L for women; systolic blood pressure ≥ 150 mm Hg and /or diastolic pressure ≥ 90 mm Hg; NYHA Class III or IV heart failure	A history of cancer (other than squamous cell or basal cell carcinoma of the skin); hemoglobin ≤ 12 g/dL (≤ 120 g/L) for males and ≤ 10 g/dL (≤ 100 g/L) for females; NYHA Class III to IV heart failure
DRUGS	**Intervention(s)**	• ALO 12.5 mg q.d. + GLY • ALO 25 mg q.d. + GLY	• ALO 12.5 mg q.d. + MET • ALO 25 mg q.d. + MET	• ALO 12.5 mg + MET 500 mg b.i.d. • ALO 25 mg + MET 1,000 mg b.i.d. • ALO 12.5 mg b.i.d. • ALO 25 mg q.d.	• ALO 12.5 mg q.d. + MET (≥ 1,500 mg or MTD) • ALO 25 mg q.d. + MET (≥ 1,500mg or MTD)
	Comparator(s)	• PL + GLY	• PL + MET	• MET 500 mg b.i.d. • MET 1,000 mg b.i.d. • PL	• GLZ 20 mg daily + OL MET (≥ 1,500 mg or MTD)
DURATION	Phase	3			
	Run-in	4 weeks			
	Double-blind	26 weeks			104 weeks
	Follow-up	2 weeks			
OUTCOMES	**Primary end point**	Change from baseline (day 1) in A1C at week 26			Change from baseline (day 1) A1C at week 52 and week 104
	Other end points	• Proportion of patients with A1C < 7.0% • Change from baseline in FPG • Change from baseline body weight			

		Study 007	Study 008	Study 302_MET	Study 305
NOTES	**Publications/ data sources**	Pratley et al. (2009)[17] Clinical Study Report 007[18] Alogliptin CDR Submission[19]	Nauck et al. (2009)[20] Clinical Study Report 008[21] Alogliptin CDR Submission[19]	Pratley et al. (2014)[22] Clinical Study Report[23] Alogliptin CDR Submission[19]	Del Prato et al. (2014)[24] Clinical Study Report 305[25] Alogliptin CDR Submission[19]

A1C = glycated hemoglobin; AC = active-controlled; ALO = alogliptin; b.i.d. = twice daily; BMI = body mass index; CDR = CADTH Common Drug Review; DB = double-blind; FPG = fasting plasma glucose; GLY = glyburide; GLZ = glipizide; MC = multi-centre; MET = metformin; MTD = maximum tolerated dose; NYHA = New York Heart Association; OL = open-label; PC = placebo-controlled; PL = placebo; q.d. = once daily; RCT = randomized controlled trial; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

3.2 Included Studies

3.2.1 Description of studies

The literature search identified four randomized controlled trials (RCTs) that met the criteria for inclusion in the review: Studies 007, 008, 305, and 302_MET (Table 6). Studies 007, 008, and 302_MET were placebo-controlled superiority studies. Of these, Studies 007, 008, and 305 were considered pivotal trials by Health Canada. Study 305 was a non-inferiority trial comparing alogliptin with glipizide.

TABLE 6: LIST OF RANDOMIZED CONTROLLED TRIALS INCLUDED IN THE CADTH COMMON DRUG REVIEW OF ALOGLIPTIN

Study ID	Interventions and Comparators	N	Duration	Primary End Point
ALO + SU combination therapy				
Study 007	ALO 12.5 mg + GLY, ALO 25 mg + GLY, PL + GLY	500	26 weeks	A1C
ALO + MET combination therapy				
Study 008	ALO 12.5 mg + MET ALO 25 mg + MET PL + MET	500	26 weeks	A1C
Study 302_MET	ALO 12.5 mg + MET 500 mg b.i.d. ALO 25 mg + MET 1,000 mg b.i.d. ALO 12.5 mg b.i.d. ALO 25 mg q.d. MET 500 mg b.i.d. MET 1,000 mg b.i.d. PL	784	26 weeks	A1C
Study 305	ALO 12.5 mg q.d. + OL MET (> 1,500 mg or MTD) ALO 25 mg q.d. + OL MET (> 1,500 mg or MTD) GLZ 20 mg daily + OL MET (> 1,500 mg or MTD)	2,639	104 weeks	A1C

A1C = glycated hemoglobin; ALO = alogliptin; b.i.d. = twice daily; GLY = glyburide; GLZ = glipizide; MET = metformin; MTD = maximum tolerated dose; OL = open-label; PL = placebo; q.d. = once daily.

Study 007 was 26-week, double-blind, placebo-controlled, three-group, multi-centre RCT of 500 patients conducted in 15 countries. Patients had type 2 diabetes with inadequate glycemic control (defined as A1C 7.0% to 10.0%) when treated with an SU monotherapy. Patients must have received an SU drug for at least three months before screening, achieving a stable SU dose equivalent to at least 10 mg of glyburide (or a maximum tolerated dose [MTD] of glyburide ≥ 5 mg and < 10 mg) for at least eight weeks before randomization. Patients were randomized to one of three treatment groups in a 1:2:2 ratio (placebo + glyburide: alogliptin 12.5 mg + glyburide: alogliptin 25 mg + glyburide). The primary objective of this study was to evaluate the efficacy of alogliptin administered in combination with SU compared with SU alone on change in A1C from baseline.

Study 008 was a 26-week, double-blind, placebo-controlled, three-group, multi-centre RCT of 500 patients conducted in 15 countries. Patients had type 2 diabetes with inadequate glycemic control (defined as A1C 7.0% to 10.0%) when treated with metformin monotherapy. Patients were also required to be treated with metformin monotherapy (≥ 1,500 mg daily) for at least three months before screening. Patients with an MTD < 1,500 mg daily could enrol in a stabilization period of at least eight weeks before randomization. Patients were randomized to one of three treatment groups in a 1:2:2 ratio (placebo + metformin: alogliptin 12.5 mg + metformin: alogliptin 25 mg + metformin). The primary objective of this study was to evaluate the efficacy of alogliptin administered in combination with metformin compared with metformin alone on change in A1C from baseline.

FIGURE 2: TRIAL DESIGN STUDIES 007 AND 008

Screening Period Week -6 through -5 Prior to randomization		**Run-in/Stabilization Weeks -4 through -1 Prior to randomization**				**Treatment Period Weeks 1 through 26 after randomization**								**End-of-treatment**	**Follow-up Period**
Week															
Screening Visit		-4	-3	-2	-1	Baseline Visit (Day 1)	1	2	4	8	12	16	20	26	28

Source: Clinical Study Report 007.[26]

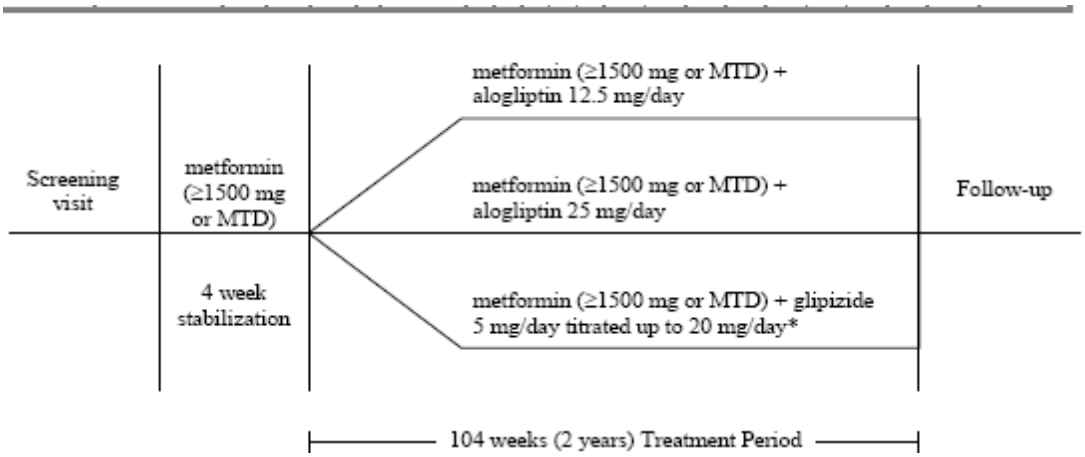
Study 305 was a 104-week, double-blind, active-controlled, three-group, multi-centre RCT of 2,639 patients conducted in 30 countries (including Canada). Patients had type 2 diabetes with inadequate glycemic control on previous metformin therapy, as follows:

- Schedule A: inadequate glycemic control (7.0% to 9.0% A1C) while treated with metformin therapy for at least two months (daily dose ≥ 1,500 mg or MTD).
- Schedule B: inadequate glycemic control while on metformin therapy (daily dose < 1,500 mg or MTD). After completing the pre-screening visit, these patients had their metformin dose immediately increased to ≥ 1,500 mg (or MTD) for an eight-week stabilization period.

After the stabilization period, Schedules A and B were identical. Patients were randomized in a 1:1:1 ratio to receive one of three treatments (alogliptin 12.5 mg once daily + metformin: alogliptin 25 mg once daily + metformin: glipizide 5 mg once daily + metformin). Glipizide was titrated up to 20 mg once daily through week 20 as needed. Throughout the study all patients received open-label metformin ≥ 1,500 mg/day or MTD. The primary objective of Study 305 was to evaluate the durability (for up to two years) of the efficacy of alogliptin + metformin compared with glipizide + metformin, as measured by

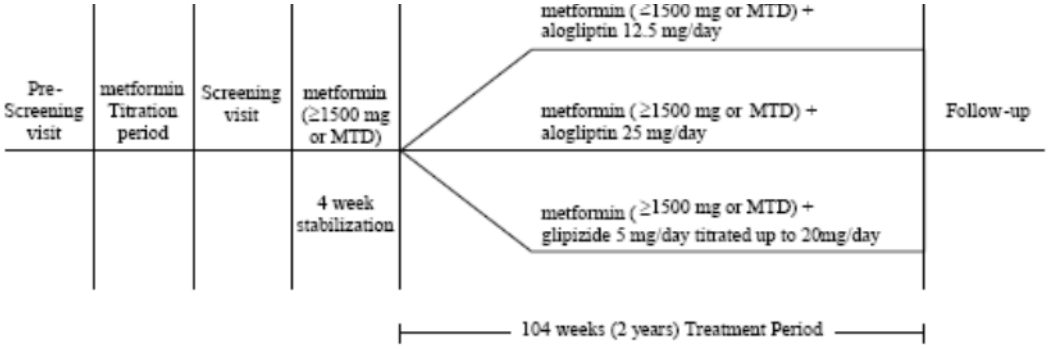
change in A1C from baseline at weeks 52 and 104. Schematics of the Study 305 trial design are presented in Figure 3 and Figure 4.

FIGURE 3: TRIAL DESIGN STUDY 305 — SCHEDULE A



MTD = maximum tolerated dose.
Source: Clinical Study Report 305.[25]

FIGURE 4: TRIAL DESIGN STUDY 305 — SCHEDULE B



MTD = maximum tolerated dose.
Source: Clinical Study Report 305.[25]

Study 302_MET was 26-week, placebo-controlled, seven-group, multi-centre RCT of 784 patients conducted in 15 countries. Patients had type 2 diabetes with inadequate glycemic control (defined as A1C between 7.5% and 10.0%) when treated with diet and exercise for at least two months before screening. Patients were randomized with equal probability to one of seven treatment groups: alogliptin 12.5 mg twice daily + metformin 500 mg twice daily, alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily, alogliptin 12.5 mg twice daily, alogliptin 25 mg once daily, metformin 500 mg twice daily, metformin 1,000 mg twice daily, and placebo twice daily (monotherapy groups consisted of appropriate placebos to mask treatment assignment in a double-dummy fashion). The primary objective of Study 302_MET was to evaluate the efficacy of alogliptin plus metformin compared with alogliptin alone and metformin alone on change in A1C from baseline at week 26. Based on the review protocol, only the findings from the alogliptin + metformin groups, metformin twice daily groups, and placebo group are presented in this review.

FIGURE 5: TRIAL DESIGN STUDY 302_MET

	Screening Period	Placebo Run-in/ Stabilization Period		Double-blind Treatment Period (Weeks 1-26 After Randomization)								End-of-Study/ Early Termination	Follow-up Period
Week	-6 to -5	-4	-1	Baseline Visit (Day 1)	1	2	4	8	12	16	20	26	28
Beginning Day		-28	-7	1	8	15	29	57	85	113	141	183	197
Window		±2	±2		±2	±2	±2	±7	±7	±7	±7	±7	±7

Source: Clinical Study Report 302.[23]

3.2.2 Populations

a) Inclusion and exclusion criteria

Eligibility criteria for Studies 007, 008, 305, and 302_MET were very similar. Patients were required to have inadequate glycemic control, most frequent defined as A1C of 7.0% to 10.0%. However, the minimum level for inclusion was as high as 7.5% (Study 302_MET), and the maximum level for inclusion was as low as 9.0% (Study 305). Patients were required to have inadequate glycemic control following treatment with an SU in Study 007, metformin in Studies 008 and 305, and diet and exercise in Study 302_MET. Patients were required to receive at least 10 mg of glyburide (or MTD 5 mg glyburide or greater) in Study 007. Patients were required to receive ≥ 1,500 mg metformin (Study 008 and Study 305 Schedule A), < 1,500 mg metformin with MTD (Study 305), or < 1,500 mg metformin without documented MTD (Study 305 Schedule B). Patients were excluded if they were treated with any antidiabetes drug other than what was specified for inclusion at three months (Study 007 and Study 008) or two months (Study 305 Schedule A) before screening. Patients in Study 302_MET were required to receive less than seven days of antidiabetes treatment in the two months before screening.

b) Baseline characteristics

Demographic and baseline characteristics of patients in Studies 007, 008, 305, and 302_MET are outlined in Table 7, Table 8, and Table 9. The proportion of male and female patients was approximately equal across the four studies. Proportions were also generally similar across treatment groups within studies, with the exception of Study 302_MET, in which the proportion of females was as low as 44% and as high as 59%.

The mean age of participants was similar among the four studies (56.6, 54.7, 56.0, and 53.5 years of age in Studies 007, 008, 305, and 302_MET, respectively), as well as among treatment groups within studies. Mean body mass index (BMI) at baseline was similar among the four included studies (30.11 kg, 31.83 kg, 31.22 kg, and 30.71 kg for Studies 007,008, 305, and 302_MET, respectively). The median BMI exceeded 30 kg/m^2 in Studies 008, 302_MET, and 305, indicating that the majority of study participants would be classified as class I obese according to World Health Organization definitions. Baseline BMI was similar among treatment groups in all four included studies.

Mean baseline A1C was lowest in Study 305 (7.60%), followed by Studies 008 (7.93%), 007 (8.09%), and 302_MET (8.43%). Baseline A1C was similar across treatment groups in all four studies. Mean FPG was generally similar among treatment groups in Studies 007, 008, and 302_MET, ranging from 9.54 mmol/L to 9.84 mmol/L, 9.34 mmol/L to 9.96 mmol/L, and 9.76 mmol/L to 10.35 mmol/L, respectively. However, FPG was considerably lower among treatment groups in Study 305, ranging from 8.19 mmol/L to 8.29 mmol/L. Mean duration of type 2 diabetes was shorter for patients in Study 302_MET among treatment

groups (3.65 years to 4.25 years) when compared with Study 007 (7.71 years), Study 008 (6.11 years), and Study 305 (5.52 years). Mean glyburide doses were similar among treatment groups in Study 007, ranging from 11.2 mg (alogliptin 12.5 mg group) to 12.4 mg (placebo group). In Study 008, mean metformin doses were generally similar among treatment groups, ranging from 1,837 mg (alogliptin 12.5 mg group) to 1,868 mg (placebo group). In Study 305, metformin doses were generally similar, ranging from 1,823 mg (glipizide group) to 1,837 mg (alogliptin 25 mg group).

TABLE 7: SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS FROM STUDIES 007 AND 008

Characteristics	007			008		
	ALO 12.5 mg + GLY (N = 203)	ALO 25 mg + GLY (N = 198)	PL + GLY (N = 99)	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
Female (%)	92 (45.3)	99 (50.0)	48 (48.5)	112 (52.6)	96 (45.7)	54 (51.9)
Age (year), mean (SD)	56.5 (11.1)	56.5 (11.7)	57.1 (10.1)	55.2 (10.6)	53.6 (10.5)	56.0 (10.6)
Weight (kg), mean (SD)	82.1 (17.7)	80.3 (18.7)	81.4 (21.3)	87.7 (18.4)	88.1 (19.5)	89.3 (20.4)
BMI (kg/m^2), mean (SD)	30.2 (4.8)	30.0 (4.8)	30.0 (5.3)	31.6 (5.2)	31.8 (5.3)	32.4 (5.8)
A1C (%), mean (SD)	8.1 (0.8)	8.1 (0.9)	8.2 (0.8)	7.9 (0.7)	7.9 (0.8)	8.0 (0.9)
FPG (mmol/L), mean (SD)	9.54 (2.81)	9.65 (2.71)	9.84 (2.90)	9.34 (2.44)	9.54 (2.54)	9.96 (2.79)
T2DM duration (years), mean (SD)	7.8 (6.1)	7.6 (6.0)	7.7 (5.3)	6.2 (5. 1)	5.9 (4.3)	6.3 (5.4)
GLY dose (mg), mean (SD)	12.3 (4.5)	12.4 (4.5)	11.2 (4.1)	NA	NA	NA
MET dose (mg), mean (SD)	NA	NA	NA	1,837.1 (479.2)	1,845.9 (470.3)	1,868.0 (444.6)

A1C = glycated hemoglobin; ALO = alogliptin; BMI = body mass index; FPG = fasting plasma glucose; GLY = glyburide; MET = metformin; NA = not applicable; PL = placebo; SD = standard deviation; T2DM = type 2 diabetes mellitus.
Source: Clinical Study Reports for Study 007[26] and Study 008.[21]

TABLE 8: SUMMARY OF BASELINE CHARACTERISTICS STUDY 305

Characteristics	305		
	MET + ALO 12.5 mg (N = 880)	MET + ALO 25 mg (N = 885)	MET + GLZ (N = 874)
Female (%)	461 (52.4)	433 (48.9)	433 (49.5)
Age (year), mean (SD)	55.2 (9.6)	55.5 (9.8)	55.4 (9.6)
Weight (kg), mean (SD)	85.3 (19.0)	86.3 (19.3)	85.6 (18.5)
BMI (kg/m^2), mean (SD)	31.3 (5.4)	31.3 (5.3)	31.1 (5.3)
A1C (%), mean (SD)	7.6 (0.6)	7.6 (0.6)	7.6 (0.6)
FPG (mmol/L), mean (SD)	8.26 (1.90)	8.29 (1.89)	8.19 (1.85)
T2DM duration (years), mean (SD)	5.7 (5.3)	5.4 (4.7)	5.5 (4.9)
Add-on therapy, MET Mean (SD) dose	1,825.2 (405.6)	1,837.2 (373.1)	1,823.4 (390.6)

A1C = glycated hemoglobin; ALO = alogliptin; BMI = body mass index; FPG = fasting plasma glucose; GLZ = glipizide; MET = metformin; SD = standard deviation; T2DM = type 2 diabetes mellitus.
Source: Clinical Study Report for Study 305.[25]

TABLE 9: SUMMARY OF BASELINE CHARACTERISTICS STUDY 302_MET

Characteristics	302_MET						
	ALO 25 mg q.d. (N = 112)	ALO 12.5 mg b.i.d. (N = 113)	MET 500 mg b.i.d. (N = 114)	MET 1,000 mg b.i.d. (N = 111)	ALO 12.5 mg + MET 500 mg b.i.d. (N = 111)	ALO 12.5 mg + MET 1,000 mg b.i.d. (N = 114)	PL (N = 109)
Female, n (%)	64 (57.1)	50 (44.2)	67 (58.8)	60 (54.1)	63 (56.8)	52 (45.6)	54 (49.5)
Age (year), mean (SD)	52.6 (9.4)	53.7 (9.7)	54.6 (10.2)	52.6 (11.3)	53.7 (11.6)	54.6 (10.4)	53.1 (9.6)
Weight (kg), mean (SD)	81.8 (17.3)	82.8 (17.5)	81.7 (17.1)	81.8 (17.6)	82.7 (16.5)	86.6 (17.5)	86.9 (17.4)
BMI (kg/m^2), mean (SD)	30.8 (5.2)	30.4 (5.2)	30.2 (4.8)	30.5 (5.0)	30.9 (5.4)	31.0 (5.4)	31.2 (5.3)
A1C (%), mean (SD)	8.3 (0.8)	8.4 (0.7)	8.5 (0.8)	8.4 (0.7)	8.5 (0.8)	8.4 (0.7)	8.5 (0.7)
FPG (mmol/L), mean (SD)	9.86 (2.90)	9.82 (2.40)	10.01 (2.75)	10.06 (2.90)	9.76 (2.82)	10.24 (2.79)	10.35 (2.49)
T2DM duration (years), mean (SD)	3.7 (4.1)	4.0 (4.8)	3.8 (3.9)	4.1 (4.6)	4.1 (4.8)	4.2 (5.0)	4.3 (4.8)

A1C = glycated hemoglobin; ALO = alogliptin; b.i.d. = twice daily; BMI = body mass index; FPG = fasting plasma glucose; MET = metformin; PL = placebo; SD = standard deviation; q.d. = once daily; T2DM = type 2 diabetes mellitus.
Source: Clinical Study Reports for Study 302_MET.[23]

3.2.3 Interventions

Alogliptin, supplied as tablets (12.5 mg or 25 mg), was administered once daily in Studies 007, 008, and 305. In Study 302_MET, alogliptin was administered once daily as monotherapy or co-administered with metformin twice daily. A double-dummy design (i.e., placebos matching metformin and alogliptin) were used to ensure masking in all treatment groups.

In Study 007, glyburide was administered in an open-label fashion in accordance with the instructions provided on the approved package label. Similarly, in Study 008, metformin was administered in an open-label fashion in accordance with instructions provided on the approved package label as the generic, immediate-release formulation. Patients in both studies were eligible for hyperglycemic rescue if FPG was 15.27 mmol/L or greater between weeks 1 and 4, 13.88 mmol/L or greater between weeks 4 and 8, or 12.49 mmol/L or greater between weeks 8 and 12, or if A1C 8.5% or greater *and* there was a 0.5% or less reduction in A1C from baseline after week 12 until study end. (Rescue treatments were not specified.) Patients who met the criteria for rescue were considered to have completed the study at the time of rescue (i.e., they did not contribute any further outcomes data, and the last observation was carried forward to week 26).

In Study 305, over-encapsulated glipizide 5 mg and matching placebo were indistinguishable in appearance and packaging. Between weeks 2 and 20, glipizide (or matching placebo in the alogliptin groups) was titrated up to a maximum daily dose of 20 mg in increments of 5 mg daily at four-week intervals if there was persistent hyperglycemia (i.e., FPG greater than 13.88 mmol/L confirmed by a repeat FPG test within seven days, after at least two weeks of treatment). Metformin was administered in an open-label fashion as the generic immediate-release formulation. All patients received a minimum dose of 1,500 mg daily during the titration or stabilization period; however, if there was documentation from screening or pre-screening that a dose of ≥ 1,500 mg metformin was not tolerated, the patient

participated in the study at the MTD. The metformin dose was to be kept unchanged throughout the study. After week 20 and before week 26, patients in Study 305 were rescued if A1C was greater than 8.5%. (Rescue treatments were not specified.) Between weeks 26 and 52, patients were rescued if A1C was greater than 8.0% and there was less than 0.5% reduction from baseline. Between 52 weeks and the end of the study, patients were rescued if A1C was greater than 7.5% and there was less than 0.5% reduction from baseline. Patients who were rescued were withdrawn from the study.

Study 302_MET adopted a double-dummy design to maintain blinding. Alogliptin or alogliptin placebo and metformin or metformin placebo were supplied as over-encapsulated tablets that were identical in appearance and packaging. Patients in this study were eligible for hyperglycemic rescue with an SU (chosen and dosed at the investigator's discretion) if FPG was greater than 15.27 mmol/L between weeks 1 and 4, greater than 13.88 mmol/L between weeks 4 and 8, greater than 12.49 mmol/L between weeks 8 and 12, or A1C was greater than 8.5% and there was less than 0.5% reduction from baseline after week 12. Patients who were rescued continued in the study on their assigned double-blind study medication.

3.2.4 Outcomes

a) Glycemic control

The primary efficacy outcome for Studies 007, 008, and 302_MET was the change in A1C levels from baseline at 26 weeks. For Study 305, the co-primary efficacy outcomes were change in A1C levels from baseline at 52 and 104 weeks. The National Institute for Health and Care Excellence (NICE) in the UK has indicated that a reduction from baseline in A1C as small as –0.5% has clinical importance, and the FDA has found that a reduction of –0.7% is clinically significant.[27,28]

Secondary glycemic control end points for all studies included change from baseline in FPG at various time points and proportion of patients with A1C less than 7.0%.

b) Hypoglycemia

Two levels of hypoglycemia intensity were defined in all trials: mild to moderate and severe hypoglycemia. In Studies 007, 008, and 305, mild to moderate hypoglycemia was defined as a blood glucose level less than 3.33 mmol/L in the presence of symptoms, or a blood glucose level less than 2.78 mmol/L with or without symptoms. In Study 302_MET, mild to moderate hypoglycemia was defined as a plasma glucose level less than 3.89 mmol/L (regardless of symptoms).

In Studies 007, 008, and 305, severe hypoglycemia was defined as any episode requiring the assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions, associated with a documented blood glucose level less than 3.33 mmol/L (unless the clinical situation made obtaining a blood glucose measurement difficult, e.g., if it involved coma or seizure). The definition of severe hypoglycemia was similar in Study 302_ MET, except that the threshold was a documented plasma glucose level less than 3.89 mmol/L.

c) Other protocol-specified outcomes

Changes from baseline body weight were measured at various time points in all studies. No data pertaining to quality of life measures were reported.

