Common Drug Review
Clinical Review Report

August 2015

Drug	alogliptin/metformin (Kazano)
Indications under review	As an adjunct to diet and exercise in patients inadequately controlled on metformin or in patients already being treated with the combination of alogliptin and metformin.
Listing request	As per indication
Manufacturer	Takeda Canada Inc.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

A1C	glycated hemoglobin
ALO	alogliptin
ANCOVA	analysis of covariance
AE	adverse event
CDEC	Canadian Drug Expert Committee
CI	confidence interval
DPP-4	dipeptidyl peptidase-4
EMA	European Medicines Agency
EXAMINE	Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care
FAS	full analysis set
FDC	fixed-dose combination
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
GLZ	glipizide
LOCF	last observation carried forward
MET	metformin
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
SU	sulfonylurea
T2DM	type 2 diabetes mellitus
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 (T2DM). T2DM 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 T2DM.

There are currently 11 classes of anti-hyperglycemic drugs approved for use in Canada for T2DM: metformin, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, sodium-glucose cotransporter-2 (SGLT2) 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. DPP-4 inhibitor/metformin fixed-dose combinations (FDCs) are marketed for all four DPP-4 inhibitors. Upon submission, the manufacturer requested listing of alogliptin/metformin (ALO/MET) FDC in a similar manner as other DPP-4 inhibitor/MET FDCs in Canada. Based on consideration of listing criteria across Canada for existing DPP-4 inhibitor/MET FDCs, and in consultation with the manufacturer, the following approved indication for ALO/MET FDC was reviewed by the CADTH Common Drug Review (CDR):

- As an adjunct to diet and exercise in patients inadequately controlled on metformin or in patients already being treated with the combination of alogliptin and metformin.

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

Of note, Canadian Expert Drug Advisory Committee/Canadian Drug Expert Committee (CEDAC/CDEC) recommendations for the existing DPP-4 inhibitors have recommended listing for patients who are unable to use insulin. Recommendations for the corresponding DPP-4 inhibitor/MET FDCs align with the recommendations for the single drugs. However, ALO/MET FDC is not approved for use in combination with sulfonylurea.

Results and Interpretation

Included Studies

Three randomized controlled trials (RCTs) met the criteria for inclusion in this review: Studies 008 (N = 500), 305 (N = 2,639) and 302 (N = 784). Of these, 008 and 305 were considered pivotal trials by Health Canada. Studies 008 and 302 were superiority studies of alogliptin/metformin versus placebo/metformin, while Study 305 was a non-inferiority trial comparing alogliptin/metformin with glipizide/metformin. None of the included studies employed ALO/MET FDC, and only Study 302 co-administered alogliptin and metformin in a manner that corresponded with the strengths of ALO/MET FDC available in Canada.

Study 008 was a 26-week, double-blind, placebo-controlled, three-group, multi-centre RCT that compared metformin plus alogliptin 12.5 mg or 25 mg daily versus metformin plus placebo. Enrolled

patients had T2DM and inadequate glycemic control metformin monotherapy. The primary outcome was change from baseline in A1C.

Study 305 was a 104-week, double-blind, active-controlled, three-group, multi-centre RCT that compared metformin plus alogliptin 12.5 mg or 25 mg daily with metformin plus glipizide up to 20 mg daily; metformin doses were > 1,500 mg daily or maximum tolerated dose. Patients had T2DM with inadequate glycemic control on previous metformin monotherapy. 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 was a 26-week, placebo-controlled, seven-group, multi-centre RCT. Patients had T2DM with inadequate glycemic control when treated with diet and exercise for at least two months prior to screening. Patients were randomized to one of seven treatment groups: alogliptin/metformin 12.5 mg/500 mg twice a day, alogliptin/metformin 12.5 mg/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 introduce biases arising from potential imbalances between treatment groups during the course of the study.

Efficacy

None of the included studies evaluated outcomes related to macrovascular or microvascular complications of T2DM, or quality of life. The latter was identified as an important outcome in patient group input received by CADTH on this submission.

In Study 008, alogliptin 12.5 mg and 25 mg daily, both in combination with metformin, demonstrated superiority compared with placebo on A1C at 26 weeks in the full analysis set (FAS) analysis (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). Alogliptin 12.5 mg and 25 mg also demonstrated statistically significantly greater decreases in fasting plasma glucose (FPG) when compared with placebo (LSMD = –1.04 mmol/L; 95% CI, –1.51 to –0.57, and LSMD = –0.97 mmol/L; 95% CI, –1.44 to –0.49], respectively). Adjusted mean changes from baseline body weight at 26 weeks were –0.4 kg to –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 between alogliptin 12.5 mg and placebo (LSMD = 0.0 kg; 95% CI, –0.7 to 0.7). However, the difference between alogliptin 25 mg and placebo was statistically significant (LSMD = –0.3 kg; 95% CI, –0.9 to 0.4).

In Study 305, alogliptin 12.5 mg and 25 mg daily, both in combination with metformin, demonstrated non-inferiority on A1C at 52 weeks compared with glipizide/metformin based on the per-protocol set (PPS) analysis (LSMD = –0.09%; one-sided 98.75% CI, 0.03%, and LSMD = –0.03%; one-sided 98.75% CI, 0.06%, respectively). Similarly, at 104 weeks, alogliptin 12.5 mg and 25 mg daily demonstrated non-inferiority compared with 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 compared with glipizide. Adjusted mean changes from baseline body weight at 52 weeks were –0.65 kg to –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 to –1.231, and LSMD = –1.58 kg; 95% CI, –1.86 to –1.30, respectively). Results were similar at week 104.

In Study 302, both alogliptin/metformin 12.5 mg/500 mg twice daily and 12.5 mg/1,000 mg twice daily were associated with statistically significantly greater reductions from baseline A1C 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 in FPG between twice-daily alogliptin/metformin 12.5 mg/500 mg and twice-daily 12.5 mg/1,000 mg versus the respective metformin monotherapy doses were not statistically significant.

Harms

In Study 008, 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 a serious adverse event (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 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 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%). 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 placebo glipizide group experienced at least one episode of hypoglycemia.

In Study 302, the proportions of patients with an SAE were similar among the dual therapy and metformin monotherapy groups. Two patients in the alogliptin/metformin 12.5 mg/500 mg twice-daily group (1.9%), two patients in the alogliptin/metformin 12.5 mg/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 (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 withdrawals due to adverse effects (WDAEs) than metformin alone: the proportions were 4.7% in the alogliptin/metformin 12.5 mg/500 mg twice-daily group and 9.6% in the alogliptin/metformin 12.5 mg/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 twice-daily alogliptin/metformin 12.5 mg/500 mg, 12.5 mg/1,000 mg, metformin 1,000 mg, metformin 500 mg, 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 Study 008, and isolated cases only in the other two studies with no apparent association with alogliptin. Recent comprehensive assessments from the FDA and EMA concluded that the currently available data did not support a causal association between incretin-based drugs and pancreatitis or pancreatic cancer.