3.2.5 Statistical analysis

a) Efficacy criteria

The primary statistical analysis plans for Studies 007 and 008 were identical. The primary analysis for both studies was an analysis of covariance (ANCOVA) model for the primary end point, change in A1C levels from baseline at 26 weeks, using data from the full analysis set (FAS) with last observation carried forward (LOCF). A step-down strategy was employed; the alogliptin 12.5 mg dose was compared with placebo only if the comparison between alogliptin 25 mg and placebo was statistically significant (based on a two-sided test at a significance level of 0.05). Study treatment and geographic region were treated as categorical variables, while baseline glyburide dose (Study 007), baseline metformin dose (Study 008), and baseline A1C level were treated as continuous covariates. Sensitivity analyses were conducted with each efficacy variable using observed, rather than LOCF, values.

Target enrolment for both studies was at least 500 patients for Studies 007 and 008, based on a randomization ratio of 1:2:2 (placebo: alogliptin 12.5 mg: alogliptin 25 mg). For a comparison of either alogliptin dose versus placebo using a two-sample *t*-test, Study 007 had 94% power to detect a treatment group difference in change in A1C level from baseline as small as 0.4% at a significance level of 0.05, assuming a standard deviation of 0.8% and at least 80% of randomized patients with evaluable data for the per protocol set (PPS). For Study 008, the only difference was that the study was estimated to have 95% power to detect a treatment difference of 0.4% in change in A1C level from baseline. No adjustments were made for multiple comparisons in either study.

In Study 305, the primary analysis of the primary end point, change in A1C level from baseline at 52 and 104 weeks, was conducted using an ANCOVA model with data from the PPS using LOCF. Study treatment, geographic region, and the study schedule (A or B) to which the patient was randomized were treated as class effects, and the baseline A1C level and baseline metformin dose were treated as continuous covariates. The primary analyses of change in A1C level from baseline at 52 weeks and 104 weeks were reported as one-sided intervals assessed at a 0.0125 significance level. The following four null hypotheses were tested:

- alogliptin 25 mg is inferior in terms of change in A1C level from baseline versus glipizide
- alogliptin 12.5 mg is inferior in terms of change in A1C level from baseline versus glipizide
- alogliptin 25 mg is not superior in terms of change in A1C level from baseline versus glipizide
- alogliptin 12.5 mg is not superior in terms of change in A1C level from baseline versus glipizide.

Sensitivity analyses were conducted for each efficacy variable using observed values as well as a repeated measures analysis for A1C and FPG.

A total of 815 patients per treatment group (2,445 patients overall) ensured at least 95% power to declare non-inferiority between either alogliptin dose (12.5 or 25 mg) and glipizide, either at week 52 or week 104, assuming a non-inferiority margin of 0.3%, no difference between either alogliptin dose and glipizide, a standard deviation for change in A1C level from baseline of 1.2%, an evaluability (i.e., protocol adherence rate) rate of 60%, and a one-sided 0.0125 significance level. For secondary and exploratory analyses, no statistical adjustments were made for multiple comparisons.

In Study 302, the primary efficacy analysis (analysis 1a) was conducted using an ANCOVA model with data from the FAS using LOCF. The primary efficacy end point was change in A1C level from baseline at week 26. Treatment and geographic region were treated as fixed effects, and baseline A1C as a continuous covariate. The primary efficacy analysis consisted of the following comparisons between combination alogliptin/metformin therapy and monotherapy:

- alogliptin 12.5 mg twice daily + metformin 500 mg twice daily versus alogliptin 12.5 mg twice daily
- alogliptin 12.5 mg twice daily + metformin 500 mg twice daily versus metformin 500 mg twice daily
- alogliptin 12.5 mg twice daily +metformin 1,000 mg twice daily versus alogliptin 12.5 mg twice daily
- alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily versus metformin 500 mg twice daily.

The null hypothesis corresponding to each set of comparisons was that the combination of alogliptin and metformin had no additional effect on glycemic control (as measured by change in A1C level from baseline) at week 26 (or at time of discontinuation of double-blind study medication or hyperglycemic rescue), either when compared with the constituent dose of alogliptin or with the constituent dose of metformin. The null hypothesis was rejected only if both comparisons between a combination and its components as monotherapy were statistically significant at the two-sided 0.025 level.

Analysis 1a included only data collected on or after baseline and within one day (seven days for A1C) after the last dose of double-blind study medication, unless a patient was rescued for hyperglycemia, in which case only data collected on or before the date of rescue was used. At each visit, the end point was analyzed using the value collected at that visit or, if the value at that visit was unavailable, LOCF. In analysis 1b, only observed end point values were analyzed for a given visit. Analyses 2a and 2b included data collected on or after baseline and within seven days of the last double-blind study medication, irrespective of hyperglycemic rescue therapy. Analysis 2a had the same criteria for analysis of end point data as analysis 1a (i.e., LOCF was used). Analysis 2b had the same criteria for end point value analysis as analysis 1b. Only the results from analysis 1a are presented in this review.

A total of 105 patients per treatment group (735 patients overall) ensured at least 90% power to declare that either of the alogliptin + metformin combinations was statistically superior to its constituent monotherapy doses of alogliptin and metformin. This power calculation assumed a treatment effect of 0.55% between combination therapy and constituent monotherapy, a standard deviation of 1.0%, and a two-sided false-rejection rate of 2.5%. Alternatively, this sample size provided 90% power to detect a treatment effect of approximately 0.45% between any pair of treatment groups, assuming a standard deviation of 1.0% and a two-sided false-rejection rate of 5%.

Missing data
Missing values were imputed with the last post-baseline value using the LOCF method in all included trials.

b) Analysis populations
Three datasets were analyzed in all four studies.[18,21,23,25] The datasets were defined as follows:
Safety set: All patients who took at least one dose of double-blind study drug. In safety summaries, patients were analyzed according to the most frequent treatment they received.

Full analysis set (FAS): All randomized patients in the safety set. For a particular variable, the FAS analysis consisted of all patients who had a baseline assessment and at least one post-baseline assessment for the variable.

Per protocol set (PPS): All FAS patients who had no major protocol violations.

3.3 Patient Disposition

The disposition of patients is presented in Table 10, Table 11, and Table 12. The overall rate of study discontinuation among randomized patients was 9.6% in Study 007, 9.9% in Study 008, 21.9% in Study 305, and 22.3% in Study 302_MET. Discontinuation rates were similar between alogliptin and comparator groups within each study. The most common reason for discontinuation was withdrawal of consent in Studies 007 (4.4%), 008 (3.4%), and 302_MET (8.4%), and adverse events in Study 305 (8.2%). More patients in the placebo groups received hyperglycemic rescue than in the alogliptin groups in Studies 007 (28.3% versus 15.2%) and 008 (24.0% versus 8.5%), while rates of hyperglycemic rescue were similar among all groups in Study 305 and were not reported in Study 302_MET. In Study 007, similar proportions of patients completed the study in the alogliptin treatment groups (75.4% and 74.7%). However, a lower proportion of patients completed the study in the placebo group (62.6%). In Study 008, a greater proportion of patients completed the study in the alogliptin 12.5 mg and 25 mg groups (82.6% and 78.6%, respectively) compared with those in the placebo group (69.2%). Completion rates were lower in Study 305 but comparable across groups, while in Study 302, more than 80% of patients completed the study in the alogliptin + metformin and metformin groups compared with 67.9% of patients in the placebo group.

The difference in PPS and FAS was greatest in Study 305, in which only between 38% and 44% of enrolled patients were included in the PPS.

TABLE 10: SUMMARY OF PATIENT DISPOSITION FROM STUDIES 007 AND 008

Disposition	Study 007			Study 008		
	ALO 12.5 mg + GLY (N = 203)	ALO 25 mg + GLY (N = 198)	PL + GLY (N = 99)	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
Screened	585			596		
Randomized, N	203	198	99	213	210	104
Full analysis set	203 (100.0)	198 (100.0)	99 (100.0)	213 (100.0)	207 (98.6)[a]	104 (100.0)
Safety analysis set	203 (100.0)	198 (100.0)	99 (100.0)	213 (100.0)	207 (98.6)[a]	104 (100.0)
PP analysis set	187 (92.1)	187 (94.4)	93 (93.9)	193 (90.6)	185 (88.1)	94 (90.4)
Completed, N (%)	153 (75.4)	148 (74.7)	62 (62.6)	176 (82.6)	165 (78.6)	72 (69.2)
Withdrawn, N (%)	50 (24.6)	50 (25.3)	37 (37.4)	36 (17.4)	45 (21.4)	32 (30.8)
Hyperglycemic rescue[b]	30 (14.8)	31 (15.7)	28 (28.3)	19 (8.9)	17 (8.1)	25 (24.0)
Discontinued, N (%)	20 (9.9)	19 (9.6)	9 (9.1)	17 (8.0)	28 (13.3)	7 (6.7)
Adverse event	6 (3.0)	4 (2.0)	2 (2.0)	7 (3.3)	6 (2.9)	1 (1.0)
Lost to follow-up	1 (0.5)	2 (1.0)	1 (1.0)	5 (2.3)	2 (1.0)	1 (1.0)
PI discretion	2 (1.0)	1 (0.5)	3 (3.0)	1 (0.5)	1 (0.5)	1 (1.0)
Protocol violation	3 (1.5)	1 (0.5)	0	2 (0.9)	4 (1.9)	2 (1.9)
Withdrawal of consent	8 (3.9)	11 (5.6)	3 (3.0)	2 (0.9)	14 (6.7)	2 (1.9)
Other	0	0	0	0	1 (0.5)	0

ALO = alogliptin; GLY = glyburide; MET = metformin; PI = principal investigator; PL = placebo; PP = per protocol.
[a] Three randomized patients in the 25 mg alogliptin group did not receive the double-blind study drug.
[b] Hyperglycemic rescue and discontinued dispositions were mutually exclusive groups, i.e., those patients rescued owing to hyperglycemia were not counted as having discontinued.
Source: Clinical Study Reports for Study 007[26] and Study 008.[21]

TABLE 11: SUMMARY OF PATIENT DISPOSITION FROM STUDY 305

Disposition	Study 305		
	MET + ALO 12.5 mg (N = 880)	MET + ALO 25 mg (N = 885)	MET + GLZ (N = 874)
Screened, N	5,789		
Randomized, N (%)	880	885	874
Full analysis set	873 (99.2)	878 (99.2)	869 (99.4)
PP analysis set	371 (42.2)	382 (43.2)	336 (38.4)
Safety analysis	873 (99.2)	878 (99.2)	870 (99.7)
Completed, N (%)	472 (53.6)	493 (55.7)	427 (48.9)
Withdrawn, N (%)	408 (46.4)	392 (44.3)	446 (51.1)
Hyperglycemic rescue[a]	231 (26.3)	201 (22.7)	235 (26.9)
Discontinued, N (%)	177 (20.1)	191 (21.6)	211 (24.1)
Adverse event	60 (6.8)	74 (8.4)	82 (9.4)
Major protocol deviation	24 (2.7)	16 (1.8)	15 (1.7)
Lost to follow-up	20 (2.3)	22 (2.5)	28 (3.2)
Voluntary withdrawal	48 (5.5)	52 (5.9)	62 (7.1)
Other	13 (1.5)	10 (1.1)	7 (0.8)
PI discretion	9 (1.0)	8 (0.9)	10 (1.1)

ALO = alogliptin; GLZ = glipizide; MET = metformin; PI = principal investigator; PP = per protocol.
[a] Hyperglycemic rescue and discontinued dispositions were mutually exclusive groups, i.e., those patients rescued owing to hyperglycemia were not counted as having discontinued.
Source: Clinical Study Report for Study 305.[25]

TABLE 12: PATIENT DISPOSITION STUDY 302_MET

Disposition	302_MET						
	ALO 25 mg q.d. (N = 112)	ALO 12.5 mg b.i.d. (N = 113)	MET 500 mg b.i.d. (N = 114)	MET 1,000 mg b.i.d. (N = 111)	ALO 12.5 mg + MET 500 mg b.i.d. (N = 111)	ALO 12.5 mg + MET 1,000 mg b.i.d. (N = 114)	PL (N = 109)
Screened, N	2,478						
Randomized, N (%)	112 (100)	113 (100)	114 (100)	111 (100)	111 (100)	114 (100)	109 (100)
Full analysis Set	112 (100.0)	110 (97.3)	109 (95.6)	111 (100)	106 (95.5)	114 (100)	106 (97.2)
PP analysis set	85 (75.9)	70 (61.9)	83 (72.8)	91 (82.0)	85 (76.6)	88 (77.2)	84 (77.1)
Safety analysis set	112 (100.0)	110 (97.3)	109 (95.6)	111 (100.0)	106 (95.5)	114 (100.0)	106 (97.2)
Completed, N (%)	89 (79.5)	71 (62.8)	94 (82.5)	95 (85.6)	92 (82.9)	94 (82.5)	74 (67.9)
Discontinued, N (%)	23 (20.5)	42 (37.2)	20 (17.5)	16 (14.4)	19 (17.1)	20 (17.5)	35 (32.1)
Adverse event	4 (3.6)	7 (6.2)	3 (2.6)	2 (1.8)	5 (4.5)	11 (9.6)	4 (3.7)
Hyperglycemic	NR	NR	NR	NR	NR	NR	NR

Disposition	302_MET						
	ALO 25 mg q.d. (N = 112)	ALO 12.5 mg b.i.d. (N = 113)	MET 500 mg b.i.d. (N = 114)	MET 1,000 mg b.i.d. (N = 111)	ALO 12.5 mg + MET 500 mg b.i.d. (N = 111)	ALO 12.5 mg + MET 1,000 mg b.i.d. (N = 114)	PL (N = 109)
rescue							
Major protocol deviation	0	3 (2.7)	0	0	0	0	2 (1.8)
Lost to follow-up	8 (7.1)	7 (6.2)	2 (1.8)	5 (4.5)	2 (1.8)	2 (1.8)	4 (3.7)
Voluntary withdrawal	8 (7.1)	16 (14.2)	10 (8.8)	6 (5.4)	8 (7.2)	5 (4.4)	13 (11.9)
PI discretion	0	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)	2 (1.8)
Pregnancy	0	0	2 (1.8)	0	1 (0.9)	0	0
Lack of efficacy	3 (2.7)	6 (5.3)	2 (1.8)	1 (0.9)	2 (1.8)	1 (0.9)	9 (8.3)
Other	0	1 (0.9)	0	1 (0.9)	0	0	1 (0.9)

ALO = alogliptin; b.i.d. = twice daily; MET = metformin; NR = not reported; PI = principal investigator; PL = placebo; q.d. = once daily.
Source: Clinical Study Report for Study 302.[23]

3.4 Exposure to Study Treatments

3.4.1 Investigational products

A summary of exposure to study treatments during the double-blind treatment period is presented in Table 13, Table 14, and Table 15. Mean treatment duration was similar among all groups within each study for Studies 007, 008, and 305, ranging from approximately 22 to 24 weeks. In Study 305, mean exposure was slightly higher in the alogliptin 12.5 mg and 25 mg groups (76.6 weeks and 78.2 weeks, respectively) compared with the glipizide group (73.1 weeks).

In Study 305, the mean final and mean maximum glipizide doses were both 5.2 mg.

TABLE 13: DURATION OF EXPOSURE TO INVESTIGATIONAL PRODUCTS IN STUDIES 007 AND 008

Exposure	007			008		
	ALO 12.5 mg + GLY (N = 203)	ALO 25 mg + GLY (N = 198)	PL + GLY (N = 99)	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
Mean (SD; weeks)	23.1 (6.1)	23.5 (5.3)	21.8 (6.4)	23.8 (5.8)	23.4 (6.3)	21.9 (7.1)
Median (weeks)	26.0	25.9	25.7	26.0	26.0	26.0
Range (weeks)	0.3 to 28.0	2.0 to 28.1	1.0 to 27.7	1.1 to 29.1	0.9 to 29.7	2.6 to 27.7

ALO = alogliptin; GLY = glyburide; MET = metformin; PL = placebo; SD = standard deviation.
Source: Clinical Study Reports for Study 007[26] and Study 008.[21]

TABLE 14: DURATION OF EXPOSURE TO INVESTIGATIONAL PRODUCTS IN STUDY 305

Exposure	305		
	MET + ALO 12.5 mg (N = 880)	MET + ALO 25 mg (N = 885)	MET + GLZ (N = 874)
Mean (SD; weeks)	76.6 (35.1)	78.2 (34.7)	73.1 (36.5)
Median (weeks)	103.0	103.1	96.9
Range (weeks)	0.3 to 107.7	0.1 to 111.1	0.6 to 108.4

ALO = alogliptin; GLZ = glipizide; MET = metformin; SD = standard deviation.
Source: Clinical Study Report for Study 305.[25]

TABLE 15: DURATION OF EXPOSURE TO INVESTIGATIONAL PRODUCTS IN STUDY 302_MET

Exposure	302_MET						
	ALO 25 mg q.d. (N = 112)	ALO 12.5 mg b.i.d. (N = 110)	MET 500 mg b.i.d. (N = 114)	MET 1,000 mg b.i.d. (N = 111)	ALO 12.5 mg + MET 500 mg b.i.d. (N = 111)	ALO 12.5 mg + MET 1,000 mg b.i.d. (N = 114)	PL (N = 109)
Mean (SD; weeks)	22.4 (7.9)	20.6 (8.7)	23.1 (7.7)	23.6 (6.7)	23.8 (6.5)	23.1 (7.6)	22.0 (7.2)
Median (weeks)	26.1	25.9	26.14	26.0	26.1	26.1	25.9
Range (weeks)	1.1 to 27.4	0.1 to 28.0	0.1 to 29.0	1.1 to 28.7	1.1 to 27.6	0.1 to 31.3	0.1 to 30.0

ALO = alogliptin; b.i.d. = twice daily; MET = metformin; PL = placebo; q.d. = once daily; SD = standard deviation.
Source: Clinical Study Report for Study 302.[23]

3.4.2 Concomitant medications

Treatment with antidiabetes drugs other than an SU (in Study 007) or metformin (in Study 008) was not allowed within three months before screening through to completion of treatment in Studies 007 and 008. For Study 305, treatment with antidiabetes drugs other than metformin was not allowed within two months before screening through to completion of treatment. Furthermore, treatment with DPP-4 inhibitors or GLP-1 analogues was not allowed within 90 days before screening and during the stabilization period. For Study 302_MET, no treatment with any antidiabetes drug was allowed within two months of screening and during the four-week stabilization period. After randomization and until the end of study treatment, an SU for hyperglycemic rescue was the only additional antidiabetes drug allowed. The exception in all studies was use of other antidiabetes therapy for less than seven days within the two months (Studies 302_MET and 305) or three months (Studies SU-007 and MET-008) before the screening period.

3.5 Critical Appraisal

3.5.1 Internal validity

The included trials demonstrated a number of methodological strengths. Participants were randomized using an interactive voice/web response system (IVRS/IWRS), which adequately concealed the allocation of participants. Randomization was stratified by A1C level at screening (e.g., less than 8.0% or 8.5% and 8.0% or 8.5% or greater), mitigating the risk of confounding due to chance imbalances in the distribution of baseline A1C values between treatment groups. Double-blinding was maintained by using active and placebo tablets of similar appearance and with similar packaging. Treatment groups were well balanced

with respect to key demographic and disease characteristics such as baseline A1C and FPG levels. Any differences were accounted for in the efficacy analysis by using baseline values as covariates in the ANCOVA analysis. Study end points were appropriately measured and consistent with guidance from the FDA and the European Medicines Agency (EMA) on RCTs for antihyperglycemic treatments.[27,28]

Study 305 was the only included non-inferiority trial. The non-inferiority margin of 0.3% selected by the investigators is reflective of guidance from the FDA and the EMA and is consistent with other trials of antihyperglycemic treatments.[27,28] In Studies 007, 008, and 302_MET, no rationale was provided for the selected superiority margin. The margin for determining superiority of alogliptin versus placebo in terms of A1C levels in Studies 007 and 008 was 0.4%, while Study 302_MET used a margin of 0.55% for comparing dual therapy to monotherapy. No rationale was provided for the margins chosen in any of the included trials.

Hyperglycemic rescue was permitted in all included studies, and patients who were rescued were withdrawn from the trial (Studies 007, 008, and 305) or data collected after rescue were excluded from the primary analysis (Study 302_MET). This allows for between-group effect estimation without confounding by rescue therapy, particularly when there were differences among treatment groups in the proportions of patients requiring rescue (such as in Studies 007 and 008). However, differential rates of withdrawal due to rescue may introduce differences between treatment groups for other characteristics, potentially introducing bias in between-group effect estimates. The proportions of patients requiring rescue were not reported for Study 302_MET; hence, it cannot be determined whether they were balanced among treatment groups.

Comparator doses were generally appropriate, with the possible exception of Study 305. The mean final dose of glipizide (5.2 mg daily) was substantially lower than the 20 mg maximum target dose. This may have been due to the relatively conservative titration algorithm used, which called for increases in glipizide dose between weeks 2 and 20 only if the FPG level was greater than 13.88 mmol/L. The Canadian Diabetes Association guidelines call for timely adjustments to therapy in order to achieve glycemic targets within three to six months;[1] therefore, doses would likely be titrated more aggressively in clinical practice than in Study 305. This aspect, in combination with the low mean baseline A1C level (7.6%), may have biased the results in favour of demonstrating that alogliptin was non-inferior to glipizide.[29]

In Study 305, a large proportion (44% to 51%) of patients withdrew from the study either because of hyperglycemic rescue or premature discontinuation. While total withdrawals and reasons for withdrawal were relatively well balanced across treatment groups, such a high rate of non-completion is a cause for concern, as biases may arise from imbalances between treatment groups over the course of the study. Furthermore, the fact that only 38% to 42% of randomized patients were included in the PPS is a concern with respect to the statistical power of the non-inferiority analysis between alogliptin and glipizide. The power calculations for this trial required an evaluability rate of 60%, assuming a sample size of 815 per treatment group (i.e., 489 patients per group in the PPS). However, the actual PPS included only 336 to 371 patients per treatment group. Therefore, the PPS non-inferiority analysis likely failed to achieve the originally anticipated statistical power of 95%.

3.5.2 External validity

Only Study 305 included Canadian sites, potentially limiting generalizability to Canadian clinical practice, although the majority of sites in the included studies were in North America and Latin America.

The generalizability of Study 302_MET to the target population of interest (i.e., patients with inadequate glycemic control on metformin monotherapy) may be limited because enrolled patients were inadequately controlled on diet and exercise only. If patients were not previously treated with antidiabetic drugs, they may have been more responsive to therapy, potentially reducing the observed differences between alogliptin or metformin monotherapy and alogliptin/metformin combination therapies. However, the observed differences in A1C between alogliptin + metformin dual therapy and metformin monotherapy in Study 008 (which did enrol patients with inadequate glycemic control on metformin monotherapy) were aligned with those observed in 302_MET.

The included studies involved extensive patient contact with health care professionals. This is unlikely to be reflective of routine clinical practice in Canada; therefore, this factor may reduce generalizability of results to the general population with type 2 diabetes.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (see Table 4 in Section 2.2). See APPENDIX 3: DETAILED OUTCOME DATA for detailed efficacy data. For Study 302_MET, results are only presented for the treatment groups that align with the review protocol; hence, findings for alogliptin 12.5 mg once daily and alogliptin 25 mg once daily monotherapy are not reported.

3.6.1 Diabetes-related complications

None of the included studies evaluated outcomes related to macrovascular or microvascular complications of type 2 diabetes.

3.6.2 Glycemic control

a) Glycated hemoglobin

Sulfonylurea combination therapy

Table 16 displays the A1C findings from the FAS of Study 007. Mean baseline A1C values were similar among treatment groups (8.1% to 8.2%). The adjusted mean change from baseline at 26 weeks was –0.4% for the alogliptin 12.5 mg group, –0.5% for the alogliptin 25 mg group, and 0.01% for the placebo group. After 26 weeks, the alogliptin 12.5 mg group and alogliptin 25 mg demonstrated superiority compared with placebo in the FAS (least squares mean difference [LSMD] = –0.4%; 95% confidence interval [CI], –0.6% to –0.2% and LSMD = –0.5%; 95% CI, –0.7% to –0.3%, respectively). The results from the PPS were consistent with the FAS. A greater proportion of patients in the alogliptin 25 mg group (34.8%) and alogliptin 12.5 mg group (29.6%) had a clinical response (A1C less than 7.0%) at 26 weeks compared with the placebo group (18.2%).

Metformin combination therapy

Table 16 displays the A1C findings from the FAS of Study 008. Mean baseline A1C values were similar among treatment groups (7.9% to 8.0%). The adjusted change from baseline to 26 weeks was –0.6% in the alogliptin 12.5 mg group, –0.6% in the alogliptin 25 mg group, and –0.1% in the placebo group. After 26 weeks, the alogliptin 12.5 mg group and alogliptin 25 mg group demonstrated superiority to placebo (LSMD = –0.5%; 95% CI, –0.7% to –0.3% for both groups versus placebo). The results from the PPS were consistent with the FAS. A greater proportion of patients in the alogliptin 12.5 group (51.6%) and alogliptin 25 mg group (44.4%) achieved clinical response at 26 weeks compared with the placebo group (18.3%).

Table 17 displays the within-group changes in A1C from the PPS for Study 305. Mean A1C values were similar among treatment groups (7.6%). The adjusted mean change from baseline at 52 weeks was –0.8% in the alogliptin and glipizide groups. Alogliptin 12.5 mg and alogliptin 25 mg once daily demonstrated non-inferiority compared with glipizide (LSMD = –0.1%; 98.75% CI, 0.00% and LSMD = –0.03%; 95% CI, 0.06%, respectively). The results from the FAS were similar to those in the PPS (Figure 6). At 104 weeks, the adjusted mean change from baseline to 104 weeks was –0.7% in the alogliptin groups and –0.6% in the glipizide group. Alogliptin 12.5 mg and alogliptin 25 mg once daily demonstrated non-inferiority compared with glipizide (LSMD = –0.7%; one-sided 98.75% CI, 0.04% and LSMD = –0.7%; one-sided 98.75% CI, 0.01%, respectively). The results from the FAS were similar to those in the PPS (Figure 7). Similar proportions of patients in the alogliptin 12.5 mg, alogliptin 25 mg, and glipizide groups achieved clinical response (56.4%, 59.2%, and 56.1%, respectively) at 52 weeks and at 104 weeks (45.6%, 48.5%, and 42.8%, respectively).

Table 18 displays the changes in A1C at 26 weeks in Study 302_MET (FAS analysis). Mean baseline A1C values were similar among treatment groups (8.3% to 8.5%). The adjusted changes from baseline A1C values were highest for alogliptin 12.5 mg twice daily + metformin 500 mg twice daily (–1.6%) and alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily (–1.2%) compared with metformin 1,000 mg twice daily (–1.1%), metformin 500 mg twice daily (–0.7%), and placebo (–0.2%). Alogliptin 12.5 mg twice daily + metformin 500 mg twice daily was associated with a statistically significantly greater reduction in change from baseline A1C than metformin 500 mg twice daily monotherapy (LSMD = –0.6%; 95% CI, –0.9% to –0.3%). Alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily was associated with a statistically significantly greater reduction in change from baseline A1C than metformin 1,000 mg twice daily (LSMD = –0.4%; 95% CI, –0.7% to –0.2%). The percentages of patients who achieved clinical response in the co-administration therapy groups (47.1% for alogliptin 12.5 mg twice daily + metformin 500 mg twice daily and 59.5% for alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily groups) was greater than in the metformin 500 mg twice daily (27.2%) and metformin 1,000 mg twice daily (34.3%) groups.

TABLE 16: CHANGES FROM BASELINE IN A1C AT 26 WEEKS IN STUDIES 007 AND 008 (FULL ANALYSIS SET)

Parameter		007			008		
		ALO 12.5 mg + GLY (N = 203)	ALO 25 q.d. mg + GLY (N = 198)	PL + GLY (N = 99)	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
A1C (%)	Baseline, mean (SD)	8.1 (0.8)	8.1 (0.9)	8.2 (0.8)	7.9 (0.7)	7.9 (0.8)	8.0 (0.9)
	End, mean (SD)	7.7 (1.0)	7.6 (1.1)	8.1 (1.2)	7.3 (1.0)	7.3 (0.9)	7.9 (1.0)
	Change from baseline, LSM (SE)	–0.4 (0.1)	–0.5 (0.1)	0.01 (0.1)	–0.6 (0.1)	–0.6 (0.1)	–0.10 (0.076)
	Change from baseline, LSMD (95% CI) versus PL	–0.4[a] (–0.6 to –0.2)	–0.5[a] (–0.7 to –0.3)	NA	–0.5[a] (–0.7 to –0.3)	–0.5[a] (–0.7 to –0.3)	NA

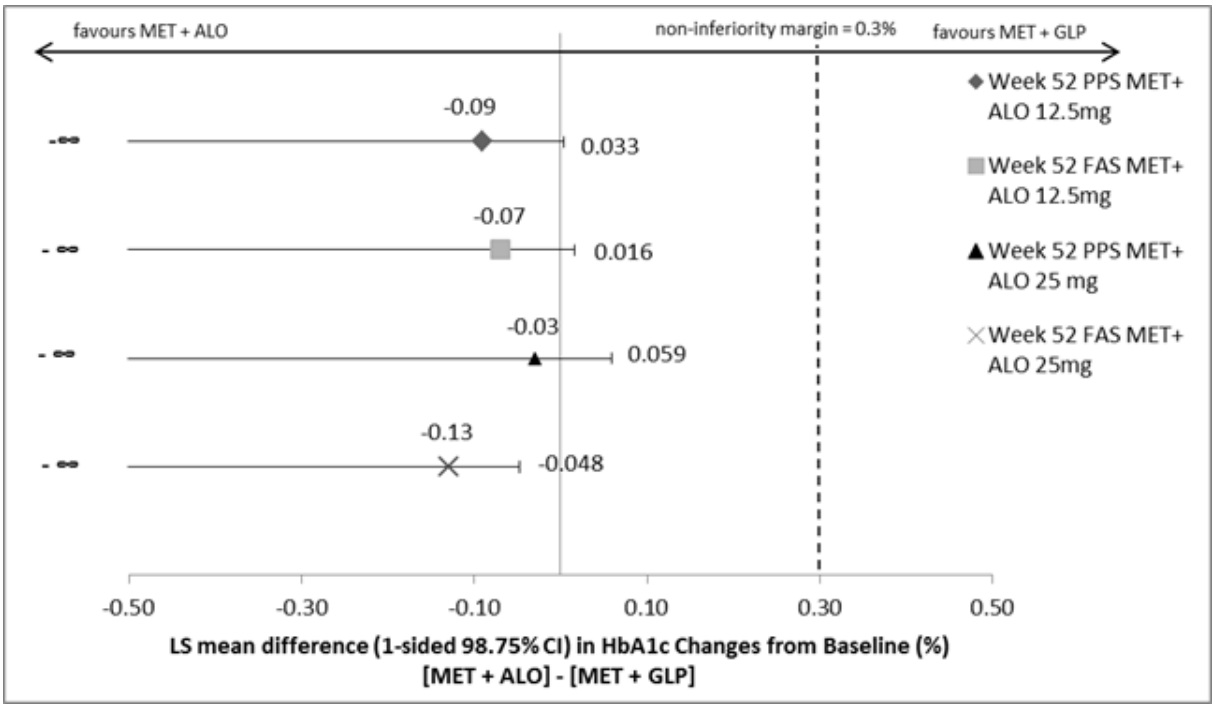
A1C = glycated hemoglobin; ALO = alogliptin; CI = confidence interval; GLY = glyburide; LSM = least squares mean; LSMD = least squares mean difference; MET = metformin; NA = not applicable; PL = placebo; SD = standard deviation; SE = standard error.
[a] $P < 0.001$.
Source: Clinical Study Reports for Study 007[26] and Study 008.[21]

TABLE 17: CHANGES FROM BASELINE IN A1C IN STUDY 305 (PER PROTOCOL SET)

Parameter	305		
	MET + ALO 12.5 mg (N = 867)	MET + ALO 25 mg (N = 867)	MET + GLZ (N = 859)
Baseline, mean (SD)	7.6 (0.6)	7.6 (0.5)	7.6 (0.5)
Week 26 change from baseline, LSM (SE) LSMD versus GLZ (95% CI)	–0.8 (0.0) 0.0 (–0.07 to 0.08)	–0.9 (0.0) 0.01 (–0.07 to 0.08)	–0.8 (0.0) NA
Week 52 change from baseline, LSM (SE) LSMD versus GLZ[a] (1-sided 98.75% CI)	–0.8 (0.0) –0.1[b] (0.00)	–0.8 (0.0) –0.03[b] (0.06)	–0.7 (0.0) NA
Week 104 change from baseline, LSM (SE) LSMD versus GLZ[a] (1-sided 98.75% CI)	–0.7 (0.037) –0.1[b] (0.04)	–0.7 (0.037) –0.1[b] (–0.01)	–0.6 (0.039) NA

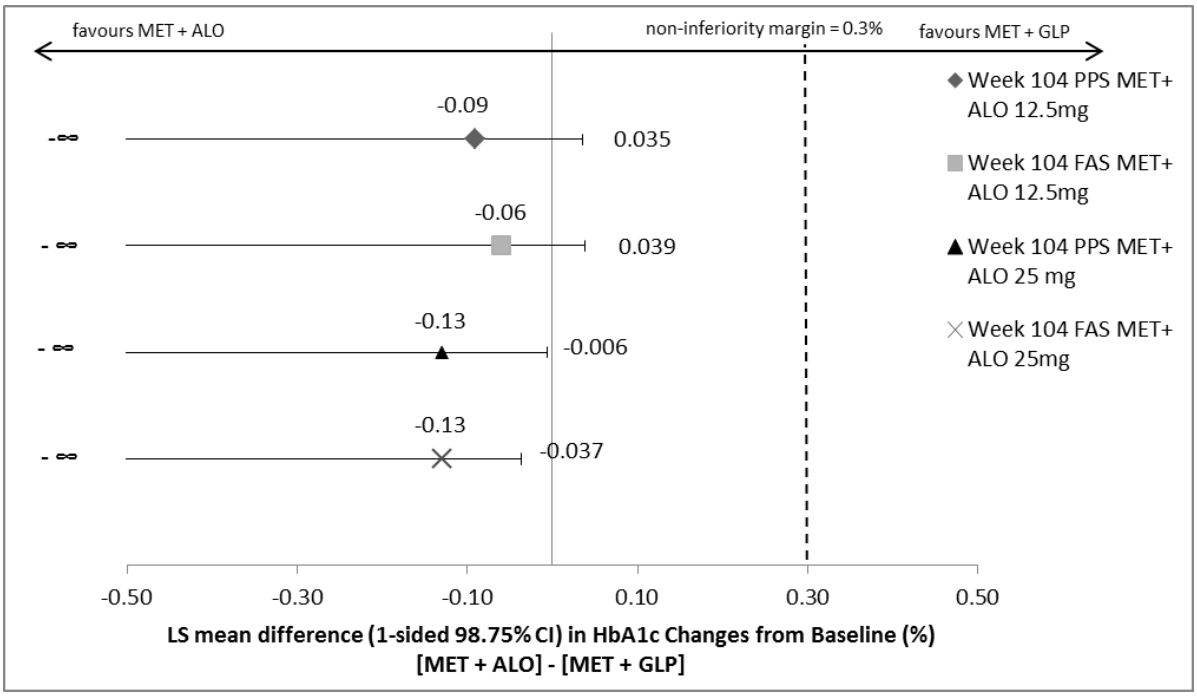
A1C = glycated hemoglobin; ALO = alogliptin; CI = confidence interval; GLZ = glipizide; LSM = least squares mean; LSMD = least squares mean difference; MET = metformin; NA = not applicable; SE = standard error.
[a] In Study 305, a non-inferiority margin of 0.3% difference in A1C was tested with a one-sided significance of 0.0125.
[b] Non-inferiority was confirmed.

FIGURE 6: LEAST SQUARES MEAN DIFFERENCES IN A1C CHANGES FROM BASELINE AT WEEK 52 IN STUDY 305



A1C = glycated hemoglobin; ALO = alogliptin; FAS = full analysis set; GLP = glipizide; LS = least squares; MET = metformin; PPS = per protocol set.
Source: Clinical Study Report for Study 305.[25]

FIGURE 7: LEAST SQUARES MEAN DIFFERENCE IN A1C CHANGES FROM BASELINE AT WEEK 104



A1C = glycated hemoglobin; ALO = alogliptin; FAS = full analysis set; GLP = glipizide; LS = least squares; MET = metformin; PPS = per protocol set.
Source: Clinical Study Report for Study 305.[25]

TABLE 18: CHANGES FROM BASELINE IN A1C (FULL ANALYSIS SET) AT 26 WEEKS IN STUDY 302_MET

Parameter		MET 500 mg b.i.d. (N = 114)	MET 1,000 mg b.i.d. (N = 111)	ALO 12.5 mg b.i.d. + MET 500 mg b.i.d. (N = 111)	ALO 12.5 mg b.i.d. + MET 1,000 mg b.i.d. (N = 114)	PL (N = 109)
A1C (%)	Baseline, mean (SD)	8.5 (0.8)	8.4 (0.7)	8.5 (0.8)	8.4 (0.7)	8.5 (0.7)
	End, mean (SD)	7.8 (1.2)	7.3 (0.9)	7.3 (1.1)	6.9 (0.9)	8.6 (1.2)
	Change from baseline, LSM (SE)	–0.7 (0.1)	–1.1 (0.1)	–1.2 (0.1)	–1.6 (0.1)	0.2 (0.1)
	Change from baseline, LSMD (97.5% CI) versus MET 500 mg	NA	NA	–0.6[a] (–0.9 to –0.3)	NA	NA
	Change from baseline, LSMD (97.5% CI) versus MET 1,000 mg	NA	NA	NA	–0.4[a] (–0.7 to –0.2)	NA
	Change from baseline, LSMD (95% CI) versus PL	NA	NA	–1.4[a] (–1.6 to –1.1)	–1.7 (–2.0 to –1.5)*	NA

A1C = glycated hemoglobin; ALO = alogliptin; b.i.d. = twice daily; CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; MET = metformin; NA = not applicable; PL = placebo; SD = standard deviation; SE = standard error.
[a] $P < 0.001$.
Source: Clinical Study Reports for Study 009[18] and Study 011.[30]

b) Fasting plasma glucose

Sulfonylurea combination therapy

In Study 007, baseline FPG values were similar among treatment groups, ranging from 9.54 mmol/L to 9.84 mmol/L. Adjusted mean changes from baseline FPG levels at 26 weeks were –0.26 mmol/L for alogliptin 12.5 mg, –0.47 mmol/L for alogliptin 25 mg, and 0.12 mg/dL for placebo. After 26 weeks, alogliptin 12.5 mg and alogliptin 25 mg did not demonstrate statistically significantly greater decreases in FPG levels compared with placebo (LSMD = –0.38 mmol/L; 95% CI, –1.02 mmol/L to 0.26 mmol/L and LSMD = –0.58 mmol/L; 95% CI, –1.22 mmol/L to 0.05 mmol/L, respectively) (Table 19).

Metformin combination therapy

In Study 008, baseline FPG values were similar among treatment groups, ranging from 9.34 mmol/L to 9.96 mmol/L. The adjusted changes from baseline at 26 weeks were similar for alogliptin 12.5 mg and alogliptin 25 mg (–0.97 mmol/L and –1.04 mmol/L, respectively) compared with placebo (0.0 mmol/L). At 26 weeks, alogliptin 12.5 mg and alogliptin 25 mg demonstrated statistically significantly greater decreases in FPG levels when compared with placebo (LSMD = –1.04 mmol/L; 95% CI, –1.51 mmol/L to –0.57 mmol/L and LSMD = –0.97; 95 CI%, –1.44 mmol/L to –0.49 mmol/L, respectively) (Table 19).

In Study 305, baseline FPG values were similar among treatment groups, ranging from 8.19 mmol/L to 8.29 mmol/L. The adjusted mean changes from baseline at 52 weeks for alogliptin 12.5 mg and alogliptin 25 mg were –0.28 mmol/L and –0.39 mmol/L, compared with 0.05 mmol/L in the placebo group. At 104 weeks, alogliptin 12.5 mg and alogliptin 25 mg were associated with higher adjusted mean reductions in

FPG within groups (least squares mean –0.05 mmol/L and –0.48 mmol/L, respectively) compared with placebo (least squares mean 0.30 mmol/L). At both 52 and 104 weeks, alogliptin 12.5 mg and 25 mg demonstrated statistically significantly greater reductions in FPG levels compared with placebo (Table 20).

In Study 302_MET, baseline FPG values were similar among the treatment groups, ranging from 9.76 mmol/L to 10.35 mmol/L. The adjusted mean changes from baseline were the highest for the co-administration groups (–1.76 mmol/L and –2.55 mmol/L in the alogliptin 12.5 mg twice daily + metformin 500 mg twice daily and alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily group, respectively) compared with all other treatment groups with the exception of metformin 1,000 mg twice daily (–1.77 mmol/L). Both alogliptin 12.5 mg twice daily + metformin 500 mg twice daily and alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily were associated with statistically significant reductions in FPG compared with the respective metformin monotherapy regimens (LSMD = –0.78 mmol/L; 95% CI, –1.45 mmol/L to –0.10 mmol/L and LSMD = –1.12 mmol/L; 95% CI, –1.81 mmol/L to –0.43 mmol/L, respectively) (Table 21).

TABLE 19: CHANGES FROM BASELINE FASTING PLASMA GLUCOSE AT 26 WEEKS IN STUDIES 007 AND 008 (FULL ANALYSIS SET)

Parameter		Study 007			Study 008		
		ALO 12.5 mg + GLY (N = 203)	ALO 25 q.d. mg + GLY (N = 198)	PL + GLY (N = 99)	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
FPG (mmol/L)	Baseline, mean (SD)	9.54 (2.81)	9.65 (2.71)	9.84 (2.90)	9.34 (2.44)	9.54 (2.54)	9.96 (2.79)
	End, mean (SD)	9.34 (3.07)	9.20 (3.05)	9.82 (2.93)	8.38 (2.50)	8.57 (2.46)	9.82 (2.96)
	Change from baseline, LSM (SE)	–0.26 (0.18)	–0.47 (0.19)	0.12 (0.27)	–1.04 (0.14)	–0.97 (0.14)	0.0 (0.20)
	Change from baseline, LSMD (95% CI) versus PL	–0.38 (–1.02 to 0.26)	–0.58 (–1.22 to 0.05)	NA	–1.04[a] (–1.51 to –0.57)	–0.97[a] (–1.44 to –0.49)	NA

ALO = alogliptin; CI = confidence interval; FPG = fasting plasma glucose; GLY = glyburide; LSM = least squares mean; LSMD = least squares mean difference; MET = metformin; NA = not applicable; PL = placebo; SD = standard deviation; SE = standard error.

[a] $P < 0.001$.

Source: Clinical Study Reports for Study 007[26] and Study 008.[21]

TABLE 20: CHANGES FROM BASELINE IN FASTING PLASMA GLUCOSE IN STUDY 305 (FULL ANALYSIS SET)

Parameter		305		
		MET + ALO 12.5 mg (N = 867)	MET + ALO 25 mg (N = 867)	MET + GLZ (N = 859)
FPG (mmol/L) (FAS LOCF)	Baseline, mean (SD)	8.26 (1.90)	8.29 (1.89)	8.19 (1.85)
	Week 26 change from baseline, LSM (SE) LSMD versus GLZ (95% CI)	–0.42 (0.06) –0.18 (–0.34 to –0.01)	–0.02 (0.00) –0.01 (–0.02 to –0.00)	–0.24 (0.06) NA
	Week 52 change from baseline, LSM (SE) LSMD versus GLZ (95% CI)	–0.28 (0.07) –0.33 (–0.52 to –0.14)	–0.39 (0.07) –0.02 (–0.03 to –0.01)	0.05 (0.07) NA
	Week 104 change from baseline, LSM (SE) LSMD versus GLZ (95% CI)	–0.05 (0.07) –0.35[a] (–0.55 to –0.15)	–0.48 (0.07) –0.02[a] (–0.03 to –0.01)	0.30 (0.07) NA

ALO = alogliptin; CI = confidence interval; FAS = full analysis set; FPG = fasting plasma glucose; GLZ = glipizide; LOCF = last observation carried forward; LSM = least squares mean; LSMD = least squares mean difference; MET = metformin; NA = not applicable; SD = standard deviation; SE = standard error.

[a] $P < 0.001$.

Source: Clinical Study Report for Study 305.[25]

TABLE 21: WITHIN-GROUP CHANGES IN FASTING PLASMA GLUCOSE (FULL ANALYSIS SET) AT 26 WEEKS IN STUDY 302_MET

Parameter		MET 500 mg b.i.d. (N = 114)	MET 1,000 mg b.i.d. (N = 111)	ALO 12.5 mg b.i.d. + MET 500 mg b.i.d. (N = 111)	ALO 12.5 mg b.i.d. + MET 1,000 mg b.i.d. (N = 114)	PL (N = 109)
FPG (mmol/L)	Baseline, mean (SD)	10.01 (2.75)	10.06 (2.90)	9.76 (2.82)	10.24 (2.79)	10.35 (2.49)
	End, mean (SD)	9.35 (3.02)	8.26 (2.25)	8.15 (2.69)	7.56 (1.90)	10.84 (3.47)
	Change from baseline, LSM (SE)	–0.64 (0.25)	–1.77 (0.24)	–1.76 (0.25)	–2.55 (0.24)	0.69 (0.25)
	Change from baseline, LSMD (97.5% CI) versus MET 500 mg	NA	NA	–1.12[a] (–1.81 to –0.43)	NA	NA
	Change from baseline, LSMD (97.5% CI) versus MET 1,000 mg	NA	NA	NA	–0.78 (–1.45 to –0.10)[b]	NA
	Change from baseline, LSMD (95% CI) versus PL	NA	NA	–2.45 (–3.15 to –1.75)[c]	–3.24 (–3.92 to –2.55)[c]	NA

ALO = alogliptin; b.i.d. = twice daily; CI = confidence interval; FPG = fasting plasma glucose; LSM = least squares mean; LSMD = least squares mean difference; MET = metformin; NA = not applicable; PL = placebo; SD = standard deviation; SE = standard error.

[a] $P < 0.01$.

[b] $P < 0.05$.

[c] $P < 0.001$.

Source: Clinical Study Report for Study 302_MET.[23]

3.6.3 Changes in body weight

a) Sulfonylurea combination therapy

In Study 007, baseline mean body weight values were similar among treatment groups (80.4 kg to 82.0 kg). At 26 weeks, adjusted mean changes from baseline were 0.6 kg, 0.7 kg, and –0.2 kg for the alogliptin 12.5 mg, alogliptin 25 mg, and placebo groups, respectively. Mean differences between the alogliptin 12.5 mg and 25 mg and placebo groups were statistically significant (LSMD = 0.8 kg; 95% CI, 0.14 kg to 1.46 kg and LSMD = 0.9 kg; 95% CI, 0.21 kg to 1.54 kg, respectively) (Table 22).

b) Metformin combination therapy

In Study 008, baseline mean body weight values were similar among treatment groups (87.7 kg to 89.3 kg). At 26 weeks, adjusted mean changes from baseline were –0.4 kg, –0.7 kg, and –0.4 kg for the alogliptin 12.5 mg, alogliptin 25 mg, and placebo groups, respectively. There were no significant differences between alogliptin 12.5 mg and placebo (LSMD = 0.0 kg; 95% CI, –0.7 kg to 0.7 kg) and alogliptin 25 mg and placebo (LSMD = –0.3 kg; 95% CI, –0.9 kg to 0.4 kg) (Table 22).

In Study 305, baseline mean body weight values were similar among treatment groups, ranging from 85.37 kg to 86.33 kg. At 52 weeks, adjusted mean changes from baseline were –0.65 kg, –0.71 kg, and 0.86 kg for the alogliptin 12.5 mg, alogliptin 25 mg, and glipizide groups, respectively. Adjusted mean differences between alogliptin 12.5 mg and 25 mg versus glipizide were statistically significant (LSMD = –1.51 kg; 95% CI, –1.79 kg to –1.231 kg and LSMD = –1.58 kg; 95% CI, –1.86 kg to –1.30 kg, respectively). At 104 weeks, adjusted mean changes from baseline body weight were –0.64 kg, –0.91 kg, and –0.89 kg for alogliptin 12.5 mg, alogliptin 25 mg, and glipizide, respectively. Adjusted mean differences between alogliptin 12.5 and 25 mg versus glipizide were statistically significant (LSMD = –1.52 kg; 95% CI, –1.85 kg to –1.20 kg and LSMD = –1.80 kg; 95% CI, –2.12 kg to –1.47 kg, respectively) (Table 23).

In Study 302_MET, baseline body weight values were similar across treatment groups, ranging from 81.8 kg to 86.9 kg. Adjusted mean changes from baseline at 26 weeks for alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily and alogliptin 12.5 mg twice daily + metformin 500 mg twice daily were –1.2 kg and 0.6 kg, respectively. This compared with values of –1.2 kg for the metformin 1,000 mg twice daily group, –0.8 kg for the metformin 500 mg twice daily group, and –0.9 kg for the placebo group. The mean differences between alogliptin 12.5 mg twice daily + metformin 500 mg twice daily versus metformin 500 mg, and alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily versus metformin 1,000 mg twice daily, were not statistically significant (LSMD = –0.2 kg, 95% –0.6 kg to 1.0 kg and LSMD = 0.1 kg; 95% CI, –0.7 kg to 0.8 kg, respectively) (Table 24).