Other Considerations

Bioequivalence

A key consideration in the assessment of ALO/MET FDC is its comparative bioavailability with ALO and MET administered as separate dosage forms. The pharmacokinetic characteristics of ALO/MET FDC were compared with co-administration of the single-drug tablets in two phase 1 studies of healthy volunteers (MET-103 and MET-101). The 90% CIs for the area under the curve (AUC) and maximum concentrations (Cmax) for ALO/MET FDC 12.5 mg/500 mg and ALO/MET FDC 12.5 mg/1,000 mg, versus ALO and MET co-administered at the same doses separately, were within the EMA-specified bioequivalence range of 80% to 125%.

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 between DPP-4 inhibitors in the monotherapy, dual therapy (with metformin or sulfonylurea), and triple therapy (with metformin and a sulfonylurea) setting. The NMA did not find evidence of differences in glycemic control, weight gain, or hypoglycemia risk between alogliptin and the other DPP-4 inhibitors in the dual therapy setting; however, the analysis did not allow for a conclusion of non-inferiority or similarity across 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 (SU) is not appropriate, or in combination with SU when metformin is not appropriate). The results were similar to the original analysis in that there were 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 on the comparison and whether a fixed- or random-effects model was used) that alogliptin has similar effects on A1C as the other DPP-4 inhibitors within a margin of 0.3%. Alogliptin/metformin dual therapy also demonstrated favourable results with respect to weight gain against saxagliptin, and with respect to hypoglycemia against sitagliptin and saxagliptin. But all other comparisons of alogliptin with other DPP-4 inhibitors on these outcomes were not statistically 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 (T2DM) and acute coronary syndrome (ACS). 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 T2DM patients. The hazard ratio for the primary MACE composite outcome confirmed the non-inferiority hypothesis (hazard ratio [one-sided 95% CI] 0.96 [1.16]). 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 during 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 a 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 [redacted] 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

Three double-blind placebo- or active-controlled RCTs were included in this review of ALO/MET FDC. In all trials, the addition of alogliptin to metformin was associated with modest but clinically relevant improvements in A1C ranging from 0.4% to 0.6%. In the only active-controlled trial in the dual therapy setting, 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 was weight-neutral versus placebo when added to metformin, and associated with lower weight gain than a sulfonylurea when either was added to metformin. Alogliptin was not associated with a higher risk of hypoglycemia than placebo when added to metformin, but was associated with lower hypoglycemia versus a sulfonylurea. 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.

None of the included trials employed ALO/MET FDC. However, the FDC was shown to be bioequivalent to ALO and MET co-administered as individual dosage forms in healthy patients, according to EMA standards for bioequivalence. There was no direct comparative evidence for alogliptin versus other DPP-4 inhibitors available in Canada in the context of metformin dual therapy. The manufacturer-submitted NMAs suggested that there are no differences across DPP-4 inhibitors on A1C, body weight, and hypoglycemia, and that alogliptin as dual therapy with metformin has a high probability of producing similar reductions in A1C (within a margin of 0.3%) as other DPP-4 inhibitors available in Canada.

TABLE 1: SUMMARY OF EFFICACY RESULTS

Parameter	Study 008		
	ALO 12.5 mg + MET (N = 213)	**ALO 25 mg + MET (N = 210)**	**PL + MET (N = 104)**
Change in baseline A1C (%), LSMD (95% CI) vs. PL	–0.5[a] (–0.7 to –0.3)	–0.5[a] (–0.7 to –0.3)	NA
Change in baseline FPG (mmol/L), LSMD (95% CI) vs. PL	–1.04[a] (–1.51 to –0.57)	–0.97[a] (–1.44 to –0.49)	NA
Change in baseline body weight (kg), LSMD (95% CI) vs. PL	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 in baseline A1C, LSMD vs. GLZ[b] (1-sided 98.75% CI)	–0.1[c] (0.00)	–0.03[c] (0.06)	NA
Week 104 change in baseline A1C, LSMD vs. GLZ[b] 1-sided 98.75% CI)	–0.1[c] (0.04)	–0.1[c] (–0.01)	NA
Week 52 change in baseline FPG, LSMD vs. GLZ (95% CI)	–0.33 (–0.52 to –0.14)	–0.02 (–0.03 to –0.01)	NA
Week 104 change in baseline FPG, LSMD vs. GLZ (95% CI)	–0.35[a] (–0.55 to –0.15)	–0.02[a] (–0.03 to –0.01)	NA
Week 52 change in baseline body weight, LSMD (95% CI) vs. MET + GLZ	–1.52[a] (–1.846 to –1.198)	–1.80[a] (–2.122 to –1.473)	NA
Week 104 change in baseline, LSMD (95% CI)	NR	NR	NR

	Study 302				
	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 in baseline A1C, LSMD (97.5% CI) vs. MET 500 mg	NA	NA	–0.6 (–0.9 to –0.3)[a]	NA	NA
Change in baseline A1C, LSMD (95% CI) vs. MET 1,000 mg	NA	NA	–0.4 (–0.7 to –0.2)[a]	NA	NA
Change in baseline FPG, LSMD (97.5% CI) vs. MET 500 mg	NA	NA	–1.12[d] (–1.81 to –0.43)	NA	NA
Change in baseline FPG, LSMD (97.5% CI) vs. MET 1,000 mg	NA	NA	NA	–0.78[e] (–1.45 to –0.10)	NA
Change in from baseline, LSMD (95% CI) vs. MET 500 mg	NA	NA	NA	0.1 (–0.7 to 0.8)	NA
Change in from baseline, LSMD (95% CI) vs. 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; FAS = full analysis set; FPG = fasting plasma glucose; GLZ= glipizide; LSM = least squares mean; LSMD = least squares mean difference; MET = metformin; NA = not applicable; NR = not reported; PL = placebo; SD = standard deviation; SE = standard error; vs = versus.

[a] $P < 0.001$.

[b] In Study 305, a non-inferiority margin of 0.3% was tested with a 1-sided significance of 0.0125.

[c] Non-inferiority was established.

[d] $P < 0.01$.

[e] $P < 0.05$.

TABLE 2: SUMMARY OF HARMS

Parameter	Study 008		
	ALO 12.5 mg + MET (N = 213)	**ALO 25 mg + MET (N = 210)**	**PL + MET (N = 104)**
SAEs	6 (2.8)	8 (3.9)	4 (3.8)
WDAEs	7 (3.3)	4 (1.9)	1 (1.0)
Deaths	1 (0.5)	0	0
Hypoglycemia	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 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%)

AE = adverse event; ALO = alogliptin; b.i.d = twice daily; GLZ = Glipizide; 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 differ between this table (n = 5) and the disposition data (n = 4) as one patient discontinued at the discretion of the principal investigator (due to hyperglycemia).

1. INTRODUCTION

1.1 Disease Prevalence/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, 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 (T2DM).[4] T2DM 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 increasingly it is being detected in adolescents and children. Diagnosis is based on an FPG level of ≥ 7.0 mmol/L, a two-hour plasma glucose level with a 75 g oral glucose tolerance test of ≥ 11.1 mmol/L, or a glycated hemoglobin (A1C) of ≥ 6.5%.[1]

The thresholds for diagnosis have been 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). The primary cause of blindness, end-stage renal disease, and non-traumatic amputation in Canadian adults is diabetes.[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 (CDA) 2013 clinical practice guidelines recommend a target A1C of 7% for most patients with type 2 diabetes, and fasting plasma glucose (FPG) and two-hour post-prandial glucose targets of 4 to 7 mmol/L and 5 to 10 mmol/L, respectively.[1] There are currently 11 classes of anti-hyperglycemic drugs approved for use in Canada: biguanides (i.e., metformin), sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, sodium-glucose cotransporter-2 (SGLT2) 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 anti-hyperglycemic 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 a sulfonylurea.[6]

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

- A sulfonylurea should be added to metformin for most adults with type 2 diabetes who are inadequately controlled on metformin alone.
- Insulin-neutral protamine Hagedorn (NPH) should be added for most adults with type 2 diabetes inadequately controlled on metformin and a sulfonylurea.
- A DPP-4 inhibitor may be added to metformin and sulfonylurea therapy in circumstances in which 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] In addition, CDEC recommendations for other DPP-4 inhibitor/metformin (MET) fixed-dose combinations (FDCs) have aligned with the above recommendations.[11-13]

1.3 Drug

Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (also known as gastric inhibitory peptide, GIP) belong to the incretin class of gastrointestinal hormones. Incretins stimulate a decrease in blood glucose levels by causing increased post-prandial 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.[14] DPP-4 is an enzyme that rapidly degrades, and thereby inactivates, both GLP-1 and GIP. DPP-4 inhibitors prolong the endogenous plasma levels and hence the activity of both of these key hormones.[15] Alogliptin (ALO), a potent and highly selective DPP-4 inhibitor, is the fourth DPP-4 inhibitor to be introduced in Canada after sitagliptin, saxagliptin, and linagliptin. Kazano (ALO/MET) is the fourth DPP-4 inhibitor/metformin (MET) FDC introduced in Canada after saxagliptin/MET, linagliptin/MET, and sitagliptin/MET.

ALO/MET FDC is indicated to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM) as follows:

- As an adjunct to diet and exercise in patients inadequately controlled on metformin or in patients already being treated with the combination of alogliptin and metformin.
- In combination with pioglitazone when diet and exercise plus dual therapy with metformin and pioglitazone do not provide adequate glycemic control.
- In combination with insulin, when insulin and metformin do not provide adequate glycemic control.

Of note, unlike other DPP-4 inhibitor/MET FDCs available in Canada, ALO/MET FDC is not approved for use in combination with a sulfonylurea.

Upon submission, the manufacturer requested listing of ALO/MET FDC in a similar manner as other DPP-4 inhibitor/MET FDCs in Canada. While listing criteria for DPP-4 inhibitors vary somewhat across Canada, the indication listed in the following table was 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 indication under review.

Indications under review
As an adjunct to diet and exercise in patients inadequately controlled on metformin or in patients already being treated with the combination of alogliptin and metformin.
Listing criteria requested by sponsor
As per indication under review.

Table 3: Key Characteristics of DPP-4 Inhibitors Available in Canada

	Alogliptin/Metformin[15]	Sitagliptin/Metformin[16]	Linagliptin/Metformin[17]	Sitagliptin/Metformin[18]
Mechanism of Action	Inhibition of DPP-4 (alogliptin)/suppressed glucose production by the liver (metformin)			
Indications[a]	Inadequate control on MET or switch from co-administered ALO + MET. In combination with PIO or INS	Inadequate control on MET or switch from co-administered saxagliptin and MET In combination with the following: a SU or premixed or long- or intermediate-acting INS	As initial therapy where appropriate Inadequate control on MET or switch from co-administered linagliptin and MET Combination with SU following inadequate control with MET and SU	Inadequate control on MET or switch from co-administered sitagliptin and MET In combination with the following: a SU, premixed-, long or intermediate-acting INS, or PIO
Route of Administration	Oral	Oral	Oral	Oral
Recommended Dose	12.5 mg/500 mg b.i.d., 12.5 mg/850 mg b.i.d., or 12.5 mg/1,000 mg b.i.d.	Saxagliptin/MET: 2.5 mg/500 mg b.i.d., 2.5 mg/850 mg b.i.d., or 2.5 mg/1,000 mg b.i.d.	Linagliptin/MET: 2.5 mg/500 mg b.i.d., 2.5 mg/850 mg b.i.d., or 2.5 mg/1,000 mg b.i.d.	Sitagliptin/MET: 50 mg/500 mg b.i.d., 50 mg/850 mg b.i.d. or 50 mg/1,000 mg b.i.d.
Dosage Adjustment for Renal Impairment	Should not be used in patients with renal impairment	Contraindicated in patients with renal impairment	Contraindicated in patients with renal insufficiency	Should not be used in patients with renal failure or renal dysfunction
Warnings and Precautions	Use with caution in patients with CHF of NYHA functional class III or IV Reports of acute pancreatitis Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment Patients should be cautioned against excessive alcohol intake, either acute or chronic, as this can potentiate the effect of metformin on lactate metabolism	Reports of acute pancreatitis Not recommended for patients with CHF Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking, as this can potentiate the effect of metformin on lactate metabolism	Reports of acute pancreatitis Not recommended for patients with CHF Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking, as this can potentiate the effect of metformin on lactate metabolism	Reports of acute pancreatitis Not recommended for patients with CHF Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking, as this can potentiate the effect of metformin on lactate metabolism

ALT = alanine aminotransferase; b.i.d. = twice daily; CHF = congestive heart failure; DPP-4 = dipeptidyl peptidase-4 inhibitor; INS = insulin; MET = metformin; NYHA = New York Heart Association; PIO = pioglitazone; 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 12.5 mg in combination with metformin 500 mg (ALO/MET FDC 12.5 mg/500 mg), 850 mg (ALO/MET FDC 12.5 mg/850 mg), or 1,000 mg (ALO/MET FDC 12.5 mg/1,000 mg) twice daily for the treatment of adults with type 2 diabetes who have experienced inadequate glycemic control with diet and exercise interventions combined with metformin, or who are currently treated with the combination of ALO and MET as separate dosage forms.