TABLE 22: CHANGES IN BODY WEIGHT FROM BASELINE AT 26 WEEKS IN STUDIES 007 AND 008

Change in Body Weight	007			008		
	ALO 12.5 mg + GLY (N = 203)	ALO 25 mg + GLY (N = 198)	PL + GLY (N = 99)	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
Baseline (kg), mean (SD)	82.0 (17.5)	80.4 (18.9)	80.8 (20.4)	87.7 (18.4)	88.1 (19.5)	89.3 (20.4)
End (kg), mean (SD)	82.6 (17.5)	81.1 (19.1)	80.6 (20.2)	85.6 (17.4)	87.3 (19.2)	86.2 (20.1)
Change from baseline, LSM (SE)	0.6 (0.2)	0.7 (0.2)	–0.2 (0.3)	–0.4 (0.2)	–0.7 (0.2)	–0.39 (0.3)
Change from baseline, LSMD (95% CI) versus PL	0.8[a] (0.14 to 1.46)	0.9[a] (0.21 to 1.54)	NA	0.0 (–0.7 to 0.7)	–0.3 (–0.9 to 0.4)	NA

ALO = alogliptin; CI = confidence interval; GLY = glyburide; LSM = least squares mean; LSMD = least squares mean difference; MET = metformin; NA = not applicable; PL = placebo; SD = standard deviation; SE = standard error.
[a] $P < 0.05$.
Source: Clinical Study Reports for Study 007[26] and Study 008.[21]

TABLE 23: CHANGES IN BODY WEIGHT FROM BASELINE IN STUDY 305

Change in Body Weight	305		
	MET + ALO 12.5 mg (N = 880)	MET + ALO 25 mg (N = 885)	MET + GLZ (N = 874)
Baseline (kg), mean (SD)	85.37 (19.0)	86.33 (19.4)	85.6 (18.5)
Week 26 change from baseline, LSM (SE)	–0.65 (0.101)	–0.71 (0.101)	0.86 (0.101)
Week 26 LSMD (95% CI) versus MET + GLZ	–1.51[a] (–1.79 to –1.23)	–1.58[a] (–1.857 to –1.296)	NA
Week 52 change from baseline, LSM (SE)	–0.64 (0.117)	–0.91 (0.117)	0.89 (0.117)
LSMD (95% CI) versus MET + GLZ	–1.52[a] (–1.846 to –1.198)	–1.80[a] (–2.122 to –1.473)	NA
Week 104 change from baseline, LSM (SE)	NR	NR	NR
Change from baseline, LSMD (95% CI)	NR	NR	NR

ALO = alogliptin; CI = confidence interval; GLZ = glipizide; LSM = least squares mean; LSMD = least squares mean difference; MET = metformin; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error.
[a] $P < 0.001$.
Source: Clinical Study Report for Study 305.[25]

TABLE 24: CHANGES IN BODY WEIGHT FROM BASELINE IN STUDY 302_MET

Change in Body Weight	302_MET				
	MET 500 mg b.i.d. (N = 109)	MET 1,000 mg b.i.d. (N = 111)	ALO 12.5 mg b.i.d. + MET 500 mg b.i.d. (N = 106)	ALO 12.5 mg b.i.d. + MET 1,000 mg b.i.d. (N = 114)	PL (N = 106)
Baseline (kg), mean (SD)	81.7 (17.1)	81.8 (17.6)	82.7 (16.5)	86.6 (17.5)	86.9 (17.4)
End (kg), mean (SD)	80.9 (17.6)	80.6 (17.3)	82.2 (16.3)	85.3 (17.0)	86.0 (17.1)
Change from baseline, mean (SD)	–0.8 (2.8)	–1.2 (3.0)	–0.6 (2.5)	–1.2 (3.5)	–0.9 (2.3)
Change from baseline, LSMD (95% CI) versus MET 500 mg	NA	NA	0.2 (–0.6 to 1.0)	NA	NA
Change from baseline, LSMD (95% CI) versus MET 1,000 mg	NA	NA	NA	0.1 (–0.7 to 0.8)	NA
Change from baseline, LSMD (95% CI) versus PL	NA	NA	0.3 (–0.5 to 1.1)	–0.3 (–1.1 to 0.5)	NA

ALO = alogliptin; b.i.d. = twice daily; CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; MET = metformin; NA = not applicable; PL = placebo; SD = standard deviation.
Source: Clinical Study Report for Study 302_MET.[23]

3.6.4 Health-related quality of life

None of the included studies reported data on quality of life.

3.7 Harms

Only those harms identified in the review protocol are reported in this section (see also Section 2.2.1, Protocol). See APPENDIX 3: DETAILED OUTCOME DATA for detailed harms data. A summary of harms data from the included studies is displayed in Table 25, Table 26, and Table 27.

3.7.1 Adverse events

a) Sulfonylurea combination therapy

In Study 007, the incidence of patients who experienced an adverse event (AE) during the 26-week treatment period was higher in the alogliptin 12.5 mg and 25 mg groups (63.1% and 63.5%, respectively) than in the placebo group (53.5%). The most common AEs in the alogliptin 12.5 mg group were diarrhea (3.9%), nasopharyngitis (3.9%), and hypertriglyceridemia (3.9%). The most common AEs in the alogliptin 25 mg group were headache (5.6%), hypertension (5.6%), and urinary tract infections (UTIs) (5.1%). The most common AEs for the placebo group were UTIs (6.1%) and influenza (4.0%). Pancreatitis was not reported (Table 34).

b) Metformin combination therapy

In Study 008, the proportion of patients who experienced an AE during the 26-week treatment period was lower in the alogliptin 12.5 mg and 25 mg groups (62.9% and 57.0%, respectively) than in the placebo group (66.3%). The most common AEs in the alogliptin 12.5 mg group were UTI (6.6%), nasopharyngitis (5.6%), and upper respiratory tract infection (4.7%). The most common AEs in the alogliptin 25 mg group were nasopharyngitis (3.4%) and diarrhea (3.4%). The most common AEs in the placebo group were diarrhea (5.8%) and nasopharyngitis (5.8%). No events of pancreatitis were reported (Table 34).

In Study 305, the proportion of patients who experienced an AE was similar among treatment groups (78.9%, 79.8, and 77.8% in the alogliptin 12.5 mg and 25 mg, and glipizide groups, respectively). The most frequent AEs in the alogliptin 12.5 mg groups were nasopharyngitis (8.9%), diarrhea (6.9%), and UTI (4.8%) (Table 35), while hypertension (7.7%), nasopharyngitis (7.6%), and headache (6.9%) were the most frequent AEs in the alogliptin 25 mg group. The most frequent AEs in the glipizide group were hypoglycemia (10.5%), nasopharyngitis (7.5%), and diarrhea (7.2%). Pancreatitis was categorized as acute pancreatitis, pancreatitis, or chronic pancreatitis in Study 305. There were two cases of acute pancreatitis (one each in the alogliptin 25 mg and glipizide groups), one case of pancreatitis in the glipizide group, and one patient who experienced chronic pancreatitis in the glipizide group.

In Study 302_MET, the percentage of patients who experienced an AE in the alogliptin 12.5 mg twice daily + metformin 500 mg twice daily and alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily groups were similar (63.2% and 64.0%, respectively). The percentages in the metformin 500 mg twice daily, 1,000 mg twice daily, and placebo groups were 68.8%, 62.2%, and 71.7%, respectively.

The most frequently reported AEs in the alogliptin 12.5 mg twice daily + metformin 500 mg twice daily group were hyperglycemia (7.5%) and headache (6.6%). The most frequently reported AEs in the alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily group were reduced creatinine renal clearance (7.9%), dyspepsia (7.0%), and diarrhea (7.0%). The most frequently reported AEs in the metformin 500 mg twice daily group were dyslipidemia (6.4%), headache (6.4%), and back pain (5.5%). The most frequently reported AEs in the metformin 1,000 mg twice daily group were diarrhea (9.0%) and hyperglycemia (8.1%). One patient (0.9%) experienced pancreatitis in the alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily group (Table 36).

TABLE 25: SUMMARY OF HARMS FROM STUDIES 007 AND 008

Summary of AEs, n (%)	007			008		
	ALO 12.5 mg + GLY (N = 203)	ALO 25 mg + GLY (N = 198)	PL + GLY (N = 99)	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 207)	PL + MET (N = 104)
Any AEs	129 (63.5)	125 (63.1)	53 (53.5)	134 (62.9)	118 (57.0)	69 (66.3)
SAEs	11 (5.4)	11 (5.6)	2 (2.0)	6 (2.8)	8 (3.9)	4 (3.8)
WDAEs	5 (2.5)	4 (2.0)	2 (2.0)	7 (3.3)	4 (1.9)	1 (1.0)
Deaths	0	0	0	1 (0.5)	0	0
Hypoglycemia	1 (0.5)	1 (0.5)	0	2 (0.9)	0	3 (2.9)

AE = adverse event; ALO = alogliptin; GLY = glyburide; MET = metformin; PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports for Study 007[26] and Study 008.[21]

TABLE 26: SUMMARY OF HARMS FROM STUDY 305

Summary of AEs,[a] n (%)	305		
	MET + ALO 12.5 mg (N = 873)	MET + ALO 25 mg (N = 878)	MET + GLZ (N = 869)
Any AEs	689 (78.9)	701 (79.8)	676 (77.8)
SAEs	86 (9.9)	97 (11.0)	81 (9.3)
WDAEs	59 (6.8)	74 (8.4)	82 (9.4)
Deaths	3 (0.3)	3 (0.3)	5 (0.6)
Hypoglycemia	18 (2.1)	6 (0.7)	91 (10.5)

AE = adverse event; ALO = alogliptin; GLZ = glipizide; MET = metformin; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for Study 305.[25]

TABLE 27: SUMMARY OF HARMS FROM STUDY 302_MET

Summary of AEs, n (%)	MET 500 mg b.i.d. (N = 109)	MET 1,000 mg b.i.d. (N = 111)	ALO 12.5 mg b.i.d. + MET 500 mg b.i.d. (N = 106)	ALO 12.5 mg b.i.d. + MET 1,000 mg b.i.d. (N = 114)	PL (N = 106)
Any AEs	75 (68.8)	69 (62.2)	67 (63.2)	73 (64.0)	76 (71.7)
SAEs	2 (1.8)	2 (1.8)	2 (1.9)	2 (1.8)	3 (2.8)
WDAEs[a]	3 (2.8)	2 (1.8)	5 (4.7)	11 (9.6)	5 (4.7)
Deaths	0	0	0	0	0
Hypoglycemia	2 (1.8%)	7 (6.3%)	2 (1.9%)	6 (5.3%)	1 (0.9%)

AE = adverse event; ALO = alogliptin; b.i.d. = twice daily; MET = metformin; PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] The number of patients who discontinued because of an AE in the placebo group differs between this table (n = 5) and the disposition data (n = 4), as one patient discontinued at the discretion of the principal investigator (owing to hyperglycemia).
Source: Clinical Study Report for Study 302_MET.[23]

3.7.2 Serious adverse events

a) Sulfonylurea combination therapy

In Study 007, 11 patients in both the alogliptin 12.5 mg (5.4%) and 25 mg (5.6%) groups experienced a serious adverse event (SAE), compared with two patients in the placebo group (2.0%).There were no deaths in Study 007 (Table 25).

b) Metformin combination therapy

In Study 008, there were similar proportions of SAEs among the treatment groups. Eight patients in the alogliptin 12.5 mg group (3.9%), six patients in the alogliptin 25 mg group (2.8%), and four patients (3.8%) in the placebo group experienced an SAE. There was one death in Study 008 in the alogliptin 12.5 mg group. The cause of death was hypertensive heart disease, which was considered unrelated to the study drug (Table 25).

In Study 305, 11% of patients in the alogliptin 25 mg group, 9.9% in the alogliptin 12.5 mg group, and 9.3% in the glipizide group experienced an SAE. There were 11 deaths in Study 305, including three in the alogliptin 12.5 group (0.3%), three in the alogliptin 25 mg group (0.3%), and five in the glipizide group (0.6%). However, only one death, due to pulmonary edema in the alogliptin 25 mg group, was determined to have possibly been related to the study drug (Table 26).

In Study 302_MET, the percentages of patients with an SAE were similar among the dual-therapy and metformin monotherapy groups. Two patients in the alogliptin 12.5 mg twice daily + metformin 500 mg twice daily group (1.9%), two patients in the alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily group (1.8%), two patients in the metformin 500 mg group (1.8%), two patients in the metformin 1,000 mg group (1.8%), and three patients in the placebo group (2.8%) experienced an SAE. There were no deaths in Study 302_MET (Table 27).

3.7.3 Withdrawal due to adverse events

a) Sulfonylurea combination therapy

In Study 007, similar percentages of patients discontinued the study due to AEs among the treatment groups: five (2.5%), four (2.0%), and two (2.0%) patients in the alogliptin 12.5 mg, alogliptin 25 mg, and placebo groups, respectively. No single AE resulted in discontinuation of 3% or more of the safety set population within each treatment group (Table 28).

b) Metformin combination therapy

In Study 008, seven patients (3.3%) discontinued due to AEs in the alogliptin 12.5 mg group compared with four patients (1.9%) in the alogliptin 25 mg group, and one patient (1.0%) in the placebo group. No single AE resulted in discontinuation of 3% or more of the safety set population in any of the treatment groups (Table 28).

In Study 305, fewer patients discontinued due to AEs in the alogliptin 12.5 mg and 25 mg groups (6.8% and 8.4%, respectively) versus the glipizide group (9.4%). No single AE resulted in discontinuation of 3% or more of the alogliptin 12.5 mg group safety set. However, in the alogliptin 25 mg group, the most frequent cause of discontinuation due to AEs was investigations, reported for 28 patients (3.2%). In addition, 28 patients in the glipizide group discontinued due to metabolism or nutrition disorders (3.2%), the most frequent cause of discontinuation due to AEs in this group (Table 29).

In Study 302_MET, there was a higher incidence of discontinuation due to AEs in the co-administration groups, with five patients (4.7%) in the alogliptin 12.5 mg twice daily + metformin 500 mg twice daily group and 11 patients (9.6%) in the alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily group, compared with three patients (2.8%) in the metformin 500 mg twice daily group and two patients (1.8%) in the metformin 1,000 mg twice daily group. Five patients (4.7%) discontinued due to AEs in the placebo group. No single AE resulted in discontinuation of 3% or more of the safety population, except in the alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily group, in which six patients (5.3%) discontinued due to investigations (Table 30).

TABLE 28: SUMMARY OF WITHDRAWALS DUE TO ADVERSE EVENT FROM STUDIES 007 AND 008 (SAFETY SET)

WDAEs by System Organ Class, n (%)	007			008[a]		
	ALO 12.5 mg + GLY (N = 203)	ALO 25 mg + GLY (N = 198)	PL + GLY (N = 99)	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 207)	PL + MET (N = 104)
Total WDAEs	**5 (2.5)**	**4 (2.0)**	**2 (2.0)**	**7 (3.3)**	**4 (1.9)**	**1 (1.0)**
Cardiac disorders	NR	NR	NR	1 (0.5)	1 (0.5)	0
Blood/lymphatic system disorders	NR	NR	NR	0	0	1 (1.0)
Gastrointestinal disorders	1 (0.5)	0	0	NR	NR	NR
General disorders	NR	NR	NR	0	1 (0.5)	0
Investigations	1 (0.5)	2 (1.0)	0	2 (0.9)	0	0
Metabolism/nutrition disorders	1 (0.5)	0	1 (1.0)	NR	NR	NR
Neoplasms	0	1 (0.5)	0	2 (0.9)	0	0
Nervous system disorders	0	0	1 (1.0)	2 (0.9)	1 (0.5)	0
Psychiatric disorders	1 (0.5)	0	0	NR	NR	NR
Renal and urinary disorders	1 (0.5)	0	0	NR	NR	NR
Skin/subcutaneous tissue disorders	NR	NR	NR	0	1 (0.5)	0
Respiratory/thoracic/mediastinal disorders	0	1 (0.5)	0	0	1 (0.5)	0

ALO = alogliptin; GLY = glyburide; MET = metformin; NR = not reported; PL = placebo; WDAE = withdrawal due to adverse event.
[a] ≥ 3% patients.
Source: Clinical Study Reports for Study 007[26] and Study 008.[21]

TABLE 29: SUMMARY OF WITHDRAWALS DUE TO ADVERSE EVENT FROM STUDY 305 (SAFETY SET)

WDAEs[a] by System Organ Class, n (%)	305		
	MET + ALO 12.5 mg (N = 873)	MET + ALO 25 mg (N = 878)	MET + GLZ (N = 869)
Total WDAEs	**59 (6.8)**	**74 (8.4)**	**82 (9.4)**
Cardiac disorders	2 (0.2)	4 (0.5)	4 (0.5)
Gastrointestinal disorders	5 (0.6)	10 (1.1)	8 (0.9)
General disorders	1 (0.1)	1 (0.1)	5 (0.6)
Infections and infestations	1 (0.1)	2 (0.2)	4 (0.5)
Investigations	24 (2.7)	28 (3.2)	17 (2.0)
Metabolism/nutrition disorders	1 (0.1)	1 (0.1)	28 (3.2)
Neoplasms	4 (0.5)	3 (0.3)	1 (0.1)
Nervous system disorders	4 (0.5)	3 (0.3)	2 (0.2)
Renal and urinary disorders	12 (1.4)	7 (0.8)	7 (0.8)
Skin/subcutaneous tissue disorders	2 (0.2)	4 (0.5)	3 (0.3)

ALO = alogliptin; GLZ = glipizide; MET = metformin; WDAE = withdrawal due to adverse event.
[a] ≥ 2 patients.
Source: Clinical Study Report for Study 305.[25]

TABLE 30: SUMMARY OF WITHDRAWALS DUE TO ADVERSE EVENT FROM STUDY 302_MET (SAFETY SET)

WDAEs by System Organ Class, n (%)	MET 500 mg b.i.d. (N = 109)	MET 1,000 mg b.i.d. (N = 111)	ALO 12.5 mg b.i.d. + MET 500 mg b.i.d. (N = 106)	ALO 12.5 mg b.i.d. + MET 1,000 mg b.i.d. (N = 114)	PL (N = 106)
Total WDAEs	**3 (2.8)**	**2 (1.8)**	**5 (4.7)**	**11 (9.6)**	**5 (4.7)**
Blood and lymphatic system disorders	0	0	0	0	0
Gastrointestinal disorders	1 (0.9)	1 (0.9)	0	3 (2.6)	1 (0.9)
General disorders and administration site conditions	0	0	0	0	1 (0.9)
Hepatobiliary disorders	0	0	0	1 (0.9)	0
Infections and infestations	0	0	0	1 (0.9)	0
Injury, poisoning and procedural complications	0	0	0	0	0
Investigations	0	1 (0.9)	2 (1.9)	6 (5.3)	0
Metabolism and nutrition disorders	0	0	0	0	2 (1.9)
Nervous system disorders	0	0	0	0	0
Psychiatric disorders	0	0	1 (0.9)	1 (0.9)	0
Renal and urinary disorders	1 (0.9)	0	2 (1.9)	0	1 (0.9)

WDAEs by System Organ Class, n (%)	MET 500 mg b.i.d. (N = 109)	MET 1,000 mg b.i.d. (N = 111)	ALO 12.5 mg b.i.d. + MET 500 mg b.i.d. (N = 106)	ALO 12.5 mg b.i.d. + MET 1,000 mg b.i.d. (N = 114)	PL (N = 106)
Respiratory, thoracic, and mediastinal disorders	1 (0.9)	0	0	0	0

ALO = alogliptin; b.i.d. = twice daily; MET = metformin; PL = placebo; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for Study 302_MET.[23]

3.7.4 Hypoglycemia

a) Sulfonylurea combination therapy

In Study 007, 32 patients (15.8%) in the alogliptin 12.5 mg group, 19 patients (9.6%) in the alogliptin 25 mg group, and 11 patients (11.1%) in the placebo group experienced at least one episode of hypoglycemia. Severe hypoglycemia was experienced by two patients (1%) in the alogliptin 12.5 mg group and one patient (1%) in the placebo group (Table 31).

b) Metformin combination therapy

In Study 008, two patients (0.9%) in the alogliptin 12.5 mg group, no patients in the alogliptin 25 mg group, and three patients (2.9%) in the placebo group experienced at least one episode of hypoglycemia. There were no reported events of severe hypoglycemia (Table 31).

In Study 305, 22 patients (2.5%) in the alogliptin 12.5 mg group, 12 patients (1.4%) in the alogliptin 25 mg group, and 202 patients (23.2%) in the glipizide group experienced at least one episode of hypoglycemia. Severe hypoglycemia occurred in one patient (0.1%) in the alogliptin 12.5 mg group and five patients (0.6%) in the glipizide group (Table 32).

In Study 302_MET, hypoglycemia occurred in two patients (1.9%) in the alogliptin 12.5 mg twice daily + metformin 500 mg twice daily group, six patients (5.3%) in the alogliptin 12.5 mg twice daily + metformin 1,000 mg twice daily group, seven patients (6.3%) in the metformin 1,000 mg twice daily group, two patients (1.8%) in the metformin 500 mg twice daily group, and one patient (1.8%) in the placebo group (Table 33). No patients experienced severe hypoglycemia in this study.

TABLE 31: HYPOGLYCEMIC EVENTS IN STUDIES 007 AND 008 (SAFETY SET)

Hypoglycemia	007			008		
	ALO 12.5 mg + GLY (N = 203)	ALO 25 mg + GLY (N = 198)	PL + GLY (N = 99)	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
Any hypoglycemia, n (%)	32 (15.8)	19 (9.6)	11 (11.1)	2 (0.9)	0	3 (2.9)
Severe hypoglycemia, n (%)	2 (1.0)	0	1 (1.0)	0	0	0

ALO = alogliptin; GLY = glyburide; MET = metformin; PL = placebo.
Source: Clinical Study Reports for Study 007[26] and Study 008.[21]

TABLE 32: HYPOGLYCEMIC EVENTS IN STUDY 305 (SAFETY SET)

Hypoglycemia	305		
	MET + ALO 12.5 mg (N = 873)	MET + ALO 25 mg (N = 878)	MET + GLZ (N = 869)
Any hypoglycemia, n (%)	22 (2.5)	12 (1.4)	202 (23.2)
Severe hypoglycemia, n (%)	1 (0.1)	0	5 (0.6)

ALO = alogliptin; GLZ = glipizide; MET = metformin.
Source: Clinical Study Report for Study 305.[25]

TABLE 33: HYPOGLYCEMIC EVENTS IN STUDY 302_MET (SAFETY SET)

Hypoglycemia	MET 500 mg b.i.d. (N = 109)	MET 1,000 mg b.i.d. (N = 111)	ALO 12.5 mg b.i.d. + MET 500 mg b.i.d. (N = 106)	ALO 12.5 mg b.i.d. + MET 1,000 mg b.i.d. (N = 114)	PL (N = 106)
Any hypoglycemia, n (%)	2 (1.8%)	7 (6.3%)	2 (1.9%)	6 (5.3%)	1 (0.9%)
Severe hypoglycemia, n (%)	0	0	0	0	0

ALO = alogliptin; b.i.d. = twice daily; MET = metformin; PL = placebo.
Source: Clinical Study Report for Study 302_MET.[23]

4. DISCUSSION

4.1 Summary of Available Evidence

The manufacturer originally requested that alogliptin be listed "equivalent to other DPP-4 inhibitors currently available in Canada." Recommendations from CDEC for other DPP-4 inhibitors (sitagliptin, linagliptin, and saxagliptin) have been consistent in recommending these drugs in combination with metformin and an SU when insulin is not an option.[8-10] While many publicly funded drug plans' listing criteria for the DPP-4 inhibitors are in alignment with these recommendations, there are some exceptions. Alogliptin is unique among the DPP-4 inhibitors in that it is not approved for use in combination with metformin and an SU. Upon consideration of these factors, and in consultation with the manufacturer, it was determined that the two approved indications of alogliptin of greatest relevance for review by CDR were combination use with metformin or with an SU. Subsequently, the manufacturer revised the requested listing criteria to align with the indications under review.

Four double-blind, phase 3 RCTs were identified for inclusion in this review. Study 007 was a 26-week, placebo-controlled trial of patients who had inadequate glycemic control when treated with an SU. Study 008 was a 26-week, placebo-controlled trial of patients who had inadequate glycemic control when treated with metformin. Study 302_MET was a 26-week, placebo-controlled trial of patients who had inadequate glycemic control when treated with diet and exercise. Study 305 was a 104-week, active-controlled, non-inferiority trial of patients who had inadequate glycemic control when treated with metformin. The population and trial design of these RCTs are consistent with current advice from the FDA and EMA regarding registration trials for new antihyperglycemic drugs, which states that confirmatory studies are typically six months in duration but at least one trial, preferably active-controlled, should demonstrate maintenance of effect over at least 12 months.[27,28]

4.2 Interpretation of Results

4.2.1 Efficacy

Similar to RCTs of most other antihyperglycemic drugs, the primary end point in the reviewed alogliptin studies was change in A1C from baseline. While the results of major trials of intensive glucose lowering conducted in the past few years have generated controversy regarding the relationship between A1C lowering and cardiovascular outcomes,[31,32] A1C is considered an appropriate primary outcome in clinical trials of antihyperglycemic drugs. NICE and the FDA have indicated that reductions in A1C from baseline as small as 0.5% and 0.7%, respectively, have clinical importance.[27,28] In Studies 007 and 008, alogliptin 12.5 mg and 25 mg added to metformin or an SU were associated with A1C reductions of 0.4% to 0.5% compared with addition of placebo. Similarly, in Study 302_MET, dual therapy with alogliptin and metformin was associated with reductions in A1C of 0.6% to 0.7% compared with metformin monotherapy. In Study 305, alogliptin 12.5 and 25 mg demonstrated non-inferiority to glipizide on A1C when added to metformin; mean reductions in A1C from baseline in each group were between 0.6% and 0.8% at weeks 52 and 104. Hence, the A1C effect sizes associated with addition of alogliptin to either metformin or an SU appear to satisfy the conventional thresholds of clinical importance. The EMA and the FDA both came to similar conclusions, describing the A1C effect sizes associated with alogliptin add-on therapy as modest but clinically relevant.[29,33]

Given the availability of three DPP-4 inhibitors on the Canadian market (i.e., sitagliptin, saxagliptin, and linagliptin), the central issue in the evaluation of alogliptin is its comparative efficacy and safety versus these drugs. Unfortunately, no direct comparative trials of alogliptin versus other DPP-4 inhibitors available in Canada were identified. A network meta-analysis (NMA) was submitted by the

manufacturer, comparing the efficacy of DPP-4 inhibitors as monotherapy and as dual or triple therapy in combination with metformin or SUs or both (see APPENDIX 6: SUMMARY AND CRITICAL APPRAISAL OF MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS). All DPP-4 inhibitors as dual therapy with metformin were statistically significantly more effective than metformin alone for achieving a mean reduction in A1C from baseline. Similarly, all DPP-4 inhibitors as dual therapy with an SU were statistically significantly more effective than an SU alone for achieving a mean reduction in A1C from baseline.[34] Based on a qualitative comparison of the effect estimates and associated credible intervals, the authors of the NMA concluded that the DPP-4 inhibitors available in Canada, including alogliptin, were similar with respect to A1C reduction. However, indirect effect estimates for one DPP-4 inhibitor over another were not reported. Hence, while there was no indication from the NMA of significant differences in effect on A1C between alogliptin and the other DPP-4 inhibitors available in Canada, the analysis does not permit a conclusion of non-inferiority or similar efficacy across drugs.

A second NMA submitted by the manufacturer assessed the relative efficacy and safety of alogliptin as dual therapy (i.e., in combination with metformin when an SU is not appropriate, or in combination with SU when metformin is not appropriate; APPENDIX 6: SUMMARY AND CRITICAL APPRAISAL OF MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS BY CRADDY ET AL. (2014).[35] This analysis addressed some of the limitations noted in the first analysis, although a degree of caution is required in its interpretation given the limited number of included studies and relatively high heterogeneity among studies. There were no statistically significant differences for change in adjusted mean A1C from baseline at 24 weeks among alogliptin and linagliptin, saxagliptin, or sitagliptin as dual therapy with either metformin or an SU. The authors also reported a high probability (between 64% and 100%, depending on the comparison and whether a random- or fixed-effects model was used) that alogliptin was associated with a similar effect on A1C as the other DPP-4 inhibitors, within a margin of 0.3%. This margin has been used as a non-inferiority margin in a number of other trials of antidiabetes drugs.

A literature search did not reveal other NMAs assessing the comparative efficacy and safety of various DPP-4 inhibitors. A drug-level analysis contained in CADTH's Therapeutic Reviews of second- and third-line therapy found similar effect sizes across DPP-4 inhibitors, although alogliptin was not included in these reviews.[5,6]

Patient group input received by CADTH on the alogliptin submission indicated that control of daily fluctuations in blood glucose was the most important aspect of diabetes management for patients, an issue that the trials included in this review did not directly address. However, glucose control, as measured by FPG, was improved by the addition of alogliptin to metformin or an SU, although the effect varied based on the drug with which it was combined. Alogliptin with an SU demonstrated no statistically significant differences in FPG when compared with placebo and an SU in Study 007. However, alogliptin in combination with metformin was associated with statistically significant reductions in FPG compared with metformin alone in Studies 008 and 302_MET. The magnitude of the difference was approximately 1 mmol/L or more in most comparisons. Alogliptin plus metformin was also associated with significantly lower FPG than glipizide plus metformin in Study 305, although the magnitude of reductions was modest (0.05 mmol/L to 0.48 mmol/L).

Patient group input received by CADTH demonstrated concern regarding the weight gain associated with some antidiabetes medications. In CADTH's review of third-line antidiabetes therapies,[6] DPP-4 inhibitors and alpha-glucosidase inhibitors were weight-neutral, GLP-1 analogues were associated with statistically significant weight loss, and insulins and thiazolidinediones were associated with weight gain (range 1.9 kg to 5.0 kg). Alogliptin 12.5 mg and 25 mg once daily administered in combination with an SU

were associated with modest but statistically significant increases in weight compared with placebo plus an SU (0.8 kg and 0.9 kg, respectively) in Study 007. Alogliptin 12.5 mg and 25 mg daily in combination with metformin were not associated with significant differences in weight compared with placebo in Studies 008 and 302_MET. Alogliptin 12.5 mg or 25 mg once daily in combination with metformin were associated with statistically significant reductions in weight compared with glipizide in combination with metformin (–1.52 kg and –1.80 kg, respectively). This is not surprising given the established weight-increasing effects of SUs. The original manufacturer-submitted NMA (Craddy et al.) assessed weight gain among DPP-4 inhibitor drugs available in Canada. There was no indication of differences between alogliptin and other DPP-4 inhibitors with respect to weight gain; differences between DPP-4 inhibitor + metformin dual therapy and metformin monotherapy, and between DPP-4 inhibitor + SU dual therapy and SU monotherapy, were statistically non-significant for all drugs. Similar results were reported in the second NMA submitted by the manufacturer (Tolley et al.), except that alogliptin with metformin was associated with significantly lower weight gain than saxagliptin with metformin.

Cardiovascular risk is an area of concern for antihyperglycemic drugs for patients with type 2 diabetes. Regulatory agencies require a comprehensive evaluation of the cardiovascular safety profile of new antidiabetes therapies.[36] The Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care (EXAMINE) trial was designed with the primary objective of determining whether alogliptin is non-inferior to placebo with respect to major adverse cardiac events (MACE) in patients with type 2 diabetes who are at very high cardiovascular risk — those with recent acute coronary syndromes.[37] EXAMINE was a phase 3, multi-centre, randomized, double-blind, placebo-controlled study (APPENDIX 5: SUMMARY OF THE EXAMINE STUDY). The pre-specified non-inferiority margin was a hazard ratio of 1.3 for the primary end point of time to composite MACE (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke). Patients were eligible for study participation if they were older than 18 years of age, had a diagnosis of type 2 diabetes, were receiving antidiabetes monotherapy or combination therapy (except with another DPP-4 inhibitor or a GLP-1 analogue), had A1C levels between 6.5% and 11.0% at screening (7.0% to 11.0% if the treatment regimen included insulin), and had a history of acute coronary syndrome within 15 to 90 days before randomization. Patients were randomized to receive either alogliptin once daily or placebo once daily, in addition to standard of care for type 2 diabetes and prophylaxis for cardiovascular comorbidities. The daily doses of alogliptin were 25 mg, 12.5 mg, or 6.25 mg, depending on estimated glomerular filtration rate. The median duration of exposure to alogliptin and placebo was 533 days and 520 days, respectively. The results demonstrated that alogliptin was statistically non-inferior to placebo with respect to the primary end point (hazard ratio = 0.96; 95% CI, upper-bound 1.16). These findings suggest that alogliptin is not associated with excess cardiovascular risk. This is in alignment with the results of a large placebo-controlled RCT assessing long-term cardiovascular end points with saxagliptin (SAVOR-TIMI), which found that saxagliptin was non-inferior but not superior to placebo for the primary composite outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal ischemic stroke (hazard ratio = 1.00; 95% CI, 0.89 to 1.12).[38]

Diabetes may have a substantial impact on quality of life. Patient input received by CADTH on the alogliptin submission suggests that the impact of antidiabetes therapy on quality of life is an important consideration. However, none of the included studies included a measure of quality of life. One trial specified satisfaction with treatment (measured using the Diabetes Treatment Satisfaction Questionnaire) as an end point, but no data were reported.

4.2.2 Harms

Overall, the percentages of patients experiencing AEs when treated with alogliptin with an SU or alogliptin with metformin were similar to the respective monotherapy groups over a 26-week treatment period. The percentage of patients experiencing an AE when treated with alogliptin and metformin increased during the 104-week duration of Study 305; however, the proportion remained similar to the glyburide + metformin group. In all cases (with the exception of alogliptin + glyburide), patients in the placebo groups had a greater frequency of AEs when compared with the alogliptin dual-therapy combinations.

Generally, there were no differences in the percentages of patients experiencing SAEs with alogliptin + metformin dual therapy compared with placebo + metformin, glipizide + metformin, and placebo. However, in Study 007, there was some evidence to suggest a higher risk of SAEs in the alogliptin + glyburide groups compared with placebo (5.6% and 5.4% in the alogliptin 12.5 and 25 mg groups versus 2.0% in the placebo group). These findings should be interpreted with caution because of the small number of events in each treatment group. In addition, there was no apparent pattern in the type of SAEs.[29] For withdrawals due to adverse events, there were no apparent differences between alogliptin + glyburide and placebo + glyburide in Study 007. Similarly, the percentage of withdrawals due to adverse event (WDAEs) was similar between alogliptin and glipizide groups in Study 305. However, combinations of alogliptin with metformin tended to be associated with more WDAEs than metformin alone: in Study 302_MET, percentages experiencing WDAE were 4.7% in the alogliptin 12.5 mg twice daily + 500 mg metformin twice daily group and 9.6% in the alogliptin 12.5 mg twice daily + 1,000 mg metformin twice daily group, compared with 2.8% and 1.8% in the respective metformin monotherapy groups.

Patient group input received by CADTH suggested that the ability to achieve optimal glycemic control may be limited by hypoglycemia. Studies 007 and 008 did not suggest the potential for an increased risk of hypoglycemia with alogliptin + glyburide dual therapy or alogliptin + metformin dual therapy compared with the respective monotherapies. Not surprisingly, given the well-established propensity for SUs to cause hypoglycemia, alogliptin + metformin dual therapy was associated with a substantially lower hypoglycemia risk than glipizide + metformin in Study 305. In the original manufacturer-submitted NMA (by Craddy et al.), odds ratios for all DPP-4 inhibitors as dual therapy with metformin or an SU versus the respective monotherapies were statistically non-significant. Similar results were reported in the second NMA (by Tolley et al.), except that alogliptin with metformin was favoured over sitagliptin and saxagliptin with respect to the risk of hypoglycemia, although this finding should be interpreted with caution, as hypoglycemia definitions differed across studies. The results of the Craddy and Tolley NMAs are broadly aligned with CADTH's Therapeutic Review of second-line diabetes therapies, which concluded that there was no evidence to suggest an increased risk of hypoglycemia with DPP-4 inhibitor + metformin dual therapy compared with other metformin dual-therapy or metformin monotherapy regimens.[5] Similarly, CADTH's review of third-line diabetes therapies concluded there was no evidence to suggest an increased risk of hypoglycemia for DPP-4 inhibitors in combination with metformin and an SU compared with placebo with metformin and an SU.[6]

All of the DPP-4 inhibitors approved for use in Canada carry a warning regarding the risk of pancreatitis in their respective product monographs.[13-16] There were no cases of pancreatitis reported in Studies 007 and 008, and isolated cases in the other two studies with no apparent association with alogliptin. Recent comprehensive assessments from the FDA and EMA of clinical and non-clinical studies investigating safety signals related to incretin-based drugs (including alogliptin) concluded that currently available data did not support a causal association between incretin-based drugs and pancreatitis or pancreatic cancer.[39]

4.3 Other Considerations

The manufacturer has requested that alogliptin be listed for combination use with metformin or with an SU. Alogliptin is not indicated for use in combination with metformin and an SU, [redacted]. The manufacturer did, however, provide some evidence related to the efficacy of alogliptin as triple therapy with metformin and an SU in the form of a post hoc exploratory subgroup analysis of patients from the EXAMINE study ([redacted]). In the subgroup of patients receiving metformin and an SU at baseline, the adjusted mean difference in effect on A1C between alogliptin and placebo [redacted] was [redacted]. The alogliptin and placebo groups [redacted] with respect to the incidence of overall adverse events ([redacted]) in the metformin + SU subgroup. The incidence of hypoglycemia was [redacted]. The incidences of acute and chronic pancreatitis were [redacted]. These findings should be interpreted with caution given the post hoc nature of the analysis. In particular, the integrity of randomization within such subgroups can be compromised, and it is uncertain whether there was sufficient statistical power to detect meaningful differences.

5. CONCLUSIONS

Four double-blind, placebo-or active-controlled RCTs were included in this review of alogliptin add-on therapy to metformin or an SU. In all trials, the addition of alogliptin was associated with modest but clinically relevant improvements in A1C, ranging from 0.4% to 0.6%. In the only active-controlled trial of a dual-therapy regimen, alogliptin + metformin dual therapy was demonstrated to be non-inferior to glipizide + metformin, although there was some concern that the conservative titration algorithm and relatively low mean doses of glipizide achieved in this study may have biased results toward a finding of non-inferiority. There were no data available from the included trials regarding the long-term complications of diabetes or quality of life. Alogliptin add-on therapy resulted in modest weight gain compared with placebo when added to an SU, was weight-neutral versus placebo when added to metformin, and was associated with lower weight gain than an SU when either was added to metformin. Alogliptin was not associated with a higher risk of hypoglycemia than placebo when added to either metformin or an SU, but was associated with lower hypoglycemia versus an SU in the context of dual therapy with metformin. There were no apparent associations between alogliptin and other adverse effects. The EXAMINE trial, which was designed to confirm the cardiovascular safety of alogliptin added to various existing antidiabetes therapies, reported that alogliptin was non-inferior to placebo in terms of MACE.

There was no direct comparative evidence for alogliptin versus other DPP-4 inhibitors available in Canada in the context of metformin or SU dual therapy. The manufacturer-submitted NMAs suggested that there are no differences among DPP-4 inhibitors in effect on A1C, body weight, and hypoglycemia, and that alogliptin as dual therapy with either metformin or an SU has a high probability of producing similar reductions in A1C (within a margin of 0.3%) as other DPP-4 inhibitors available in Canada.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

1. Brief Description of Patient Group Supplying Input

One patient group, the Canadian Diabetes Association (CDA), provided a joint patient input submission for Nesina and Kazano, given that the patient experience for these drugs will be similar. The CDA provides education and services, advocates on behalf of people with diabetes, supports research, and translates research into practical applications. The association is supported in its efforts by a community-based network of volunteers, employees, health care professionals, researchers, and partners.

The CDA solicits and receives unrestricted educational grants from multiple manufacturers and vendors of medications, supplies, and devices for diabetes and its complications; these are listed in this appendix. These funds are used to help the CDA support community programs and services for people with diabetes and to fund research and advocacy across Canada. The CDA declared no conflicts of interest in the preparation of this submission.

2. Condition and Current Therapy-Related Information

The CDA solicited patient input through a two-week survey distributed through social media and email blasts. The survey data reported in this submission are from those people living with diabetes or caring for someone with type 2 diabetes (n = 376). Of those 376 responding, 93% are taking (or had taken) diabetes medication. Forty-eight of 178 respondents to the question about dipeptidyl peptidase-4 (DPP-4) use had taken DPP-4 inhibitors, including Nesina, and 14 of 164 respondents to the question about Kazano use had taken it.

Type 2 diabetes is a progressive chronic 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 majority of patients indicated that daily fluctuations in blood sugar were the most important aspect of diabetes to control during the day and overnight. The fluctuations affect the ability to work, to interact with friends and family, and to participate in normal activities of daily living, as well as causing stress and worry. Uncontrolled diabetes and the stigma associated with the disease can result in reduced quality of life. Respondents frequently emphasized the psychological and emotional impact of diabetes on their lives (effect on stress, anxiety, adjusting to changes in diet and lifestyle, medication and treatment management as well as relationships with family) as well as fatigue and lack of energy. One patient noted: “It is a life-altering disease that impacts every aspect of life. There is constant blood monitoring, diet, level of activity, and cost of expensive supplies and medication.” Maintaining control of diabetes has potential to reduce anxiety and avoid or delay complications as well as improve overall quality of life.

Diabetes requires considerable self-management, including eating healthy food, making lifestyle changes (regular physical activity, healthy body weight, and stress management), taking diabetes medications (oral and/or injection) as prescribed, and monitoring blood glucose. The goal of diabetes management is to keep glucose levels within the target range to minimize symptoms and avoid or delay the complications. Initial therapy is most often with metformin, but, over time, most patients 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 help patients achieve optimal glycemic control may be limited by hypoglycemia.

Many patients with diabetes do not take oral glucose-lowering therapy as prescribed. Almost 30% of respondents found it somewhat difficult, difficult, or very difficult to take multiple medications during the day to manage diabetes. The most important benefit of therapy was noted as "blood sugars kept at satisfactory levels" during the day and overnight. Respondents also acknowledged "gastrointestinal side effects" and "losing or not gaining weight" as important factors in selecting their individual drug therapy.

The majority of those with DPP-4 inhibitor experience reported that they were mostly satisfied with drug therapy (similar to overall response) and that their blood sugar levels were kept at target levels, although some indicated lack of glycemic control. Many patients indicated frustration with having to take multiple medications, including drugs to maintain blood sugar, to treat hypertension, to lower cholesterol, and others. Several respondents stated that previously prescribed drugs had intolerable side effects — mainly hypoglycemia, morning hyperglycemia, and gastrointestinal effects. There were no specific side effects experienced with DPP-4 inhibitors. Most concerns were related to the need for multiple medications, cost of treatment, and lack of insurance coverage.

Overall, respondents were more satisfied than dissatisfied with their medications in terms of the ability to manage their blood sugar levels. However, there were many issues with gastrointestinal side effects and administration.

3. Related Information About the Drug Being Reviewed

The availability of alogliptin offers patients an alternative treatment option for stabilizing blood glucose. Kazano further offers a fixed-dose combination of metformin with alogliptin for patients stabilized on previous therapy of metformin plus alogliptin (with a sulfonylurea [SU] or insulin) and thereby reduces pill burden and promotes adherence. However, 95% of respondents had little or no knowledge of Nesina, and 86% had little or no knowledge of Kazano. Most with no exposure to DPP-4 inhibitors had little or no expectations for these drugs. Among those with experience, the most frequent expectation was to have better blood glucose control, including fewer instances of hyperglycemia and hypoglycemia. While most indicated they expected fewer side effects (including hypoglycemia and weight gain), others indicated they worry about side effects of all medications. Overall, most patients (75%) felt that the availability of Nesina and Kazano for treatment of diabetes is important. Approximately 30% indicated that they found it difficult to take multiple medications. This is significant, considering that these patients are also experiencing high rates of comorbid conditions such as hypertension, heart failure, depression, and renal disease. Simplifying the drug regimen is a serious and important issue for this patient population. When asked whether a pill that combined two medicines should be made available, respondents were very supportive. Patients with DPP-4 experience collectively stated good results from DPP-4 use. Patients expressed frustration with the weight gain associated with metformin use. Responses to this survey reinforce the understanding that most patients are required to make several changes in their lifestyle and drug regimen over the course of their disease. Their preference and

tolerance of therapy are influenced by many individual factors. The availability of the DPP-4 inhibitors provides an important option for patients, especially when metformin alone is no longer effective. It may promote adherence to treatment by reducing pill burden and can offer some patients a good alternative for effective treatment of diabetes.

FIGURE 8: ORGANIZATIONS AND FOUNDATIONS THAT MADE DONATIONS TO THE CANADIAN DIABETES ASSOCIATION BETWEEN SEPTEMBER 2012 AND AUGUST 2013[40]

593123 Alberta Ltd.
A. Lassonde Inc.
Abbott Laboratories, Ltd.
Aecon Group Inc.
Affinity Credit Union
Agway Metals Inc.
Amgen Canada Inc.
Amor Da Patria Community Centre of Toronto
Animas Canada
AstraZeneca Canada Inc.
Balmoral Office Group Inc.
Bayer HealthCare – Diabetes Care Division
Bayshore Home Health
BD Medical – Diabetes Care
BHP Billiton Matched Giving Program
Blistex Corporation
Boehringer Ingelheim (Canada) Ltd.
Brian & Susan Thomas Foundation
Bristol-Myers Squibb/ AstraZeneca Canada Allianance
Cal LeGrow Foundation
Cal Wenzel Family Foundation
Cameco Corporation
Canadian Footwear Ltd.
Canadian National Railway Company
Canola Info/Canola Council of Canada
Cenovus Energy – Employee Foundation
Chadi & Company
Chartwell Retirement Residences
Children's Hospital Aid Society
Chippendale Foundation
CIBC
Clifford & Lily Fielding Foundation
CMG Computer Modelling Group Ltd.
Community Foundation of Ottawa
Community Initiatives Fund
Compass Pharmacies
Conexus Credit Union
Co-operators/CUMIS
Covidien Canada
Dauphin Clinic Pharmacy
Donors Choice – Killarney & Area
E-L Financial Corporation Ltd.
Eli Lilly Canada Inc.
Eli Lilly Canada Inc./ Boehringer Ingelheim Alliance
Excelleris Technologies LP
Flame Of Hope Golf Classic London
General Mills Canada Corporation
Genzyme Canada Inc.
GlaxoSmithKline Inc.
Glenn's Helping Hand Foundation Inc.
Gold Bond Ultimate
Government of Canada – Province of New Brunswick
Grand Court Order of The Amaranth
Great-West Life, London Life & Canada Life
Green Shield Canada
Guelph Community Foundation
Home Hardware Stores Ltd.
Honeybush Health Ltd.
HOPE Ottawa Carleton Inc.
Husky Energy Inc.
Information Services Corporation (ISC)
Janssen Inc.
Janzen's Pharmacy Ltd.
Jarrod Oils Ltd.
Jewish Foundation of Manitoba
John Ung-Ling Ting Professional Corporation
John Zubick Ltd.
Johnson & Johnson Inc.
Kiwanis Club of Vancouver
KPMG
Kraft Canada Inc.
Lagniappe Foundation
Lawson Foundation
Leon's Furniture Ltd.
LifeScan Canada Ltd.
Lions Clubs of Canada
Loblaw Companies Ltd.
Loyal Protestant Association
Manitoba Association of Health Care Professionals
Manulife Financial
Mark's Work Wearhouse
Masonic Foundation of Ontario
Masons
McNeil Consumer Healthcare
Medavie Health Foundation
MEDEC
MedicAlert
Medisys Health Group
Medtronic of Canada Ltd.
Merck Canada
MLF Consulting Ltd.
National Bank of Canada
Nestlé Health Science
Newfound Foundation
Novartis Pharmaceuticals Canada Inc.
Novo Nordisk Canada Inc.
Order Of The Eastern Star – Grand Chapter of NS & PEI
Pacific Blue Cross Health Foundation
Performance Boat Club Charities
Pfizer Canada Inc.
Pharmasave Central
Progressive Foods Inc.
Project Read Literacy Network
Raymond James Canada Foundation
RBC Foundation
Realty Executives Western Canada
Regina Capital Cosmopolitan Club
Regina Queen City Kinsmen
Rexall Foundation
Roche Diagnostics Canada
Rubicon/ Pharmasave
Rx&D, Canada's Research-Based Pharmaceutical Companies
Sandra & Leo Kolber Foundation
Sanofi Aventis Canada Inc.
Saskatchewan Indian Gaming Authority
Saskatoon Community Foundation
Saskatoon Subway
Shaw Communications Inc.
Shopease Foods Inc.
Silver Hills Bakery
South Saskatchewan Community Foundation Inc.
Stickling's Specialty Bakery Ltd.
Storck Canada Inc.
Strategic Charitable Giving Foundation
Subway Franchisee Advertising
Sudbury Rocks Running Club
Sun Life Financial
Sunrise Soya Foods
Sure Flow Equipment Inc.
Takeda Canada Inc.
TD Waterhouse
TELUS
The Arthur J E Child Foundation
The Calgary Foundation
The Cash Store Financial Services Inc.
The Charles Norcliffe Baker & Thelma Scott Baker Foundation
The Chastell Foundation
The Community Foundation of Prince Edward Island
The John & Judy Bragg Family Foundation
The Kinsmen Club of Saskatoon
The London & District Concrete Forming Contractors Assoc.
The Lorne & Evelyn Johnson Foundation
The North West Company Inc.
The Poker For Diabetes Foundation
The Toronto Star Fresh Air Fund
The Toronto-Dominion Bank
The Winnipeg Foundation
TransCanada Pipelines Ltd.
Unilever Canada Inc.
Union 52 Benevolent Society
United Way Newfoundland & Labrador
Wellington Laboratories Inc.
Williamsburg Arms

APPENDIX 2: LITERATURE SEARCH STRATEGY

See Section 2.2 Methods for more details on literature search methods.

Database Search

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:	August 15, 2014
Alerts:	Bi-weekly search updates until project completion
Study Types:	No study design filters used
Limits:	Date limit: none Language limit: none Conference abstracts: 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
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
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.nm	Name of Substance Word
.ot	Original title
.pt	Publication type
.rn	CAS registry number
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	*alogliptin/
2	(alogliptin* or Nesina or Incresina or Vipidia or SYR 322 or SYR322).ti,ab.
3	*alogliptin plus metformin/
4	(Kazano or Nesimet or Nesina Met or Vipdomet).ti,ab.
5	or/1-4
6	5 not conference abstract.pt.
7	6 use oemezd
8	(alogliptin* or Nesina or Incresina or Vipidia or SYR 322 or SYR322).ti,ab,ot,sh,hw,rn,nm.
9	(Kazano or Nesimet or Nesina Met or Vipdomet).ti,ab,ot,sh,hw,rn,nm.
10	(850649-61-5 or 850649-62-6 or JHC049LO86 or EEN99869SC).rn,nm.
11	or/8-10
12	11 use pmez
13	7 or 12
14	remove duplicates from 13

OTHER DATABASES	
PubMed	Same MeSH, keywords and limits 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

Date of Search:	August 2014
Keywords:	Diabetes type 2, alogliptin, Nesina and Kazano.
Limits:	No date limit, English only

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

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trials
- databases (free).