2.2 Methods

All studies identified by Health Canada as pivotal trials that are relevant to the indication 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

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 are already being treated with alogliptin plus metformin (as separate dosage forms)
Intervention	ALO 12.5 mg in combination with MET 500 mg, 850 mg, or 1,000 mg twice daily (ALO and MET as either FDC or as separate dosage forms)
Comparators	• ALO 12.5 mg and MET 500 mg, 850 mg, or 1,000 mg twice daily as separate dosage forms (if the Intervention is ALO/MET FDC) • MET combined with one other antidiabetic drug available in Canada (i.e., another DPP-4 inhibitor, sulfonylurea, thiazolidinedione, insulin/insulin analogue, SGLT2 inhibitor, GLP-1 agonist) or placebo
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 • Withdrawals due to adverse events • Total adverse events **Other outcomes:** • Health Care Resource Utilization
Study design	Published and unpublished RCTs excluding phase II and below

A1C = glycated hemoglobin; ALO = alogliptin; DPP-4 = Dipeptidyl peptidase-4 inhibitor; FDC = fixed-dose combination; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; MET = metformin; SGLT2 = sodium-glucose cotransporter-2; RCT = randomized controlled trial.

2.2.1 Supplemental issues

- Bioequivalence of co-administered alogliptin and metformin to alogliptin/metformin fixed-dose combination
- Critical appraisal of the manufacturer's network meta-analysis
- Summary of the EXAMINE study

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, and keywords. The main search concepts were alogliptin, metformin, 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.

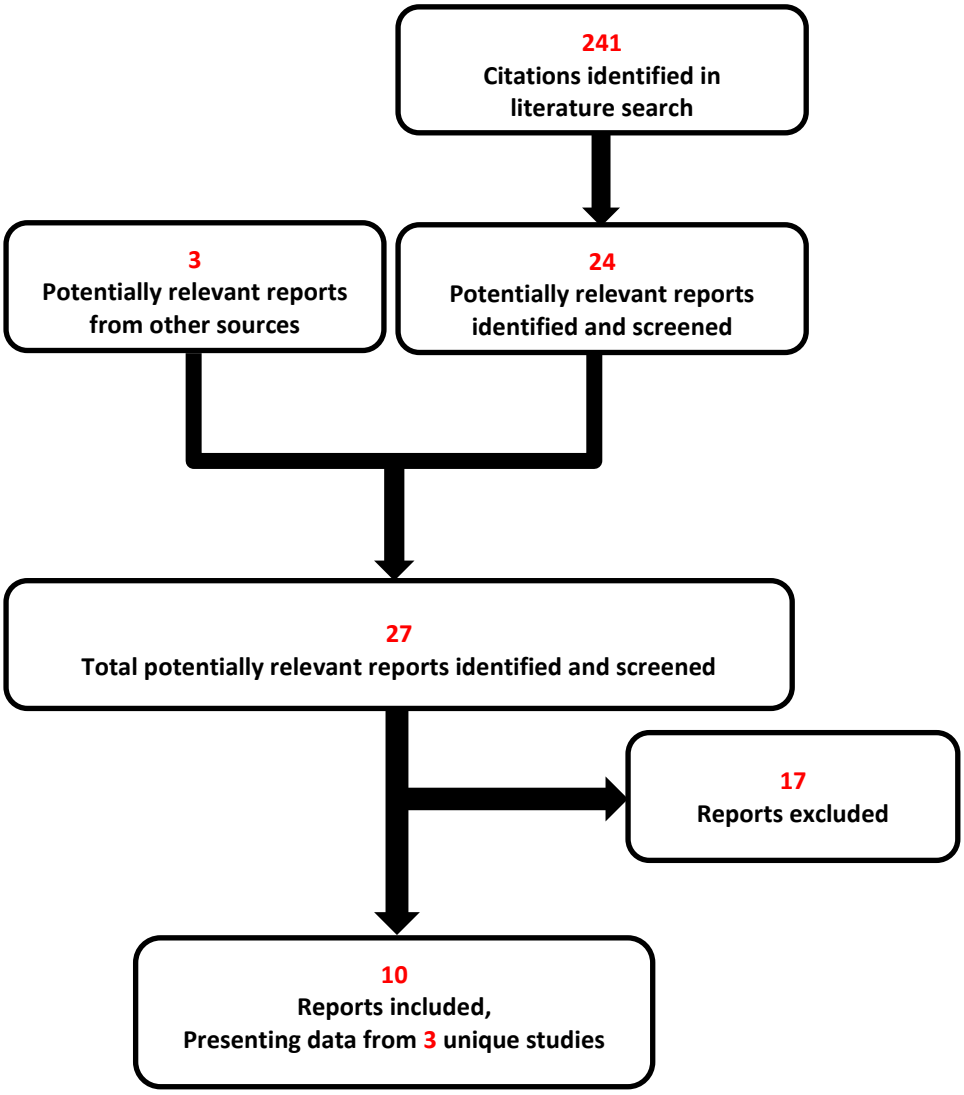
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final 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 three 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 MET-008	302	Study 305
DESIGNS & POPULATIONS	**Study design**	DB, PC, MC, 3-group RCT	DB, MC, PC, 7-group RCT	DB, AC, MC, 3-group RCT
	Locations	United States, Brazil, Chile, Guatemala, and Mexico	United States, Czech Republic, Hungary, Israel, Lithuania, Poland, Romania, Russia, Slovakia, Ukraine	United States, Canada, Brazil, Chile, Mexico, Peru, and Puerto Rico
	Randomized (N)	500	784	2,639
	Inclusion criteria	Aged 18 to 80 years with T2DM and inadequate glycemic control when treated with MET; A1C between 7.0% and 10.0%; BMI ≥ 23 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 between 7.5 to 10.0% inclusive at screening; BMI ≥ 23 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 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 metformin 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 metformin therapy (daily dose < 1,500 mg without documented MTD)
	Exclusion criteria	Urine albumin/creatine 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/LL 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 gm/L) for males and ≤ 10 g/dL (≤ 100 gm/L) for females NYHA class III to IV heart failure
DRUGS	**Intervention(s)**	• 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 (≥ 1,500 mg or MTD)
	Comparator(s)	• PC + MET	• MET 500 mg b.i.d. • MET 1,000 mg b.i.d. • PC	• GLZ 20 mg daily + OL MET (≥ 1,500 mg or MTD)

		Study MET-008	302	Study 305
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		
NOTES	**Publications or data sources**	Nauck et al. 2009[19] Clinical Study Report 008[20] Kazano CDR Submission[21]	Pratley et al. 2014[22] Clinical Study Report[23] Kazano CDR Submission[21]	Del Prato et al. 2014[24] Clinical Study Report 305[25] Kazano CDR Submission[21]