APPENDIX 3: DETAILED OUTCOME DATA

TABLE 34: SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS FROM STUDIES 007 AND 008 OCCURRING IN 3% OR MORE OF PATIENTS IN ANY TREATMENT GROUP

AEs by System Organ Class, n (%)	007			008		
	ALO 12.5 mg + GLY (N = 203)	ALO 25 mg + GLY (N = 198)	PL + GLY (N = 99)	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 207)	PL + MET (N = 104)
Any AEs	**129 (63.5)**	**125 (63.1)**	**53 (53.5)**	**134 (62.9)**	**118 (57.0)**	**69 (66.3)**
Diarrhea	8 (3.9)	9 (4.5)	0	6 (2.8)	7 (3.4)	6 (5.8)
Edema, peripheral	4 (2.0)	7 (3.5)	0	NR	NR	NR
Urinary tract infection	9 (4.4)	10 (5.1)	3 (3.0	14 (6.6)	6 (2.9)	4 (3.8)
Nasopharyngitis	8 (3.9)	8 (4.0)	2 (2.0)	12 (5.6)	7 (3.4)	6 (5.8)
Upper respiratory tract infection	4 (2.0)	5 (2.5)	6 (6.1)	10 (4.7)	5 (2.4)	7 (6.7)
Influenza	4 (2.0)	5 (2.5)	4 (4.0)	NR	NR	NR
Bronchitis	3 (1.5)	1 (0.5)	3 (3.0)	9 (4.2)	6 (2.9)	2 (1.9)
Sinusitis	NR	NR	NR	5 (2.3)	4 (1.9)	5 (4.8)
Hypertriglyceridemia	8 (3.9)	8 (4.0)	2 (2.0)	NR	NR	NR
Hyperuricemia	3 (1.5)	1 (0.5)	3 (3.0)	NR	NR	NR
Arthralgia	NR	NR	NR	4 (1.9)	3 (1.4)	5 (4.8)
Back pain	4 (2.0)	9 (4.5)	3 (3.0)	NR	NR	NR
Pain in extremity	4 (2.0)	5 (2.5)	3 (3.0)	5 (2.3)	3 (1.4)	4 (3.8)
Headache	5 (2.5)	11 (5.6)	3 (3.0)	8 (3.8)	4 (1.9)	2 (1.9)
Dizziness	4 (2.0)	6 (3.0)	3 (3.0)	NR	NR	NR
Pruritus	3 (1.5)	6 (3.0)	0	NR	NR	NR
Hypertension	7 (3.4)	11 (5.6)	2 (2.0)	4 (1.9)	6 (2.9)	5 (4.8)

AE = adverse event; ALO = alogliptin; GLY = glyburide; MET = metformin; NR = not reported; PL = placebo.
Source: Clinical Study Reports for Study 007[26] and Study 008.[21]

TABLE 35: SUMMARY OF ADVERSE EVENTS FROM STUDY 305 INVOLVING 3% OR MORE OF PATIENTS IN ANY TREATMENT GROUP

AEs by System Organ Class, n (%)	305		
	MET + ALO 12.5 mg (N = 873)	MET + ALO 25 mg (N = 878)	MET + GLZ (N = 869)
Any AEs	**689 (78.9)**	**701 (79.8)**	**676 (77.8)**
Anemia	16 (1.8)	37 (4.2)	32 (3.7)
Diarrhea	60 (6.9)	60 (6.8)	63 (7.2)
Nausea	28 (3.2)	32 (3.6)	21 (2.4)
Fatigue	20 (2.3)	19 (2.2)	28 (3.2)
Asthenia	15 (1.7)	27 (3.1)	14 (1.6)
Upper respiratory tract infection	34 (3.9)	39 (4.5)	42 (4.8)
Nasopharyngitis	78 (8.9)	67 (7.6)	61 (7.0)
Urinary tract infection	42 (4.8)	34 (3.9)	39 (4.5)
Influenza	36 (4.1)	36 (4.1)	42 (4.8)
Bronchitis	39 (4.5)	36 (4.1)	37 (4.3)
Sinusitis	26 (3.0)	29 (3.3)	23 (2.6)
Creatinine renal clearance decreased	23 (2.6)	34 (3.9)	32 (3.7)
Hypoglycemia	18 (2.1)	6 (0.7)	91 (10.5)
Dyslipidemia	22 (2.5)	20 (2.3)	34 (3.9)
Back pain	54 (6.2)	45 (5.1)	50 (5.8)
Arthralgia	39 (4.5)	42 (4.8)	40 (4.6)
Pain in extremity	28 (3.2)	28 (3.2)	33 (3.8)
Headache	46 (5.3)	61 (6.9)	46 (5.3)
Dizziness	25 (2.9)	24 (2.7)	30 (3.5)
Tremor	5 (0.6)	3 (0.3)	29 (3.3)
Cough	35 (4.0)	26 (3.0)	33 (3.8)
Hypertension	46 (5.3)	68 (7.7)	65 (7.5)

AE = adverse event; ALO = alogliptin; GLZ = glipizide; MET = metformin.
Source: Clinical Study Report for Study 305.[25]

TABLE 36: SUMMARY OF ADVERSE EVENTS FROM STUDY 302 INVOLVING 3% OR MORE OF PATIENTS IN ANY TREATMENT GROUPS

AEs, n (%)	302_MET						
	ALO 25 mg q.d. (N = 112)	ALO 12.5 mg b.i.d. (N = 110)	MET 500 mg b.i.d. (N = 109)	MET 1,000 mg b.i.d. (N = 111)	ALO 12.5 mg + MET 500 mg b.i.d. (N = 106)	ALO 12.5 mg + MET 1,000 mg b.i.d. (N = 114)	PL (N = 106)
Any AEs	**61 (54.5)**	**67 (60.9)**	**75 (68.8)**	**69 (62.2)**	**67 (63.2)**	**73 (64.0)**	**76 (71.7)**
Hyperglycemia	19 (17.0)	13 (11.8)	19 (17.4)	9 (8.1)	8 (7.5)	1 (0.9)	29 (27.4)
Dyslipidemia	1 (0.9)	2 (1.8)	7 (6.4)	6 (5.4)	6 (5.7)	2 (1.8)	6 (5.7)
Hypertriglyceridemia	2 (1.8)	0	2 (1.8)	6 (5.4)	5 (4.7)	1 (0.9)	3 (2.8)
Hypercholesterolemia	3 (2.7)	3 (2.7)	1 (0.9)	4 (3.6)	0	1 (0.9)	1 (0.9)
Hyperkalemia	1 (0.9)	2 (1.8)	0	4 (3.6)	1 (0.9)	0	0
Upper respiratory tract Infection	3 (2.7)	3 (2.7)	4 (3.7)	3 (2.7)	8 (7.5)	2 (1.8)	3 (2.8)
Nasopharyngitis	6 (5.4)	1 (0.9)	2 (1.8)	3 (2.7)	2 (1.9)	2 (1.8)	2 (1.9)
Urinary tract infection	3 (2.7)	1 (0.9)	1 (0.9)	4 (3.6)	1 (0.9)	3 (2.6)	1 (0.9)
Sinusitis	2 (1.8)	2 (1.8)	2 (1.8)	0	1 (0.9)	4 (3.5)	2 (1.9)
Influenza	0	2 (1.8)	1 (0.9)	1 (0.9)	4 (3.8)	2 (1.8)	2 (1.9)
Diarrhea	1 (0.9)	3 (2.7)	4 (3.7)	10 (9.0)	6 (5.7)	8 (7.0)	3 (2.8)
Nausea	0	3 (2.7)	4 (3.7)	6 (5.4)	3 (2.8)	6 (5.3)	1 (0.9)
Dyspepsia	0	1 (0.9)	0	2 (1.8)	0	8 (7.0)	3 (2.8)
Constipation	0	4 (3.6)	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.9)	3 (2.8)
Gastritis	1 (0.9)	2 (1.8)	2 (1.8)	5 (4.5)	0	1 (0.9)	0
Vomiting	0	0	0	4 (3.6)	2 (1.9)	1 (0.9)	1 (0.9)
Creatinine renal clearance decreased	1 (0.9)	4 (3.6)	0	6 (5.4)	5 (4.7)	9 (7.9)	3 (2.8)
Glycated hemoglobin increased	1 (0.9)	2 (1.8)	2 (1.8)	1 (0.9)	1 (0.9)	2 (1.8)	4 (3.8)
Headache	5 (4.5)	5 (4.5)	7 (6.4)	4 (3.6)	7 (6.6)	6 (5.3)	3 (2.8)
Back pain	0	1 (0.9)	6 (5.5)	1 (0.9)	4 (3.8)	0	1 (0.9)
Pain in extremity	2 (1.8)	1 (0.9)	1 (0.9)	4 (3.6)	2 (1.9)	0	1 (0.9)
Asthenia	2 (1.8)	0	2 (1.8)	2 (1.8)	3 (2.8)	2 (1.8)	4 (3.8)
Pyrexia	1 (0.9)	2 (1.8)	1 (0.9)	5 (4.5)	1 (0.9)	1 (0.9)	0
Dysuria	1 (0.9)	0	0	4 (3.6)	0	1 (0.9)	0
Hypertension	3 (2.7)	2 (1.8)	4 (3.7)	1 (0.9)	4 (3.8)	8 (7.0)	4 (3.8)

AE = adverse event; ALO = alogliptin; b.i.d. = twice daily; MET = metformin; PL = placebo; q.d. = once daily.
Source: Clinical Study Report for Study 302_MET.[23]

APPENDIX 4: EXCLUDED STUDIES

Reference	Reason for Exclusion
DeFronzo RA, Fleck PR, Wilson CA, Mekki Q, Alogliptin Study 010 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control: a randomized, double-blind, placebo-controlled study. Diabetes Care. 2008 Dec;31(12):2315-7.	Irrelevant Intervention
Pratley RE, Reusch JE, Fleck PR, Wilson CA, Mekki Q, Alogliptin Study 009 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin. 2009 Oct;25(10):2361-71	
Rosenstock J, Rendell MS, Gross JL, Fleck PR, Wilson CA, Mekki Q. Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA(1C) without causing weight gain or increased hypoglycemia. Diabetes Obes Metab. 2009 Dec;11(12):1145-52.	
Bosi E, Ellis GC, Wilson CA, Fleck PR. Alogliptin as a third oral antidiabetic drug in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone: a 52-week, randomized, double-blind, active-controlled, parallel-group study. Diabetes Obes Metab. 2011 Dec;13(12):1088-96.	
White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013 Oct 3;369(14):1327-35.	
Clinical study report: SYR-322-TZD-009.	
Clinical study report: 01-06-TL-322OPI-002	
Clinical study report: SYR-322_303.	
Clinical study report: SYR-322-PLC-010.	
Clinical study report: 01-05-TL-322OPI-001.	
Clinical study report: SYR-322-INS-011	
Rosenstock J, Wilson C, Fleck P. Alogliptin versus glipizide monotherapy in elderly type 2 diabetes mellitus patients with mild hyperglycaemia: a prospective, double-blind, randomized, 1-year study. Diabetes Obes Metab. 2013 Oct;15(10):906-14.	
DeFronzo RA, Burant CF, Fleck P, Wilson C, Mekki Q, Pratley RE. Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes. J Clin Endocrinol Metab. 2012 May;97(5):1615-22.	
White WB, Bakris GL, Bergenstal RM, Cannon CP, Cushman WC, Fleck P, et al. EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl peptidase four inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. Am Heart J. 2011 Oct;162(4):620-6.	
Rosenstock J, Inzucchi SE, Seufert J, Fleck PR, Wilson CA, Mekki Q. Initial combination therapy with alogliptin and pioglitazone in drug-naive patients with type 2 diabetes. Diabetes Care. 2010 Nov;33(11):2406-8.	

APPENDIX 5: SUMMARY OF THE EXAMINE STUDY

Objective

To summarize the clinical efficacy and safety outcomes from The Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE) study,[41] in which alogliptin once daily was compared with placebo once daily in combination with standard of care among individuals with type 2 diabetes mellitus and acute coronary syndrome (ACS).

Study Characteristics

EXAMINE[41] was a phase 3, multi-centre, randomized, double-blind, placebo-controlled study. The primary objective of this study was to demonstrate non-inferiority of alogliptin versus placebo with respect to a composite of major adverse cardiac events (MACE) in high-risk patients with type 2 diabetes. A total of 8,033 patients were screened, and 5,380 patients were randomized to either alogliptin (N = 2,701) or placebo (N = 2,679). The length of study participation was variable, but the median duration of study drug treatment was 17.5 months, and maximum length of follow-up was 40.7 months. Patients were eligible for study participation if they were older than 18 years of age, had a diagnosis of type 2 diabetes, were receiving antidiabetes monotherapy or combination therapy (except with another dipeptidyl peptidase-4 [DPP-4] inhibitor or a glucagon-like peptide-1 [GLP-1] analogue), had glycated hemoglobin (A1C) levels between 6.5% and 11.0% at screening (7.0% to 11.0% if the treatment regimen included insulin), and had a history of ACS within 15 days to 90 days before randomization. Patients were excluded if they had signs or a diagnosis of type 1 diabetes mellitus, were pregnant, had a hemodynamically unstable cardiovascular disorder, or had received dialysis within 14 days before screening.

Patients were randomized to receive either alogliptin once daily or placebo once daily, in addition to standard of care for type 2 diabetes and to continuing current prophylaxis for cardiovascular comorbidities. Investigators were allowed to modify concomitant medications for type 2 diabetes and cardiovascular comorbidities throughout the duration of the study, with the exception of adding a DPP-4 inhibitor or a GLP-1 analogue. Randomization was stratified by geographic region and renal function (normal or mild renal impairment, moderate renal impairment, and severe renal impairment including end-stage renal disease). The daily doses of alogliptin were 25 mg, 12.5 mg, or 6.25 mg, depending on estimated glomerular filtration rate. The primary end point was time to an event within the primary MACE composite (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke). The secondary end point was time to an event within a secondary MACE composite (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and urgent revascularization due to unstable angina). Additional efficacy end points of interest included changes in A1C, fasting plasma glucose (FPG), and high sensitivity C-reactive protein levels. Incidence and severity of adverse events were assessed. Study visits were performed at the time of screening, at randomization, and at one, three, six, nine, and 12 months after randomization. After the first year, study visits were performed every four months throughout the duration of study participation.

Cox proportional hazards models were applied to the full analysis set to analyze the time to first event for the primary and secondary MACE composites, with stratification according to geographical region and renal function. Interim analyses were conducted after the occurrence of 80, 100, 125, and 150 adjudicated primary end point events, using an O'Brien and Fleming–type spending function (overall alpha of 2.5%) to test the null hypothesis that the hazard ratio of the primary MACE composite was

greater than 1.8 following treatment with alogliptin compared with placebo. Upon completion of the first four sequential analyses and rejection of the first null hypothesis, additional analyses were planned at 550 and 650 events to rule out a hazard ratio of greater than 1.3. The analysis at 550 events showed non-inferiority but not superiority of alogliptin to placebo, and the conditional power for superiority at 650 events was 20%, so the study was stopped. The analyses were performed by an independent statistician blinded to the patient group allocation.

Baseline characteristics are described inTable 37. Approximately 68% of patients were male, with a mean age of 61 years and mean weight of 82 kg. No notable differences in baseline characteristics were observed between the alogliptin and placebo groups. The proportion of patients within each category of renal disease severity and concomitant medication use were similar between treatment groups.

TABLE 37: BASELINE CHARACTERISTICS IN THE EXAMINE STUDY

Characteristic	ALO (N = 2,701)	PL (N = 2,679)
Sex, n (%)		
Male	1,828 (67.7)	1,823 (68.0)
Female	873 (32.3)	856 (32.0)
Age (years), mean (SD)	61.0 (10.0)	60.7 (9.9)
Weight (kg), mean (SD)	82.3 (19.3)	82.1 (19.0)
BMI (kg/m^2), mean (SD)	29.4 (5.4)	29.5 (5.8)
A1C (%), mean (SD)	8.0 (1.1)	8.0 (1.1)
FPG (mmol/L), mean (SD)	(n = 2,680) 8.8 (3.2)	(n = 2,655) 8.8 (3.1)
T2DM duration (years), mean (SD)	9.1 (8.2)	9.2 (8.1)
Index ACS event type, n (%)		
MI	2,084 (77.2)	2,068 (77.2)
MI, post-PCI	161 (6.0)	162 (6.0)
MI, post-CABG	19 (0.7)	26 (1.0)
Unstable angina	609 (22.5)	605 (22.6)
Time from index ACS event to randomization, days		
Mean (SD)	47.6 (22.0)	48.0 (22.0)
Median (min, max)	43.0 (8, 141)	45.0 (8, 120)

A1C = glycated hemoglobin; ALO = alogliptin; BMI = body mass index; CABG = coronary artery bypass graft; FPG = fasting plasma glucose; max = maximum; MI = myocardial infarction; min = minimum; PCI = percutaneous coronary intervention; PL = placebo; SD = standard deviation; T2DM = type 2 diabetes mellitus.
Source: EXAMINE Clinical Study Report.[41]

A total of 2,701 patients and 2,679 patients were randomized to the alogliptin and placebo groups, respectively. The disposition of patients is summarized in Table 38. A total of 564 patients (20.9%) in the alogliptin group and 606 patients (22.6%) in the placebo group discontinued the study drug for any reason, the most common of which were adverse events (10.1% overall) and voluntary withdrawal (6.7% overall). The median time of drug exposure was 17.5 months in the alogliptin group and 17.1 months in the placebo group. The proportion of patients receiving therapy for greater than one, two, and three years was similar for both groups.

TABLE 38: PATIENT DISPOSITION IN THE EXAMINE STUDY

	ALO (N = 2,701)	PL (N = 2,679)
Screened	8,033	
Randomized	2,701	2,679
Full analysis set	2,701	2,679
Safety analysis set	NR	NR
PP analysis set	NR	NR
Completed study drug (%)	2,137 (79.1)	2,073 (77.4)
Received rescue medication (%)	NR	NR
Discontinued study drug (%)	564 (20.9)	606 (22.6)
Adverse event (%)	270 (10.0)	275 (10.3)
Major protocol deviation (%)	9 (0.3)	15 (0.6)
Lost to follow-up (%)	20 (0.7)	26 (1.0)
Voluntary withdrawal (%)	169 (6.3)	192 (7.2)
Study termination (%)	0	0
Pregnancy (%)	0	0
Investigator discretion (%)	27 (1.0)	23 (0.9)
Other (%)	69 (2.6)	75 (2.8)

NR = not reported; PP = per protocol.
Source: EXAMINE Clinical Study Report.[41]

Results

Cardiovascular outcomes

As seen in Table 39, the complete analysis demonstrated that alogliptin was statistically non-inferior to placebo with respect to the primary end point, with similar rates of occurrence of the primary MACE composite in both groups. Likewise, the hazard ratios of each component of the primary MACE composite were similar to the hazard ratio for the composite primary end point. Furthermore, the hazard ratio for the secondary MACE composite, which included urgent revascularization due to unstable angina, was statistically non-significant. Alogliptin was not shown to be statistically superior to placebo with respect to cardiovascular outcomes. A1C levels in the alogliptin group were consistently significantly lower than in the placebo group over the course of the study. There was a significant difference between the least squares mean difference values of the alogliptin and placebo groups for both A1C and FPG values at the last study visit.

TABLE 39: CARDIOVASCULAR AND EFFICACY OUTCOMES

End Point		ALO (N = 2,701)	PL (N = 2,679)	Hazard Ratio for ALO (95% CI)
Primary and Secondary End Points				
		n (%)	**n (%)**	
Primary MACE composite[a]		305 (11.3)	316 (11.8)	0.96 (≤ 1.16)[b]
Cardiovascular death		89 (3.3)	111 (4.1)	0.79 (0.60, 1.04)
Non-fatal MI		187 (6.9)	173 (6.5)	1.08 (0.88, 1.33)
Non-fatal stroke		29 (1.1)	32 (1.2)	0.91 (0.55, 1.50)
Secondary MACE composite[c]		344 (12.7)	359 (13.4)	0.95 (≤ 1.14)[b]
Exploratory End Points				
A1C (%)	Baseline, mean (SD)	8.0 (1.1)	8.0 (1.1)	NA
	Last visit, mean (SD)	7.7 (1.5) (n = 2,648)	8.1 (1.6) (n = 2,621)	NA
	Change from baseline, LSM (SE)	–0.3 (0.03)	0.03 (0.03)	NA
	Change from baseline, LSMD (95% CI) versus PL	–0.4[d] (–0.4 to –0.3)	NA	NA
FPG (mmol/L)	Baseline, mean (SD)	8.8 (3.2) (n = 2,680)	8.8 (3.1) (n = 2,655)	NA
	Last visit, mean (SD)	8.9 (3.7)	9.3 (3.5)	NA
	Change from baseline, LSM (SE)	0.1 (0.1)	0.5 (0.1)	NA
	Change from baseline, LSMD (95% CI) versus PL	–0.3[d] (–0.5 to –0.1)	NA	NA

A1C = glycated hemoglobin; ALO = alogliptin; CI = confidence interval; FPG = fasting plasma glucose; LSM = least squares mean; LSMD = least squares mean difference; MACE = major adverse cardiac event; MI = myocardial infarction; NA = not applicable; SD = standard deviation; SE = standard error.

[a] Composite of death from cardiovascular causes, non-fatal MI, or non-fatal stroke.

[b] The parenthetical value is the upper boundary of the one-sided repeated CI, at an alpha level of 0.01.

[c] Composite of death from cardiovascular causes, non-fatal MI, non-fatal stroke, or urgent revascularization due to unstable angina within 24 hours of hospital admission.

[d] $P < 0.001$.

Source: EXAMINE Clinical Study Report.[41]

Harms

The rates of on-study adverse events, serious adverse events, and withdrawals due to adverse events are summarized in Table 40. A summary of adverse events occurring with a frequency greater than 3% in either study group is presented in Table 41. The overall safety profile of alogliptin was similar to placebo over the course of the study, and there were no apparent differences in the rates of serious adverse events between the two groups.

TABLE 40: SUMMARY OF HARMS

Summary of AEs	ALO (N = 2,701)	PL (N = 2,679)
Any AEs (%)	2,160 (80.0)	2,111 (78.8)
SAEs (%)	907 (33.6)	952 (35.5)
WDAEs (%)	270 (10.0)	274 (10.2)
Deaths (%)	153 (5.7)	173 (6.5)
Any hypoglycemia (%)	181 (6.7)	173 (6.5)
Severe hypoglycemia (%)	NR	NR

AE = adverse event; ALO = alogliptin; NR = not reported; PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

TABLE 41: ON-STUDY ADVERSE EVENTS OCCURRING IN 3% OR MORE OF PATIENTS IN EITHER TREATMENT GROUP (FULL ANALYSIS SET)

AEs n (%)	ALO (N = 2,701)	PL (N = 2,679)
Any AEs	2,160 (80.0)	2,111 (78.8)
Anemia	140 (5.2)	109 (4.1)
Angina pectoris	199 (7.4)	205 (7.7)
Angina unstable	122 (4.5)	144 (5.4)
Acute myocardial infarction	126 (4.7)	104 (3.9)
Cardiac failure congestive	83 (3.1)	70 (2.6)
Cardiac failure	72 (2.7)	80 (3.0)
Diarrhea	129 (4.8)	107 (4.0)
Peripheral edema	104 (3.9)	105 (3.9)
Non-cardiac chest pain	79 (2.9)	87 (3.2)
Nasopharyngitis	112 (4.1)	120 (4.5)
Urinary tract infection	109 (4.0)	104 (3.9)
Bronchitis	93 (3.4)	75 (2.8)
Upper respiratory tract infection	81 (3.0)	85 (3.2)
Pneumonia	83 (3.1)	65 (2.4)
Blood creatinine phosphokinase increased	140 (5.2)	116 (4.3)
Glomerular filtration rate decreased	132 (4.9)	116 (4.3)
Lipase increased	82 (3.0)	84 (3.1)
Blood creatinine increased	92 (3.4)	72 (2.7)
Hypoglycemia	181 (6.7)	173 (6.5)
Hyperglycemia	99 (3.7)	108 (4.0)
Hyperkalemia	85 (3.1)	72 (2.7)
Back pain	84 (3.1)	85 (3.2)

AEs n (%)	ALO (N = 2,701)	PL (N = 2,679)
Dizziness	81 (3.0)	71 (2.7)
Renal impairment	208 (7.7)	179 (6.7)
Proteinuria	103 (3.8)	107 (4.0)
Cough	98 (3.6)	99 (3.7)
Dyspnea	76 (2.8)	82 (3.1)
Hypertension	198 (7.3)	209 (7.8)

AE = adverse event; ALO = alogliptin; PL = placebo.

Critical Appraisal

The randomized, double-blind study design minimized bias associated with expectations of patients and investigators. An independent statistician created a random number series to operate a randomization algorithm for the assignment of patients to their respective study groups, and this series was not shared with blinded study personnel. Blinding was not broken to any investigator for any patient in this study. An appropriate non-inferiority hazard ratio of less than 1.3 was employed and is in concordance with US Food and Drug Administration guidelines.[36] The study appeared to be powered appropriately (91%), with a sufficient sample size to determine non-inferiority of alogliptin to placebo with respect to the initial (1.8) and final (1.3) hazard ratios. The baseline demographic data between the two groups were generally well balanced.

The results showing non-inferiority of alogliptin to placebo with respect to the primary end point appear to be robust, as the analyses accounted for regional differences in standard of care therapies and varying levels of renal function. The hazard ratios of the individual components of the primary MACE composite were aligned with the hazard ratio of the primary MACE composite. The median duration of study drug exposure was approximately 18 months, and therefore the impact of alogliptin treatment on cardiovascular risk beyond this time point cannot be extrapolated. The EXAMINE study enrolled patients with a relatively long duration of type 2 diabetes and existing atherosclerotic disease. Hence, the results may not be applicable to other subgroups of patients with type 2 diabetes, such as those who have been recently diagnosed.

Summary

Alogliptin administered once daily in combination with standard of care was statistically non-inferior to placebo once daily in combination with standard of care with respect to a MACE composite in patients with type 2 diabetes and recent ACS. These findings suggest no increased risk of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke with alogliptin treatment compared with placebo. The observed safety profile in both groups was similar, with no significant differences in the rate of serious adverse events between the two groups.

APPENDIX 6: SUMMARY AND CRITICAL APPRAISAL OF MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS BY CRADDY ET AL. (2014)

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Objective

To summarize the methods and results and to conduct a critical appraisal of a manufacturer-sponsored network meta-analysis (NMA)[34] comparing the efficacy of alogliptin and other dipeptidyl peptidase-4 (DPP-4) inhibitors available in Canada as mono-, dual, and triple therapy. The analysis compared alogliptin, linagliptin, saxagliptin, and sitagliptin effects on the key efficacy outcomes of mean changes in glycated hemoglobin (A1C), mean changes in weight, and hypoglycemic events.

Rationale

According to the investigators, the NMA was undertaken because there are currently limited head-to-head comparative efficacy data for DPP-4 inhibitors.

Methods

TABLE 42: INCLUSION CRITERIA FOR TRIALS ELIGIBLE TO BE INCLUDED IN THE NETWORK META-ANALYSIS

Population	Patients of any age or sex with type 2 diabetes and insufficient glycemic control with first-, second-, and third-line treatment regimens
Interventions/ comparators	Any of the following used in the treatment of type 2 diabetes (as mono-, dual, or triple therapy): • any DPP-4 inhibitor (alogliptin, linagliptin, saxagliptin, sitagliptin) • GLP-1 or sodium-glucose cotransporter-2 inhibitors • pioglitazone Dual-therapy comparisons were between these drugs combined with metformin, a sulfonylurea, pioglitazone, or insulin. Triple-therapy comparisons were between these drugs combined with metformin and a sulfonylurea.
Outcomes	• A1C (mean change from baseline) • Body weight • Hypoglycemic events
Study design	Published blinded and open-label RCTs, health economic evaluation studies, systematic reviews, and meta-analyses

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; RCT = randomized controlled trial.

The investigators did not include observational studies, crossover studies, or any retrospective analysis and excluded extension-phase data because the study population was no longer randomized and the size was generally limited. Studies were excluded if they used an inappropriate study population (e.g., patients with adequate glycemic control, mixed population with type 1 diabetes), did not have a comparator that connected to the treatment network, or did not report sufficient data for standard error imputation (i.e., patient numbers not given).

Network meta-analysis and systematic review

A systematic review was carried out by the authors of the NMA to identify all randomized controlled trials (RCTs) investigating DPP-4 inhibitors as mono-, dual or triple therapy compared with other oral and injectable antidiabetes pharmacologic interventions, including insulin, in the treatment of patients with type 2 diabetes with inadequate glycemic control (Table 42). The following databases were searched: Dialog ProQuest for MEDLINE and MEDLINE In-Process, EMBASE and BIOSIS for conference abstracts (limited to the previous three years), EBSCO (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews), NHS Economic Evaluation Database, and Heath Economic Evaluations Databases for systematic reviews of health economic outcomes. The databases were searched on November 30, 2012, and grey literature searches were also conducted.

Two independent reviewers assessed the data to establish whether relevant outcomes were sufficiently and appropriately reported.

Study quality was assessed by the Institute for Quality and Efficiency in Health Care (IQWiG, Germany) guidelines on methods for conducting systematic reviews,[42] by the checklist criteria recommended in the Agence nationale d'accréditation et d'évaluation en santé (France) guide to the literature and grading of recommendations,[43] and the quality-assessment criteria recommended by the National Institute for Health and Care Excellence (NICE), UK, in its single-technology appraisal template.[44] Included trials were also assessed as to whether they had been reported according to the Consolidated Standards of Reporting Trials (CONSORT).[45]

Random-effects meta-analyses using a frequentist approach were used to pool the direct evidence for each DPP-4 inhibitor (as monotherapy, dual therapy or triple therapy) against common comparator groups (placebo, metformin, sulfonylurea [SU], metformin plus SU, pioglitazone, and insulin).

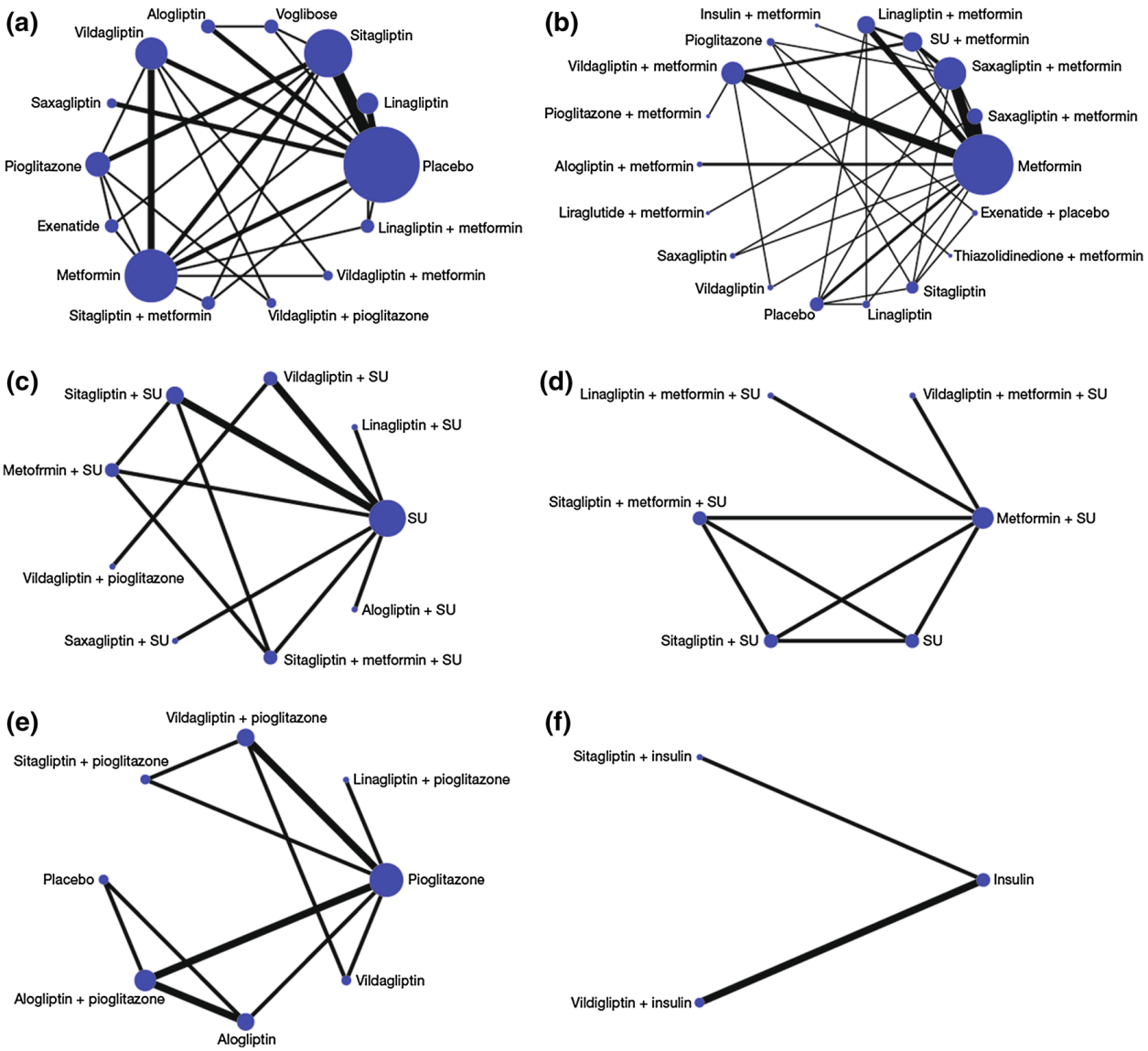
Bayesian meta-analytical techniques were employed for the NMA using WinBUGS software. Separate NMAs were conducted for DPP-4 inhibitors as monotherapy compared with placebo, and for dual- and triple-therapy combinations compared with the backbone monotherapy and dual-therapy regimens, respectively. To account for heterogeneity, random-effects models were used. Both absolute and relative (versus comparator) treatment effects were estimated. Analyses of absolute treatment effects required assumptions regarding the efficacy estimates for the comparator groups, which appear to have been derived from direct meta-analyses, although the methodology used is not described in detail. Both absolute and relative effect estimates are presented in this summary; however, the relative estimates form the main focus, as they were based directly on the available trial data included in each NMA and did not require assumptions regarding the efficacy of the comparator groups.

Weighted mean differences in A1C and body weight from baseline were measured as continuous outcomes, while hypoglycemic events were measured as dichotomous outcomes. Continuous outcomes were estimated using a vague prior normal distribution to allow maximum leverage over iterative process, while the hypoglycemic events outcome was estimated using a binomial distribution. The NMA analysis did not report effect estimates for one DPP-4 inhibitor compared with another; rather, similarity among drugs was concluded if there was overlap of the 95% credible intervals of effect sizes against the common comparator.

To maximize the amount of data available for analysis, standard errors were imputed where needed. For studies that reported multiple doses, all DPP-4 inhibitor and comparator doses were included in the analyses. The models typically consisted of 100,000 iterations with a 50% burn-in sample. Consistency

between direct and indirect comparisons was assessed for nodes comparing DPP-4 inhibitors using Bucher's method. Convergence was assessed using standard diagnostic tools, including observing random walk plots for each node and the Gelman-Rubin statistic.

Figure 9: Network of Eligible Comparisons for Mean Change in A1C From Baseline



Note: (a) = DPP-4 monotherapy, (b) = DPP-4 plus metformin, (c) = DPP-4 plus a sulfonylurea, (d) = DPP-4 plus metformin plus a sulfonylurea, (e) = DPP-4 plus pioglitazone, and (f) = DPP-4 plus insulin.
Source: Figure 2 in Craddy et al. 2014.[34]

Study Characteristics

A total of 83 RCTs (including five open-label studies) were included in the meta-analysis. Eighty-two RCTs compared DPP-4 inhibitor treatment regimens (alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin) with placebo, metformin (with or without SU, pioglitazone, or insulin), SU alone, pioglitazone, or insulin, while one RCT directly compared sitagliptin with saxagliptin, both in combination with metformin. The total number of RCTs retrieved were as follows (note that the

numbers do not add up to 83 because each RCT could be used in multiple sets analyses): 24 RCTs for monotherapy, 38 RCTs for DPP-4 plus metformin, 8 RCTs for DPP-4 plus SU, 3 RCTs for DPP-4 plus metformin plus SU, 9 RCTs for DPP-4 plus pioglitazone, 1 RCT for DPP-4 plus metformin plus pioglitazone, 4 RCTs for DPP-4 plus insulin, and 1 RCT for DPP-4 plus metformin plus insulin (Table 43). Results for vildagliptin, a DPP-4 inhibitor not approved in Canada, are not presented. The study durations of included RCTs ranged from four weeks to 104 weeks. The majority of studies had baseline inclusion criteria of A1C levels between 6.5% and 12% and BMI of 40 kg/m^2 or greater. Change in A1C from baseline was the primary outcome in most studies, although eight trials reported co-primary outcomes such as change from baseline in FPG, two-hour postprandial glucose level, BMI, body weight, fasting lipid level, fasting plasma insulin level, fasting insulin level, fasting C-peptide level, vital signs, and number or proportion of patients with adverse events.

TABLE 43: NUMBER OF RANDOMIZED CONTROLLED TRIALS INCLUDED IN NETWORK META-ANALYSIS BY TREATMENT

Treatment	Included RCTs
Monotherapy	24
DPP-4 plus metformin	38
DPP-4 plus SU	8
DPP-4 plus metformin plus SU	3
DPP-4 plus pioglitazone	9
DPP-4 plus metformin plus pioglitazone	1
DPP-4 plus insulin	4
DPP-4 plus metformin plus insulin	1

DPP-4 = dipeptidyl peptidase-4; RCT = randomized controlled trial; SU = sulfonylurea.

Results

DPP-4 inhibitor monotherapy

In the direct comparison analysis, all DPP-4 inhibitors as monotherapy were statistically significantly more effective than placebo in reducing A1C from baseline. As seen in Table 44, the greatest mean reduction in A1C from baseline among the DPP-4 inhibitors was with alogliptin –0.797% (95% confidence interval [CI], –0.943% to –0.651%). Mean increases in weight from baseline only reached statistical significance versus placebo for linagliptin and sitagliptin; mean weight changes from baseline were 0.431 kg (95% CI, 0.004 kg to 0.86 kg) and 0.717 kg (95% CI, 0.37 kg to 1.06 kg), respectively. The differences in the frequency of hypoglycemic events were not statistically significant compared with placebo for any of the DPP-4 inhibitors.

In the NMA analysis (Table 45), all DPP-4 inhibitors as monotherapy were statistically significantly more effective than placebo in reducing A1C from baseline, with mean effect sizes ranging from –0.61% (saxagliptin) to –0.74% (alogliptin and linagliptin). Treatment with sitagliptin resulted in a statistically significant increase in mean body weight relative to placebo of 0.70 kg (95% CI, 0.33 kg to 1.08 kg); there were no significant differences between alogliptin or linagliptin and placebo; and data for this comparison were unavailable for saxagliptin. Statistically significantly lower odds of a hypoglycemic event (odds ratio 0.18; 95% CI, 0.0074 to 0.77) were observed for linagliptin when compared with placebo, but odds ratios were statistically non-significant for the other DPP-4 inhibitors. Absolute treatment effects are presented in Table 46.

DPP-4 inhibitor + metformin dual therapy

In the direct comparison analysis, all DPP-4 inhibitors as dual therapy with metformin were statistically significantly more effective than metformin alone for reducing A1C from baseline (Table 44). The results for mean increases in weight from baseline and hypoglycemic events were not statistically significantly different from metformin alone for any of the DPP-4 inhibitors in combination with metformin. One head-to-head RCT compared sitagliptin plus metformin versus saxagliptin plus metformin. The adjusted mean changes in A1C following the addition of saxagliptin or sitagliptin to stable metformin therapy were –0.52% and –0.62%, respectively. The between-group difference for mean change in A1C from baseline was 0.09% (95% CI, –0.01% to 0.20%), and within the study's predefined criterion (less than 0.3%) for non-inferiority. The direct and indirect treatment effects for mean change in A1C from baseline were consistent (P = 0.16).

In the NMA analysis, all DPP-4 inhibitors as dual therapy with metformin were statistically significantly more effective than metformin alone for achieving a mean reduction in A1C from baseline. There were no statistically significant differences in body weight or the odds of hypoglycemia between dual therapy and metformin monotherapy (Table 45). Results from the analysis of absolute treatment effects are presented in Table 46.

DPP-4 inhibitor + SU dual therapy

In the direct comparison analysis, all DPP-4 inhibitors as dual therapy with SUs were statistically significantly more effective than SU alone for reducing A1C from baseline, although results for linagliptin and saxagliptin were based solely on one study (Table 44). There were no significant differences between dual therapy and SU monotherapy in body weight for any of the DPP-4 inhibitors. Statistically significant greater odds of a hypoglycemic event (odds ratio 3.43; 95% CI, 1.00 to 11.78) were reported only for sitagliptin combined with SU compared with SU alone.

In the NMA analysis (Table 45), all DPP-4 inhibitors as dual therapy with SU were statistically significantly more effective than SU alone for reducing A1C from baseline. There were no statistically significant differences between dual therapy and SU monotherapy with respect to changes in body weight or odds of hypoglycemia. Results from the analysis of absolute treatment effects are presented in Table 46.

DPP-4 inhibitor + pioglitazone dual therapy

In the direct comparison analysis, all DPP-4 inhibitors (with the exception of saxagliptin, for which data were not available) as dual therapy with pioglitazone were statistically significantly more effective than pioglitazone alone for reducing A1C from baseline (Table 44). Alogliptin, sitagliptin, and linagliptin combined with pioglitazone were all associated with statistically significant mean increases in weight compared with pioglitazone monotherapy. There were no significant differences between dual therapy and monotherapy with respect to the odds of hypoglycemia.

In the NMA analysis (Table 45), all DPP-4 inhibitors (with the exception of saxagliptin, for which data were not available) as dual therapy with pioglitazone were statistically significantly more effective than pioglitazone alone for reducing A1C from baseline. Only linagliptin plus pioglitazone was associated with a statistically significant increase in body weight (1.20 kg; 95% CI, 0.06 kg to 2.34 kg) compared with pioglitazone alone. There were no statistically significant differences in the odds of hypoglycemic events between dual therapy and monotherapy. Results from the analysis of absolute treatment effects are presented in Table 46.

DPP-4 inhibitor + insulin dual therapy

In the direct comparison analysis, data for dual therapy with DPP-4 plus insulin were available only for sitagliptin. None of the results for mean reduction in A1C from baseline, weight change from baseline, or hypoglycemic events reached statistical significance (Table 44). Because of the lack of trials for alogliptin, saxagliptin, and linagliptin in combination with insulin, the NMA analysis was not informative regarding the relative efficacy of various DPP-4 inhibitors in this setting.

DPP-4 inhibitor + metformin + SU triple therapy

The direct comparison analysis of triple therapy included only linagliptin and sitagliptin, as studies were not identified for the other two drugs (Table 44, Table 45, and Table 46). However, a trial of saxagliptin versus placebo in combination with metformin and sulfonylurea has in fact been conducted, and was previously reviewed by the CADTH Common Drug Review (CDR).[8,46] The mean differences versus placebo in change in A1C from baseline for sitagliptin and linagliptin were –0.89% (95% CI, –2.41% to 0.63%) and –0.20% (95% CI, –0.73% to –0.51%), respectively, and mean differences in change from baseline body weight were 0.33 kg (95% CI, –0.30 kg to 0.69 kg) and 0.70 kg (95% CI, –0.22 kg to 1.62 kg), respectively. The odds ratios of a hypoglycemic event versus placebo were 1.69 (95% CI, 1.16 to 2.47) and 8.70 (95% CI, 1.07 to 70.76) for linagliptin and sitagliptin, respectively. The corresponding effect estimates reported in the CDR review of saxagliptin were –0.66% (95% CI, –0.86 to –0.47) for A1C, 0.8 kg (95% CI, 0.3 to 1.3) for body weight, and 1.61 (95% CI, 0.69 to 3.76) for the relative risk of hypoglycemia.[8,46] As seen in Table 45 and Table 46, MTC results for relative and absolute treatment effects for linagliptin or sitagliptin triple therapy versus metformin + sulfonylurea dual therapy were not statistically significant.

TABLE 44: RESULTS FROM DIRECT COMPARISONS OF DPP-4 INHIBITORS VERSUS COMPARATORS

End Point	Monotherapy Versus Placebo			
	Alogliptin 25 mg P.O. daily	Linagliptin 5 mg P.O. daily	Saxagliptin 5 mg P.O. daily	Sitagliptin 100 mg P.O. daily
Weighted mean difference (95% CI)				
A1C change from baseline	–0.797[a] (–0.943 to –0.651) N = 2 studies	–0.734[a] (–0.88 to –0.588) N = 3 studies	–0.593[a] (–0.811 to –0.375) N = 2 studies	–0.788[a] (–0.954 to –0.622) N = 5 studies
Weight change from baseline (kg)	0.049 (–0.53 to 0.62) N = 2 studies	0.431[a] (0.004 to 0.86) N = 2 studies	–	0.717[a] (0.37 to 1.06) N = 3 studies
Odds ratio (95% CI)				
Patients with hypoglycemic events	0.949 (0.06 to 15.45) N = 2 studies	0.311 (0.04 to 2.55) N = 3 studies	0.257 (0.49 to 13.13) N = 2 studies	0.924 (0.23 to 3.77) N = 6 studies
	Dual Therapy Versus Respective Monotherapy			
	Alogliptin 25 mg P.O. daily + metformin	Linagliptin 5 mg P.O. daily + metformin	Saxagliptin 5 mg P.O. daily + metformin	Sitagliptin 100 mg P.O. daily + metformin
Weighted mean difference (95% CI)				
A1C change from baseline	–0.699[a] (–1.05 to –0.35) N = 2 studies	–0.679[a] (–0.79 to –0.57) N = 3 studies	–0.585[a] (–0.76 to –0.41) N = 3 studies	0.649[a] (–0.78 to –0.52) N = 6 studies
Weight change from baseline (kg)	0.1470 (–0.23 to 0.51) N = 1 study	0.100 (–5.60 to 5.80) N = 1 study	–	0.384 (–0.18 to 0.94) N = 2 studies
Odds ratio (95% CI)				
Patients with hypoglycemic events	0.069 (0.004 to 1.34) N = 1 study	1.394 (0.17 to 11.62) N = 2 studies	0.950 (0.54 to 1.66) N = 1 study	0.910 (0.48 to 1.74) N = 3 studies
	Alogliptin 25 mg P.O. daily + SU	**Linagliptin 5 mg P.O. daily + SU**	**Saxagliptin 5 mg P.O. daily + SU**	**Sitagliptin 100 mg P.O. daily + SU**
Weighted mean difference (95% CI)				
A1C change from baseline	–0.540[a] (–0.82 to –0.26) N = 1 study	–0.470[a] (–0.71 to –0.23) N = 1 study	–0.720[a] (–1.22 to –0.22) N = 1 study	–0.676[a] (–0.90 to –0.45) N = 2 studies
Weight change from baseline (kg)	0.880[a] (0.22 to 1.54) N = 1 study	0.440 (–0.34 to 1.22) N = 1 study	–0.700 (–1.62 to 0.22) N = 1 study	0.611[a] (0.10 to 1.13) N = 2 studies
Odds ratio (95% CI)				
Patients with hypoglycemic events	0.849 (0.39 to 1.86) N = 1 study	1.184 (0.35 to 3.97) N = 1 study	1.523 (0.90 to 2.58) N = 1 study	3.438[a] (1.00 to 11.78) N = 2 studies

	Alogliptin 25 mg P.O. daily + pioglitazone	Linagliptin 5 mg P.O. daily + pioglitazone	Saxagliptin 5 mg P.O. daily + pioglitazone	Sitagliptin 100 mg P.O. daily + pioglitazone
Weighted mean difference (95% CI)				
A1C change from baseline	–0.606[a] (–0.97 to –0.25) N = 2 studies	–0.500[a] (–0.71 to –0.29) N = 1 study	–	–0.900[a] (–1.18 to –0.62) N = 1 study
Weight change from baseline (kg)	0.568[a] (0.23 to 0.91) N = 2 studies	1.200[a] (1.10 to 1.30) N = 1 study	–	1.100[a] (0.019 to 2.181) N = 1 study
Odds ratio (95% CI)				
Patients with hypoglycemic events	7.32 (0.38 to 143.28) N = 1 study	3.561 (0.18 to 69.47) N = 1 study	–	1.494 (0.25 to 9.02) N = 1 study
	Alogliptin 25 mg P.O. daily + insulin	**Linagliptin 5 mg P.O. daily + insulin**	**Saxagliptin 5 mg P.O. daily + insulin**	**Sitagliptin 100 mg P.O. daily + insulin**
Weighted mean difference (95% CI)				
A1C change from baseline	–	–	–	–0.410 (–0.84 to 0.019) N = 1 study
Weight change from baseline (kg)	–	–	–	–1.800 (–2.61 to 0.99) N = 1 study
Odds ratio (95% CI)				
Patients with hypoglycemic events	–	–	–	0.934 (0.23 to 3.80) N = 2 studies
Triple Therapy Versus Respective Dual Therapy				
	Alogliptin 25 mg P.O. daily + metformin + SU	**Linagliptin 5 mg P.O. daily + metformin + SU**	**Saxagliptin 5 mg P.O. daily + metformin + SU**	**Sitagliptin 100 mg P.O. daily + metformin + SU**
Weighted mean difference (95% CI)				
A1C change from baseline	–	–0.620[a] (–0.73 to –0.51) N = 1 study	–	–0.890 (–2.41 to 0.63) N = 1 study
Weight change from baseline (kg)	–	0.330 (–0.3 to 0.69) N = 1 study	–	0.700 (–0.22 to 1.62) N = 1 study
Odds ratio (95% CI)				
Patients with hypoglycemic events	–	1.689[a] (1.16 to 2.47) N = 1 study	–	8.699[a] (1.07 to 70.76) N = 1 study

A1C = glycated hemoglobin; CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; P.O. = oral administration; SU = sulfonylurea.

[a] Statistically significant versus comparator.