A1C = glycated hemoglobin; AC = active-controlled; ALO = alogliptin; b.i.d. = twice daily; BMI = body mass index; DB = double-blind; FPG = fasting plasma glucose; GLZ = glipizide; MC = multi-centre; MET = metformin; MTD = maximum tolerated dose; NYHA = New York Heart Association; OL = open-label; PC = placebo-controlled; q.d. = once daily; RCT = randomized controlled trial; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.
Other Sources: FDA reviews,[26,27] Health Canada Reviewers report.[28]

3.2 Included Studies

3.2.1 Description of studies

The literature search identified four RCTs that met the criteria for inclusion in the review: Study 008, Study 305, and Study 302 (Table 6). Of these, Studies 008 and 305 were considered pivotal trials by Health Canada. Studies 008 and 302 were superiority studies. Study 305 was a non-inferiority trial comparing ALO/MET with glipizide (GLZ)/MET. All of the included trials employed ALO and MET as separate dosage forms; there were no studies of ALO/MET FDC. Studies 008 and 305 allowed various doses of MET; only Study 302 contained treatment groups in which ALO and MET were co-administered in a manner corresponding to the strengths of ALO/MET FDC available in Canada.

TABLE 6: LIST OF RANDOMIZED CONTROLLED TRIALS INCLUDED IN THE CADTH COMMON DRUG REVIEW OF ALOGLIPTIN/METFORMIN FIXED-DOSE COMBINATION

Study ID	Interventions and Comparators	N	Duration	Primary End Point
Study 008	ALO 12.5 mg + MET, ALO 25 mg + MET, PL + MET	500	26 weeks	A1C
Study 302	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; GLZ = glipizide; ID = identifier; MET = metformin; MTD = maximum tolerated dose; OL = open-label; PL= placebo; q.d. = once daily.

Study 008 was a 26-week, double-blind, placebo-controlled, three-group, multi-centre RCT of 500 patients conducted in 15 countries. Patients had T2DM with inadequate glycemic control (defined as A1C 7.0 to 10.0%) when treated with MET monotherapy. Patients were also required to be treated with MET monotherapy (≥ 1,500 mg daily) for at least three months prior to screening. Patients with a maximum tolerated dose (MTD) < 1,500 mg daily could enroll in a stabilization period of at least eight weeks prior to randomization. Patients were randomized to one of three treatment groups in a 1:2:2 ratio (placebo + MET: ALO 12.5 mg + MET : ALO 25 mg + MET). The primary objective of this study was to evaluate the efficacy of ALO co-administered with MET as compared with MET alone on change from baseline in A1C.

TABLE 7: TRIAL DESIGN STUDY 008

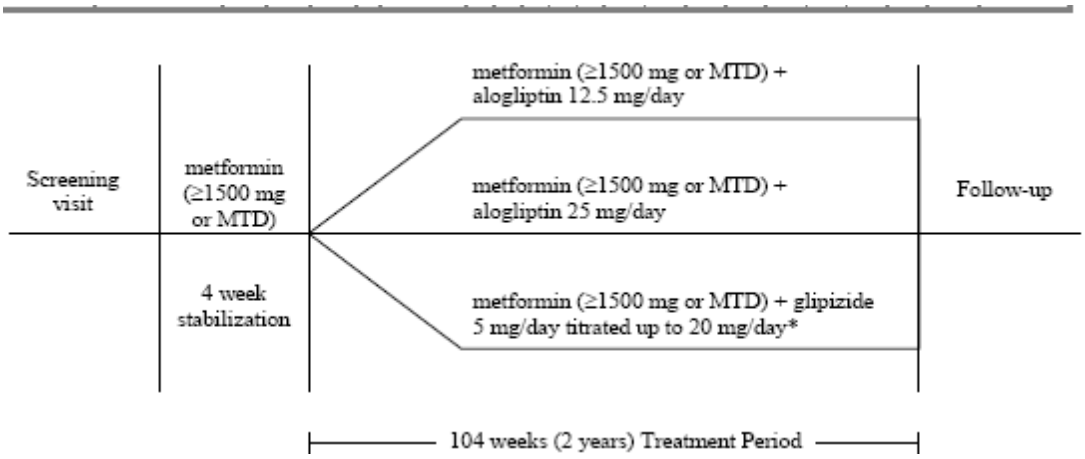
Screening Period Week –6 Through –5 Prior to Randomization	Run-in Stabilization Weeks –4 Through –1 Prior to Randomization				Treatment Period Weeks 1 Through 26 After Randomization							End of Treatment	Follow-up Period
Week													
Screening visits	–4	–3	–2	–1	**Baseline visit (Day 1)**	1	2	4	8	12	16	20	26	28

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 T2DM with inadequate glycemic control on previous MET therapy, as follows:

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

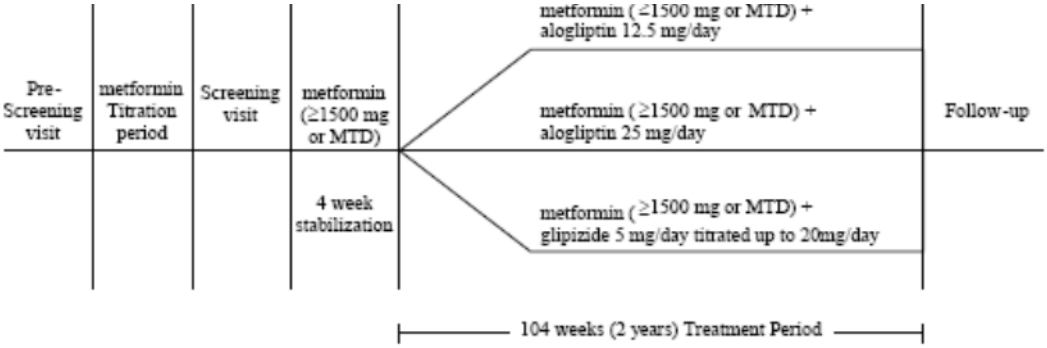
After the stabilization period, Schedules A and B were identical. Patients were randomized in a 1:1:1 ratio to receive one of three treatments [ALO 12.5 mg once daily + MET: ALO 25 mg once daily + MET : GLZ 5 mg once daily + MET]. GLZ was titrated up to 20 mg once daily through week 20 as needed. Throughout the study all patients received open-label MET ≥ 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 ALO/MET as compared with GLZ/MET, as measured by change from baseline A1C at week 52 and 104. Schematics of the Study 305 trial design are presented in Figure 2 and Figure 3.