TABLE 45: NETWORK META-ANALYSIS RESULTS FOR RELATIVE EFFECTS OF DPP-4 INHIBITORS VERSUS COMPARATORS

Monotherapy Versus Placebo				
End point	**Alogliptin 25 mg P.O. daily**	**Linagliptin 5 mg P.O. daily**	**Saxagliptin 5 mg P.O. daily**	**Sitagliptin 100 mg P.O. daily**
Weighted mean difference (95% CrI)				
A1C change from baseline %	–0.74 (–0.99 to –0.49)[a]	–0.74 (–0.96 to –0.51)[a]	–0.61 (–0.91 to –0.31)[a]	0.75 (–0.90 to –0.60)[a]
Weight change from baseline in kg	0.32 (–0.08 to 0.70)	0.37 (–0.11 to 0.86)	–	0.70 (0.33 to 1.08)[a]
Odds ratio (95% CI)				
Patients with hypoglycemic events	0.27 (0.008 to 1.39)	0.18 (0.0074 to 0.77)[a]	1.86 (0.169 to 7.39)	0.61 (0.14 to 1.66)
Dual Therapy Versus Respective Monotherapy				
	Alogliptin 25 mg P.O. daily + metformin	**Linagliptin 5 mg P.O. daily + metformin**	**Saxagliptin 5 mg P.O. daily + metformin**	**Sitagliptin 100 mg P.O. daily + metformin**
Weighted mean difference (95% CrI)				
A1C change from baseline %	–0.68 (–0.96 to –0.40)[a]	–0.57 (–0.75 to –0.40)[a]	–0.61 (–0.79 to –0.44)[a]	–0.64 (–0.79 to –0.50)[a]
Weight change from baseline in kg	0.26 (–1.50 to 2.02)	0.17 (–5.58 to 5.80)	–	0.28 (–1.65 to 1.05)
Odds ratio (95% CrI)				
Patients with hypoglycemic events	0.24 (0.02 to 1.00)	0.72 (0.32 to 1.35)	0.81 (0.44 to 1.40)	1.32 (0.72 to 2.23)
	Alogliptin 25 mg P.O. daily + SU	**Linagliptin 5 mg P.O. daily + SU**	**Saxagliptin 5 mg P.O. daily + SU**	**Sitagliptin 100 mg P.O. daily + SU**
Weighted mean difference (95% CrI)				
A1C change from baseline %	–0.47 (–0.87 to –0.08)[a]	–0.47 (–0.90 to –0.03)[a]	–0.66 (–1.17 to –0.15)[a]	–0.68 (–1.00 to –0.37)[a]
Weight change from baseline in kg	0.83 (–0.60 to 2.26)	0.44 (–1.25 to 2.14)	0.48 (–0.92 to 1.89)	0.68 (–0.42 to 1.91)
Odds ratio (95% CrI)				
Patients with hypoglycemic events	1.44 (0.31 to 4.13)	1.71 (0.22 to 6.33)	1.73 (0.42 to 4.67)	4.74 (0.87 to 15.75)

	Alogliptin 25 mg P.O. daily + pioglitazone	Linagliptin 5 mg P.O. daily + pioglitazone	Saxagliptin 5 mg P.O. daily + pioglitazone	Sitagliptin 100 mg P.O. daily + pioglitazone
Weighted mean difference (95% CrI)				
A1C change from baseline %	–0.64 (–0.86 to –0.39)[a]	–0.50 (–0.89 to –0.11)[a]	–	–0.88 (–1.28 to –0.45)[a]
Weight change from baseline in kg	0.54 (–0.20 to 1.32)	1.20 (0.06 to 2.34)[a]	–	1.10 (–0.42 to 2.61)
Odds ratio (95% CrI)				
Patients with hypoglycemic events	20.15 (0.68 to 110.3)	13.24 (0.14 to 78.65)	–	3.22 (0.089 to 14.99)
	Alogliptin 25 mg P.O. daily + insulin	**Linagliptin 5 mg P.O. daily + insulin**	**Saxagliptin 5 mg P.O. daily + insulin**	**Sitagliptin 100 mg P.O. daily + insulin**
Weighted mean difference (95% CrI)				
A1C change from baseline %	–	–	–	–0.41 (–5.07 to 4.25)
Weight change from baseline in kg	–	–	–	–1.81 (–8.07 to 4.50)
Odds ratio (95% CrI)				
Patients with hypoglycemic events	–	–	–	2.74 (0.057 to 13.79)
Triple Therapy Versus Respective Dual Therapy				
	Alogliptin 25 mg P.O. daily + metformin + SU	**Linagliptin 5 mg P.O. daily + metformin + SU**	**Saxagliptin 5 mg P.O. daily + metformin + SU**	**Sitagliptin 100 mg P.O. daily + metformin + SU**
Weighted mean difference (95% CrI)				
A1C change from baseline %	–	–0.62 (–6.84 to 5.63)	–	–0.91 (–7.30 to 5.43)
Weight change from baseline in kg	–	0.32 (–5.93 to 6.58)	–	1.78 (–4.54 to 8.07)
Odds ratio (95% CrI)				
Patients with hypoglycemic events	–	7.17 (0.05 to 33.96)	–	12.92 (0.095 to 62.92)

A1C = glycated hemoglobin; CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; NMA = network meta-analysis; P.O. = oral administration; SU = sulfonylurea.

TABLE 46: NETWORK META-ANALYSIS RESULTS FOR ABSOLUTE TREATMENT EFFECTS OF DPP-4 INHIBITORS

Monotherapy				
End Point	**Alogliptin 25 mg P.O. daily**	**Linagliptin 5 mg P.O. daily**	**Saxagliptin 5 mg P.O. daily**	**Sitagliptin 100 mg P.O. daily**
Weighted mean difference (95% CrI)				
A1C change from baseline %	–0.58 (–0.83 to –0.33)	–0.58 (–0.81 to –0.35)	–0.45 (–0.75 to –0.15)	–0.59 (–0.75 to –0.43)
Weight change from baseline in kg	–0.17 (–0.60 to 0.23)	–0.12 (–0.62 to 0.38)	–	0.20 (–0.18 to 0.60)
Odds ratio (95% CrI)				
Patients with hypoglycemic events	0.0013 (0.000032 to 0.0071)	0.008 (0.000028 to 0.0042)	0.0088 (0.00062 to 0.038)	0.0029 (0.00046 to 0.0097)
Dual Therapy				
	Alogliptin 25 mg P.O. daily + metformin	**Linagliptin 5 mg P.O. daily + metformin**	**Saxagliptin 5 mg P.O. daily + metformin**	**Sitagliptin 100 mg P.O. daily + metformin**
Weighted mean difference (95% CrI)				
A1C change from baseline %	–1.10 (–1.38 to –0.82)	–0.99 (–1.17 to –0.82)	–1.03 (–1.21 to –0.85)	–1.06 (–1.22 to –0.91)
Weight change from baseline in kg	–0.45 (–2.22 to 1.31)	–0.54 (–6.31 to 5.09)	–	–0.99 (–2.38 to 0.35)
Odds ratio (95% CrI)				
Patients with hypoglycemic events	0.0039 (0.00028 to 0.017)	0.012 (0.0036 to 0.028)	0.013 (0.0045 to 0.030)	0.021 (0.0074 to 0.047)
	Alogliptin 25 mg P.O. daily + SU	**Linagliptin 5 mg P.O. daily + SU**	**Saxagliptin 5 mg P.O. daily + SU**	**Sitagliptin 100 mg P.O. daily + SU**
Weighted mean difference (95% CrI)				
A1C change from baseline %	–0.40 (–0.81 to –0.01)	–0.40 (–0.84 to 0.04)	–0.60 (–1.11 to –0.08)	–0.61 (–0.94 to –0.29)
Weight change from baseline in kg	0.87 (–0.58 to 2.30)	0.47 (–1.22 to 2.18)	–	0.72 (–0.39 to 1.96)
Odds ratio (95% CrI)				
Patients with hypoglycemic events	0.043 (0.0035 to 0.18)	0.05 (0.0026 to 0.23)	0.05 (0.0045 to 0.20)	0.11 (0.0096 to 0.44)

	Alogliptin 25 mg P.O. daily + pioglitazone	Linagliptin 5 mg P.O. daily + pioglitazone	Saxagliptin 5 mg P.O. daily + pioglitazone	Sitagliptin 100 mg P.O. daily + pioglitazone
Weighted mean difference (95% CrI)				
A1C change from baseline %	–1.29 (–1.52 to –1.05)	–1.16 (–1.56 to –0.76)	–	–1.53 (–1.95 to –1.11)
Weight change from baseline in kg	1.59 (0.84 to 2.37)	2.24 (1.10 to 3.38)	–	2.14 (0.63 to 3.65)
Odds ratio (95% CrI)				
Patients with hypoglycemic events	0.059 (0.00021 to 0.47)	0.036 (0.00055 to 0.33)	–	0.014 (0.000031 to 0.11)
	Alogliptin 25 mg P.O. daily + insulin	**Linagliptin 5 mg P.O. daily + insulin**	**Saxagliptin 5 mg P.O. daily + insulin**	**Sitagliptin 100 mg P.O. daily + insulin**
Weighted mean difference (95% CrI)				
A1C change from baseline %	–	–	–	–0.56 (–5.22 to 4.09)
Weight change from baseline in kg	–	–	–	–1.03 (–7.31 to 5.32)
Odds ratio (95% CrI)				
Patients with hypoglycemic events	–	–	–	0.22 (0.0086 to 0.7903)
Triple Therapy				
	Alogliptin 25 mg P.O. daily + metformin + SU	**Linagliptin 5 mg P.O. daily + metformin + SU**	**Saxagliptin 5 mg P.O. daily + metformin + SU**	**Sitagliptin 100 mg P.O. daily + metformin + SU**
Weighted mean difference (95% CrI)				
A1C change from baseline %	–	–0.65 (–6.87 to 5.60)	–	–0.94 (–7.34 to 5.40)
Weight change from baseline in kg	–	0.14 (–6.11 to 6.39)	–	1.60 (–4.73 to 7.89)
Odds ratio (95% CrI)				
Patients with hypoglycemic events	–	0.13 (0.00057 to 0.76)	–	0.21 (0.0011 to 0.89)

A1C = glycated hemoglobin; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; P.O. = oral administration; SU = sulfonylurea.
[a] Statistically significant versus comparator.

Sensitivity Analyses
Sensitivity analyses were conducted to examine the impact of including studies contributing to moderate levels of heterogeneity in direct meta-analyses (I^2 > 30%). Two studies comparing DPP-4 inhibitors (saxagliptin and vildagliptin) plus metformin versus metformin alone were identified as outliers for the A1C outcome. Sensitivity analyses removing these studies from the NMA indicated that there was little or no impact on the overall conclusions.

Critical appraisal of network meta-analysis
The quality of the manufacturer-submitted NMA was assessed according to recommendations provided by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons. Details and commentary for each of the relevant items identified by ISPOR are provided in Table 47.

Strengths
The NMA appears to satisfy most of the ISPOR criteria. The rationale and objectives for the NMA were clearly stated. The inclusion criteria for individual RCTs were clearly stated, and study selection and the data extraction process were provided. A comprehensive search strategy was employed to identify and select relevant RCTs. The methodological quality of the included RCTs was assessed based on the IQWiG (Germany) guidelines on methods for conducting systematic reviews,[42] checklist criteria recommended by l'Agence nationale d'accréditation et d'évaluation en santé (France),[43] and quality-assessment criteria recommended by NICE (UK) in its single-technology appraisal template.[44] Study reporting in accordance with CONSORT was also determined.[45]

The direct and indirect comparisons were conducted using appropriate statistical methodology (i.e., a frequentist approach with a random-effects model was used for the direct comparison, while a Bayesian approach was used for the NMA). The outcome measures assessed in the NMA were appropriate and clearly stated. Statistical heterogeneity in the direct comparison meta-analyses was assessed, and random-effects models were used to account for heterogeneity between studies. Both relative and absolute effect measures were reported in the NMA. Vague priors were used in the NMA to allow maximum leverage over iterative process. Sensitivity analyses confirmed that removal of studies contributing to heterogeneity in the direct analyses from the NMA did not impact the overall findings for mean change in A1C from baseline. The direct and indirect treatment effects for A1C change from baseline for saxagliptin plus metformin and sitagliptin plus metformin were shown to be consistent.

Limitations
There was heterogeneity between included RCTs in baseline characteristics and study durations. Specifically, six studies included patients with baseline A1C levels of up to 12%, seven studies included patients with a lower maximum baseline BMI, and 18 studies included patients with a higher maximum baseline BMI. Four studies included only patients 65 years of age or older. Furthermore, the included studies varied considerably in duration, and the authors of the NMA did not specify what time periods were selected and analyzed for all outcomes. Finally, the included studies of sulfonylureas employed various drugs within this class. Sensitivity analyses or meta-regression techniques to determine the potential impact of these sources of heterogeneity could have added greater confidence in the findings.

The main objective of the submitted analysis was to determine the relative efficacy and safety of the DPP-4 inhibitors available in Canada. It was therefore unclear why the various analyses (monotherapy, dual therapy, and triple therapy) were not restricted to trials of DPP-4 inhibitors in each of these settings. For example, the NMA of DPP-4 inhibitor + metformin dual therapy included nodes for SU + metformin, exenatide + metformin, and thiazolidinedione + metformin, as well as nodes for each of the DPP-4 inhibitors as monotherapy. While this approach may have added statistical power to the model, it could also have increased the level of heterogeneity across included trials, potentially confounding the analysis. At the very least, a scenario analysis in which only the trials assessing each DPP-4 inhibitor in the regimen of interest (e.g., DPP-inhibitor + metformin dual therapy versus metformin monotherapy) could have been conducted to validate the findings from the larger model.

Another limitation was that the methodological quality of the included studies was generally poor or indeterminate, with only two studies deemed to be of high quality. The investigators also indicated that unpublished data were not specifically sought. Thus, it remains possible some unpublished studies may not have been identified (indeed, a study of saxagliptin as triple therapy with metformin and sulfonylurea previously reviewed by CDR was missed). It was also unclear whether the treatment effect was affected by the assumptions made for imputation of missing standard errors to include data for all DPP-4 inhibitors and comparator doses. No sensitivity analyses were performed to address this.

As described under Methods, previously in this appendix, the analysis of absolute treatment effects was considered to have limitations arising from the need to make assumptions regarding comparator treatment effects. Hence, the main focus of this summary was on the analyses of relative treatment effects. Although the overall statistical approach to the relative effects NMA appeared sound, it was unclear why indirect effect estimates were not reported for one DPP-4 inhibitor versus another. Standard reporting of NMA analyses normally includes effect estimates for all possible comparisons within the NMA. Rather, the investigators inappropriately concluded similar numerical efficacy between DPP-4 inhibitors as long as there was overlap in the 95% credible intervals of the effect estimates for each DPP-4 inhibitor versus the common comparator.[47]

Summary

The manufacturer-submitted NMA demonstrated numerically similar efficacy between DPP-4 inhibitors either as monotherapy or combination therapy for mean change in A1C from baseline. The relative treatment effect results for mean change in body weight and hypoglycemic events from baseline were also generally similar between DPP-4 inhibitors. The results of the manufacturer-submitted NMA were in alignment with the findings of the CADTH Therapeutic Review on second-line and third-line treatments for type 2 diabetes, although alogliptin was not included in these analyses.[5,6] While the NMA did not find any evidence of differences between the DPP-4 inhibitors on A1C, body weight, or hypoglycemia, the analysis does not allow for a definitive conclusion of similar efficacy and safety across DPP-4 inhibitors.

TABLE 47: APPRAISAL OF NETWORK META-ANALYSIS USING ISPOR CRITERIA

ISPOR Checklist Item		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting a network meta-analysis and the study objectives were clearly stated.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• Eligibility criteria for individual RCTs were clearly stated. • Search strategy, study selection process and data extraction were clearly stated for all comparators. • Search strategy was provided. • Study selection and data extraction process were identified. • Assessment of the risk of bias and study quality was conducted. • Heterogeneity between studies was assessed.
3.	Are the outcome measures described?	• Specific outcomes were clearly stated.
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• A description of the statistical model was provided. • A frequentist approach with a random-effects model was used for the direct comparison, while a Bayesian approach was used for the mixed treatment comparison. • Both relative and absolute effect measures were used in the mixed treatment comparison. • A vague prior was used for the mixed treatment comparison for normal distribution to allow maximum leverage over iterative process.
5.	Are sensitivity analyses presented?	• Sensitivity analyses removing studies with heterogeneity (I^2 > 30%) were presented for mean change from baseline in A1C.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• A table with study characteristics was provided. • A figure showing the network of studies was provided. • Individual study results were provided.
7.	Does the study describe an assessment of model fit?	Model fit was not assessed. Consistency testing using Bucher's method between the direct and indirection comparisons was assessed for nodes comparing DPP-4 inhibitors directly.
8.	Are the results of the evidence synthesis presented clearly?	• Tables were provided with both absolute and relative results for each outcome.

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; RCT = randomized controlled trial.

APPENDIX 7: SUMMARY AND CRITICAL APPRAISAL OF MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS BY TOLLEY ET AL. (2014)

The manufacturer submitted a second network meta-analysis (NMA) of alogliptin by Tolley et al. This was an unpublished NMA that was submitted to the Scottish Medicines Consortium (SMC) after this body expressed many of the same concerns as the CADTH Common Drug Review (CDR) regarding the NMA by Craddy et al. A summary and critical appraisal of the Tolley NMA is presented here.

Objective

The objective of the Tolley et al. (2014)[35] NMA was to assess the relative efficacy and safety of alogliptin for dual therapy (i.e., in combination with metformin when a sulfonylurea [SU] is not appropriate, or in combination with SU when metformin is not appropriate). The analysis was performed to address limitations noted by SMC in the previous NMA analysis (Craddy et al. 2014[34]), specifically the heterogeneity of outcomes at different time points between studies. The Tolley review was more decision-focused than Craddy et al. in that it included only dual-therapy studies for alogliptin 25 mg daily (in combination with metformin or SU) compared with sitagliptin, saxagliptin, linagliptin, and vildagliptin at their recommended daily dose. Results for vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor not approved in Canada, are not presented in this summary.

Methods

Studies were included in the Tolley et al. NMA if they consisted of adult patients with type 2 diabetes and inadequate glycemic control despite treatment with metformin or an SU. The primary efficacy outcome of interest was mean change in glycated hemoglobin (A1C) from baseline at the final visit. Mean change in body weight from baseline and proportion of patients with A1C less than 7% (results not shown or discussed in this summary) were exploratory outcomes. Safety outcomes included occurrence of one or more hypoglycemic event(s) and discontinuations due to adverse events (AEs) or intolerance. Blinded and unblinded randomized controlled trials (RCTs) and open-label extensions of RCTs were included in the systematic review; however, the open-label extensions were excluded from the NMA. Study quality was assessed using adapted questions from the National Institute for Health and Care Excellence (NICE, UK) single-technology appraisal specifications checklist, and categorized as good (all questions were answered “yes”), moderate (up to two questions were answered “not clear”), or poor quality (any of the questions were answered “no”). Bayesian meta-analytical techniques were conducted for the NMAs using the OpenBUGS software. The investigators used fixed- or random-effects approaches where possible based on the deviance information criterion and residual deviance statistics. Heterogeneity was assessed using chi-squared and I^2 statistics for direct pairwise comparisons. Leverage plots were used to identify studies that appeared to be outliers. Sensitivity analyses were performed to: 1) restrict analysis to studies of 52 weeks’ duration; 2) exclude “outlier” studies with higher or lower baseline A1C values; 3) remove studies that have been identified as outliers by leverage plots; 4) include two studies in the 24-week metformin dual-therapy network that reported A1C results only in the per protocol population; 5) exclude studies judged to be of poor quality; and 6) group the comparator DPP-4 inhibitors to perform an analysis of alogliptin versus the grouped DPP-4s.

The investigators also performed, for the change in A1C from baseline, an analysis of the probability of alogliptin 25 mg daily being non-inferior to the other DPP-4 inhibitors within a margin of 0.3%. This margin is typical of non-inferiority RCTs of antidiabetes treatments.

Results

For dual therapy with metformin, a total of 14 RCTs were available for the 24-week NMA and six RCTs for the 52-week NMA. A total of five RCTs were available for the SU dual-therapy NMA. Four studies (consisting of all of the metformin dual-therapy studies) were deemed to be of poor quality.

Metformin dual therapy

In the metformin dual-therapy analyses, there were no statistically significant differences for change in adjusted mean A1C from baseline at 24 weeks using the random- or fixed-effects models for comparisons of alogliptin with linagliptin, saxagliptin, and sitagliptin (Table 48). The probability of alogliptin 25 mg being non-inferior to linagliptin, saxagliptin, and sitagliptin was 95%, 100%, and 96%, respectively, with the fixed-effects model, and 64%, 77%, and 61%, respectively, with the random-effects model. Only a fixed-effects model was run for mean change in body weight at 24 weeks. Statistically significant differences in body weight change favourable to alogliptin 25 mg were seen for the comparisons with saxagliptin 5 mg, with a mean difference of 1.18 kg (95% CrI, 0.30 to 2.06). There was a statistically significant difference in favour of alogliptin compared with sitagliptin and saxagliptin in the log odds ratio for proportion of patients with one or more hypoglycemic episode(s) with both the fixed- and random-effects models.

TABLE 48: NETWORK META-ANALYSIS RESULTS AT 24 WEEKS: METFORMIN + DPP-4 INHIBITOR DUAL THERAPY

End Point	DPP-4 Inhibitor Versus Alogliptin (Fixed-Effects Model)		
	Linagliptin 5 mg P.O. daily	Saxagliptin 5 mg P.O. daily	Sitagliptin 100 mg P.O. daily
A1C change from baseline, WMD (95% CI)	–0.10 (–0.34 to 0.14)	0.11 (–0.11 to 0.32)	–0.11 (–0.33 to 0.11)
Probability of non-inferiority on A1C[a]	0.95	1.00	0.96
Weight change from baseline (kg), WMD (95% CI)	NA	1.18 (0.30 to 2.06)	0.68 (–0.19 to 1.55)
Patients with ≥ 1 hypoglycemic event, log odds ratio (95% CrI)	2.09 (–1.60 to 7.99)	4.40 (1.07 to 10.19)	3.92 (0.58 to 9.71)
	DPP-4 Inhibitor Versus Alogliptin (Random-Effects Model)		
	Linagliptin 5 mg P.O. daily	Saxagliptin 5 mg P.O. daily	Sitagliptin 100 mg P.O. daily
A1C change from baseline, WMD (95% CI)	–0.10 (–1.46 to 1.26)	0.06 (–1.04 to 1.17)	–0.17 (–1.28 to 0.94)
Probability of non-inferiority on A1C[a]	0.64	0.77	0.61
Weight change from baseline (kg), WMD (95% CI)	NA	NA	NA
Patients with ≥ 1 hypoglycemic event, log odds ratio (95% CrI)	2.16 (–2.24 to 8.35)	4.51 (0.62 to 10.52)[a]	3.94 (0.00 to 9.97)[a]

A1C = glycated hemoglobin; CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; NA = not applicable; P.O. = oral administration; WMD = weighted mean difference.

[a] At a margin of 0.3%. The probability that alogliptin is non-inferior to at least one DPP-4 inhibitor was 1.00 with fixed-effects modelling (0.88 with random-effects model).

Note: A positive mean difference indicates a favourable outcome for alogliptin. A positive log odds ratio for hypoglycemia indicates a favourable outcome for alogliptin.

Sensitivity analyses

In the 52-week analysis based on the fixed-effects model, sitagliptin 100 mg demonstrated a significantly lower reduction in A1C at 52 weeks than alogliptin 25 mg, with a mean difference of 0.13% (95% CrI, 0.02 to 0.24). Results were not statistically significant for the random-effects model. Most other sensitivity analyses for change in A1C at 24 weeks supported the base-case analysis finding of no statistically significant differences for each comparison of a DPP-4 inhibitor and alogliptin 25 mg. Results were only marginally changed from the base case when removing studies of poor methodological quality. Comparison of alogliptin with all other DPP-4 inhibitors combined did not reveal a statistically significant difference.

Sulfonylurea dual therapy

For the SU dual-therapy analyses, there were no statistically significant differences for change in mean A1C from baseline at 24 weeks using the fixed-effects model for comparisons of alogliptin with linagliptin, saxagliptin, and sitagliptin. The probability of alogliptin 25 mg being non-inferior to linagliptin, saxagliptin, and sitagliptin was 99%, 80%, and 94%, respectively, with the fixed-effects model. There were no statistically significant differences in mean body weight change or log odds of hypoglycemic events for any of the comparisons (Table 48).

TABLE 49: NETWORK META-ANALYSIS RESULTS AT 24 WEEKS: SULFONYLUREA + DPP-4 INHIBITOR DUAL THERAPY

End Point	DPP-4 Inhibitor Versus Alogliptin (Fixed-Effects Model)		
	Linagliptin 5 mg P.O. daily	Saxagliptin 5 mg P.O. daily	Sitagliptin 100 mg P.O. daily
A1C change from baseline, WMD (95% CI)	0.06 (–0.25 to 0.37)	–0.19 (–0.44 to 0.06)	–0.04 (–0.36 to 0.28)
Probability of non-inferiority on A1C[a]	0.99	0.80	0.94
Weight change from baseline (kg), WMD (95% CI)	–0.44 (–1.30 to 0.42)	NA	0.22 (–0.83 to 1.27)
Patients with ≥ 1 hypoglycemic event, log odds ratio (95% CrI)	0.39 (–1.07 to 1.93)	0.20 (–2.19 to 2.60)	1.29 (–0.29 to 3.04)

A1C = glycated hemoglobin; CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; NA = not applicable; P.O. = oral administration; WMD = weighted mean difference.

[a] At a margin of 0.3%. The probability that alogliptin is non-inferior to at least one DPP-4 inhibitor was 0.998 with fixed-effects model.

Note: A positive mean difference indicates a favourable outcome for alogliptin. A positive log odds ratio for hypoglycemia indicates a favourable outcome for alogliptin.

Strengths and limitations

The investigators appeared to use appropriate methods for the NMA, providing estimates of the relative efficacy and safety of alogliptin in combination with metformin or an SU compared with other available DPP-4 inhibitors. Both fixed- and random-effects modelling was performed based on model fit statistics. Unlike the NMA by Craddy et al. 2014,[34] the investigators used a decision-focused approach that is directly related to the populations of interest. Several sensitivity analyses were performed to support the base-case analyses.

The results of this NMA are limited, given the high heterogeneity between studies. As a result, this led to poor model fit with the fixed-effects models. There was considerable uncertainty seen within the random-effects models, as evidenced by the wide credible intervals. With limited evidence for the SU NMA, only fixed-effects modelling was performed. The evidence pertaining to change in body weight was limited across all DPP-4s; thus, an NMA could not be performed for all comparators. Lastly, as noted by the investigators, hypoglycemia was defined differently across studies or was poorly defined. The safety results were therefore limited by not being able to distinguish between severe and less severe hypoglycemic events.

Conclusion

The NMA by Tolley et al. demonstrated no statistically significant differences in change in A1C from baseline when alogliptin combined with metformin or an SU was compared with other DPP-4 inhibitors. There was a high probability that alogliptin was similar to other DPP-4 inhibitors on change in A1C from baseline within a margin of 0.3%. Based on the fixed-effects model, dual therapy with alogliptin and metformin was more favourable for mean weight change from baseline than saxagliptin and for the outcome of hypoglycemic events than saxagliptin and sitagliptin. Limitations of the Tolley analysis were the relatively small number of included studies and high between-study heterogeneity.

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