FIGURE 2: TRIAL DESIGN STUDY 305 (SCHEDULE A)



MTD = maximum tolerated dose.
Note: Figure from Clinical Study Report 305.[25]

FIGURE 3: TRIAL DESIGN STUDY 305 (SCHEDULE B)



MTD = maximum tolerated dose.
Note: Figure from Clinical Study Report 305.[25]

Study 302 was 26-week, placebo-controlled, seven-group, multi-centre RCT of 784 patients conducted in 15 countries. Patients had T2DM with inadequate glycemic control (defined as A1C between 7.5 to 10.0%), when treated with diet and exercise for at least two months prior to screening. Patients were randomized with equal probability to one of seven treatment groups: ALO/MET 12.5 mg/500 mg twice daily, ALO/MET 12.5 mg/1,000 mg twice daily, ALO 12.5 mg twice daily, ALO 25 mg once daily, MET 500 mg twice daily, MET 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 was to evaluate the efficacy of ALO plus MET as compared with ALO alone and MET alone on change from baseline in A1C at week 26. Based on the review protocol, only the findings from the ALO/MET groups, MET twice-daily groups, and placebo group are presented in this review.

TABLE 8: TRIAL DESIGN STUDY 302

	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

Note: Figure from Clinical Study Report 302.[23]

3.2.2 Populations

a) Inclusion and exclusion criteria

Eligibility criteria for Studies 008, 305, and 302 were very similar. Patients were required to have inadequate glycemic control, most frequently defined as A1C of 7.0 to 10.0%. However, the minimum level for inclusion was as high as 7.5% (Study 302) and the maximum level for inclusion was as low as 9.0% (Study 305). Patients were required to have inadequate glycemic control following treatment MET in Study 008 and Study 305, and diet and exercise in Study 302. Patients were required to receive ≥ 1,500 mg MET (Study 008 and Study 305-Schedule A), < 1,500 mg MET with MTD (Study 305) or < 1,500 mg MET without documented MTD (Study 305-Schedule B). Patients were excluded if they were treated with any other antidiabetic treatment than what was specified for inclusion at three months (Study 008) or two months (Study 305-Schedule A) before screening. Patients in Study 302 were required to receive < 7 days of antidiabetic treatment in the two months prior to screening.

b) Baseline characteristics

Demographic and baseline characteristics of patients in Studies 008, 305, and 302 are outlined in Table 9, Table 10, and Table 11. 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, 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 three studies (54.7, 56.0, and 53.5 years in Studies 008, 305, and 302, respectively), as well as across treatment groups within studies. Mean body mass index (BMI) at baseline was also similar among the three included studies (31.83 kg/m^2, 31.22 kg/m^2, and 30.71 kg/m^2 for Studies 008, 305, and 302, respectively). The median BMI exceeded 30 kg/m^2 in Studies 008, 302, 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 across treatment groups in all four included studies.

Mean baseline A1C was lowest in Study 305 (7.60%), followed by Study 008 (7.93%), and 302 (8.43%). Baseline A1C was similar across treatment groups in all three studies. Mean FPG was generally similar across treatment groups in Studies 008 and 302, ranging from 9.34 to 9.96 mmol/L, and 9.76 to 10.35 mmol/L, respectively. However, FPG was considerably lower across treatment groups in Study 305, ranging from 8.19 to 8.29 mmol/L. Mean duration of T2DM was shorter for patients in Study 302 across treatment groups (3.65 to 4.25 years) when compared with Study 008 (6.11 years) and Study 305 (5.52 years). In Study 008, mean baseline MET doses were generally similar across treatment groups, ranging from 1,837 mg (ALO 12.5 mg group) to 1,868 mg (placebo group). In Study 305, mean

baseline MET doses were generally similar, ranging from 1,823 mg (GLZ group) to 1,837 mg (ALO 25 mg group).

TABLE 9: SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS FROM STUDY 008

Characteristics	008		
	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
Female (%)	112 (52.6)	96 (45.7)	54 (51.9)
Age (year), mean (SD)	55.2 (10.6)	53.6 (10.5)	56.0 (10.6)
Weight (kg), mean (SD)	87.7 (18.4)	88.1 (19.5)	89.3 (20.4)
BMI (kg/m^2), mean (SD)	31.6 (5.2)	31.8 (5.3)	32.4 (5.8)
A1C (%), mean (SD)	7.9 (0.7)	7.9 (0.8)	8.0 (0.9)
FPG (mmol/L), mean (SD)	9.34 (2.44)	9.54(2.54)	9.96 (2.79)
T2DM duration (years), mean (SD)	6.2 (5. 1)	5.9 (4.3)	6.3 (5.4)
MET dose (mg), mean (SD)	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; MET = metformin; NA = not applicable; PL = placebo; SD = standard deviation; T2DM = type 2 diabetes mellitus.
Note: Data from Clinical Study Report for Study 008.[20]

TABLE 10: SUMMARY OF BASELINE CHARACTERISTICS FROM 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.
Note: Data from Clinical Study Report for Study 305.[25]

TABLE 11: SUMMARY OF BASELINE CHARACTERISTICS FROM STUDY 302

Characteristics	302						
	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)

Characteristics	302						
	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)
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.
Note: Data from Clinical Study Report for Study 302.[23]

3.2.3 Interventions

ALO was administered once daily in Studies 008 and 305. ALO was supplied as tablets (12.5 mg or 25 mg) in the three trials. In Study 302, ALO was administered once daily as monotherapy or co-administered with MET twice daily. A double-dummy design (i.e., placebos matching MET and ALO) was used to ensure masking across all treatment groups.

In Study 008, MET was administered in an open-label fashion as the generic, immediate-release formulation. MET was administered in accordance with instructions provided on the approved package label. Patients were eligible for hyperglycemic rescue if FPG was ≥ 15.27 mmol/L between weeks 1 and 4, ≥ 13.88 mmol/L between weeks 4 and 8, or ≥ 12.49 mmol/L between weeks 8 and 12, or if A1C ≥ 8.5% AND there was ≤ 0.5% 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 GLZ 5 mg and matching placebo were indistinguishable in appearance and packaging. Between weeks 2 and 20, GLZ (or matching placebo in the ALO 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 > 13.88 mmol/L confirmed by a repeat FPG test within seven days, after at least two weeks of treatment). MET was administered in an open-label fashion as the generic immediate-release formulation. All patients received a minimum dose of MET 1,500 mg daily during the Titration and/or Stabilization Period; however, if there was documentation from screening or pre-screening that a dose of ≥ 1,500 mg MET was not tolerated, the patient participated in the study at the MTD. The MET dose was to be kept unchanged throughout the study. After week 20 and prior to 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, rescue occurred 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 adopted a double-dummy design to maintain blinding. ALO or ALO placebo and MET or MET placebo were supplied as over-encapsulated tablets that were identical in appearance and packaging. Patients in this study were eligible for hyperglycemic rescue with a sulfonylurea (chosen and dosed at the investigator's discretion) if: FPG > 15.27 mmol/L between weeks 1 and 4; FPG > 13.88 mmol/L between weeks 4 and 8; FPG > 12.49 mmol/L between weeks 8 and 12; or A1C > 8.5% and there was < 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 008 and 302 was the change in A1C levels at 26 weeks. For Study 305, the co-primary efficacy outcomes were change in A1C levels at 52 and 104 weeks. Of note, the National Institute for Health and Clinical Excellence (NICE) and the US FDA have indicated that reductions from baseline in A1C as small as –0.5% and –0.7%, respectively, have clinical importance.[29,30]

Secondary glycemic control end points for all studies included change from baseline in fasting plasma glucose at various time points and proportion of patients with A1C < 7.0%.

b) Hypoglycemia

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

In Studies 008 and 305, severe hypoglycemia was defined as any episode requiring the assistance of another person to actively administer carbohydrate or glucagons, or perform other resuscitative actions, associated with a documented blood glucose of < 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, except that the threshold for documented plasma glucose was < 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 plan for Study 008 consisted of an Analysis of Covariance (ANCOVA) model for the primary end point, change from baseline A1C at 26 weeks, using data from the full analysis set (FAS) with last observation carried forward (LOCF). A step-down strategy was employed such that only if the comparison between ALO 25 mg and placebo was statistically significant (based on a two-sided test at a significance level of 0.05) would the ALO 12.5 mg dose be compared with placebo. Study treatment and geographic region were treated as categorical variables, while baseline MET dose and baseline A1C were treated as continuous covariates. Sensitivity analyses were conducted with each efficacy variable using observed rather than LOCF values.

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

In Study 305, the primary analysis of the primary end point, change from baseline A1C at 52 and 104 weeks, was conducted using an ANCOVA model with data from the PPS using LOCF imputation. Study treatment, geographic region, and the study schedule the patient was randomized under were treated as class effects, and baseline A1C and baseline MET dose as continuous covariates. The primary analyses of change from baseline A1C 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:

- ALO 25 mg is inferior in A1C change from baseline versus GLZ
- ALO 12.5 mg is inferior in A1C change from baseline versus GLZ
- ALO 25 mg is not superior in A1C change from baseline versus GLZ
- ALO 12.5 mg is not superior in A1C change from baseline versus GLZ.

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 ALO dose (12.5 or 25 mg) and GLZ either at week 52 or week 104, assuming a non-inferiority margin of 0.3%, no difference between either ALO dose and GLZ, a standard deviation for change from baseline A1C 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 from baseline A1C 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 ALO/MET therapy and monotherapy:

- ALO/MET 12.5 mg/500 mg twice daily versus ALO 12.5 mg twice daily
- ALO/ MET 12.5 mg/500 mg twice daily versus MET 500 mg twice daily
- ALO/MET 12.5 mg/1,000 mg twice daily versus ALO 12.5 mg twice daily
- ALO/ MET 12.5 mg/1,000 mg twice daily versus MET 500 mg twice daily.

The null hypothesis corresponding to each set of comparisons was that the combination of ALO and MET had no additional effect on glycemic control (as measured by A1C change 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 ALO or with the constituent dose of MET. The null hypothesis was rejected only if both comparisons between a combination and its components as monotherapy were statistically significant at the two-sided 2.5% 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 prior to the date of rescue were used. At each visit, the end point was analyzed using the value collected at that visit or LOCF if the value at that visit was unavailable. 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 7 days of the last double-blind study medication, irrespective of hyperglycemic rescue therapy. Analysis 2a had the same criteria for how end point data were analyzed 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 ALO/MET combinations was statistically superior to its constituent monotherapy doses of ALO and MET. 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%.

b) Missing data

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

c) Analysis populations

Three datasets were analyzed in all four studies.[20,23,25] The datasets were defined as follows:

Safety set

All patients who took at least one dose of the double-blind study drug. In safety summaries, patients were analyzed according to the most frequent treatment they received.

Full analysis set

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

All FAS patients who had no major protocol violations.

3.3 Patient Disposition

The disposition of patients is presented in Table 12, Table 13, and Table 14. The overall rate of study discontinuation among randomized patients was 9.9% in Study 008, 21.9% in Study 305, and 22.3% in Study 302. Discontinuation rates were similar between alogliptin and non-alogliptin comparator groups within each study. The most common reason for discontinuation was withdrawal of consent in Studies 008 (3.4%) and 302 (8.4%), and adverse events in Study 305 (8.2%). More patients in the placebo groups received hyperglycemic rescue than in the ALO groups in Study 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. In Study 008, a greater proportion of patients completed in the ALO 12.5 mg and 25 mg groups (82.6% and 78.6%, respectively) compared with placebo (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 ALO/MET and MET groups compared with 67.9% of patients in the placebo group.

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

TABLE 12: SUMMARY OF PATIENT DISPOSITION FROM STUDY 008

Disposition	008		
	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
Screened	596		
Randomized, N	213	210	104
Full analysis set	213 (100.0)	207 (98.6)[a]	104 (100.0)
Safety analysis set	213 (100.0)	207 (98.6)[a]	104 (100.0)
PP analysis set	193 (90.6)	185 (88.1)	94 (90.4)
Completed, N (%)	176 (82.6)	165 (78.6)	72 (69.2)
Withdrawn, N (%)	36 (17.4)	45 (21.4)	32 (30.8)
Hyperglycemic rescue[b]	19 (8.9)	17 (8.1)	25 (24.0)
Discontinued, N (%)	17 (8.0)	28 (13.3)	7 (6.7)
Adverse event	7 (3.3)	6 (2.9)	1 (1.0)
Lost to follow-up	5 (2.3)	2 (1.0)	1 (1.0)
PI discretion	1 (0.5)	1 (0.5)	1 (1.0)
Protocol violation	2 (0.9)	4 (1.9)	2 (1.9)
Withdrawal of consent	2 (0.9)	14 (6.7)	2 (1.9)
Other	0	1 (0.5)	0

ALO = alogliptin; MET = metformin; NR = not reported; 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 were mutually exclusive groups (i.e., those patients rescued due to hyperglycemia were not counted as discontinued).
Note: Data from Clinical Study Report for Study 008.[20]

TABLE 13: 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 (%)	174 (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.
[a] Hyperglycemic rescue and discontinued were mutually exclusive groups (i.e., those patients rescued due to hyperglycemia were not counted as discontinued).
Note: Data from Clinical Study Report for Study 305.[25]

TABLE 14: PATIENT DISPOSITION STUDY 302

Disposition	302						
	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 rescue	NR	NR	NR	NR	NR	NR	NR
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)

Disposition	302						
	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)
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.
Note: Data from 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 15, Table 16, and Table 17. Mean treatment duration was similar among all groups within each study for Studies 008 and 305, ranging from approximately 22 to 24 weeks. In Study 305, mean exposure was slightly higher in the ALO 12.5 mg and 25 mg groups (76.6 weeks and 78.2 weeks) compared with the GLZ group (73.1 weeks).

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

TABLE 15: DURATION OF EXPOSURE TO INVESTIGATIONAL PRODUCTS IN STUDY 008

Exposure	008		
	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
Mean (SD; weeks)	23.8 (5.8)	23.4 (6.3)	21.9 (7.1)
Median (weeks)	26.0	26.0	26.0
Range (weeks)	1.1, 29.1	0.9, 29.7	2.6, 27.7

ALO = alogliptin; MET = metformin; PL = placebo; SD = standard deviation.
Note: Data from Clinical Study Report for Study 008.[20]

TABLE 16: 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, 107.7	0.1, 111.1	0.6, 108.4

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

TABLE 17: DURATION OF EXPOSURE TO INVESTIGATIONAL PRODUCTS IN STUDY 302

Exposure	302						
	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, 27.4	0.1, 28.0	0.1, 29.0	1.1, 28.7	1.1, 27.6	0.1, 31.3	0.1, 30.0

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

3.4.2 Concomitant medications

Treatment with antidiabetic drugs other than a sulfonylurea or MET was not allowed within three months prior to screening through to completion of treatment in Study 008. For Study 305, treatment with antidiabetic drugs other than MET was not allowed within two months prior to 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, no treatment with any antidiabetic drug within two months of screening and during the four-week stabilization period was allowed. After randomization and until the end-of-study treatment, sulfonylurea for hyperglycemic rescue was the only additional antidiabetic drug allowed. The exception in all studies was use of other antidiabetic therapy for less than seven days within the two months (Studies 302 and 305) or three months (Study 008) prior to 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 at screening (e.g., < 8.0% or 8.5% and ≥ 8.0% or 8.5%), 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. Study end points were appropriately measured and consistent with guidance from the FDA and EMA on RCTs for anti-hyperglycemic treatments.[29,30]

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 EMA and is consistent with other trials of anti-hyperglycemic treatments.[29,30]

In Studies 008 and 302 no rationale was provided for the selected superiority margin. The margin for determining superiority of ALO versus placebo on A1C in Study 008 was 0.4%, while Study 302 used a margin of 0.55% for comparing dual therapy with monotherapy. No rationale was provided for the margins chosen in any of the included trials.

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

Comparator doses were generally appropriate, with the possible exception of Study 305. The mean final dose of GLZ (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 GLZ dose between weeks 2 and 20 only if FPG was over 13.88 mmol/L. The CDA guidelines call for timely adjustments to therapy such that glycemic targets are achieved within three to six months.[1] Therefore it is likely that titration would occur more aggressively in clinical practice than in Study 305. This aspect, in combination with the low mean baseline A1C (7.6%), may have biased the results in favour of demonstrating that ALO was non-inferior to GLZ.[31]

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 with respect to biases arising from potential imbalances between treatment groups over the course of the study. On a related note, 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 ALO and GLZ. 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 did not 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/or Latin America.

The generalizability of Study 302 to the target population of interest (i.e., patients with inadequate glycemic control on MET 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 ALO or MET monotherapy and ALO/MET combination therapies. However, the observed differences in A1C between ALO + MET dual therapy and MET monotherapy in Study 008 (which did enroll patients with inadequate glycemic control on MET monotherapy) were aligned with those observed in 302.

There were no studies that used ALO/MET FDC. Only Study 302 contained treatment groups in which ALO and MET were administered in a manner that corresponds with the strengths of ALO/MET FDC available in Canada. In the other two studies, various doses of MET were used, not all of which can be achieved with ALO/MET FDC (unless single-drug MET is added to the treatment regimen). This represents a limitation to the generalizability of these studies in determining the efficacy and safety of ALO/MET FDC.

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 Section 2.2, Table 4). (For detailed efficacy data, see APPENDIX 3: DETAILED OUTCOME DATA.) For Study 302, results are presented only for the treatment groups that align with the review protocol; hence findings for ALO 12.5 mg once daily and ALO 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) Hemoglobin A1C

Table 18 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 ALO 12.5 mg group to –0.6% in the ALO 25 mg group, and –0.1% in the placebo group. After 26 weeks, the ALO 12.5 mg group and ALO 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 ALO 12.5 group (51.6%) and ALO 25 mg group (44.4%) achieved clinical response at 26 weeks compared with the placebo group (18.3%).

Table 19 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 ALO and GLZ groups. ALO 12.5 mg and ALO 25 mg once daily demonstrated non-inferiority compared with GLZ (LSMD = –0.1%; 98.75% CI, 0.00%, and LSMD = –0.03%; 98.75% CI, 0.06%, respectively). The results from the FAS were similar to those in the PPS (Figure 4). At 104 weeks, the adjusted mean change from baseline to 104 weeks was –0.7% in the ALO groups and –0.6% in the GLZ group. ALO 12.5 mg and ALO 25 mg once daily demonstrated non-inferiority compared with GLZ (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 5). Similar proportions of patients in the ALO 12.5 mg, ALO 25 mg, and GLZ groups achieved clinical response (56.4%, 59.2%, and 56.1%, respectively) at 52 weeks and 104 weeks (45.6%, 48.5%, and 42.8%, respectively).

Table 20 displays the changes in A1C at 26 weeks in Study 302 (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 the ALO/MET 12.5 mg/500 mg once daily (–1.6%) and ALO/MET 12.5 mg/MET 1,000 mg once daily (–1.2%) compared with MET 1,000 mg once daily (–1.1%), MET 500 mg once daily (–0.7%), and placebo (–0.2%). ALO/MET 12.5 mg/500 mg once daily was associated with a statistically significantly greater reduction in change from baseline A1C versus MET 500 mg once daily monotherapy (LSMD = –0.6%; 95% CI, –0.9 to –0.3). ALO/MET 12.5 mg/1,000 mg once daily was associated with a statistically significantly greater reduction in change from baseline A1C versus MET 1,000 mg once daily (LSMD = –0.4%; 95% CI, –0.7 to –0.2%). The proportions of patients who achieved clinical response in the co-administration therapy groups (47.1% for ALO/MET 12.5 mg/500 mg once daily and 59.5% for ALO/MET 12.5 mg/1,000 mg once daily groups) was greater than in the MET 500 mg once daily (27.2%) and MET 1,000 mg once daily groups (34.3%).

TABLE 18: CHANGES FROM BASELINE IN A1C AT 26 WEEKS IN STUDY 008 (FULL ANALYSIS SET)

Parameter		008		
		ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
A1C (%)	Baseline, mean (SD)	7.9 (0.7)	7.9 (0.8)	8.0 (0.9)
	End, mean (SD)	7.3 (1.0)	7.3 (0.9)	7.9 (1.0)
	Change in baseline, LSM (SE)	–0.6 (0.1)	–0.6 (0.1)	–0.10 (0.076)
	Change in baseline, LSMD (95% CI) vs. PL	–0.5[a] (–0.7 to –0.3)	–0.5[a] (–0.7 to –0.3)	NA

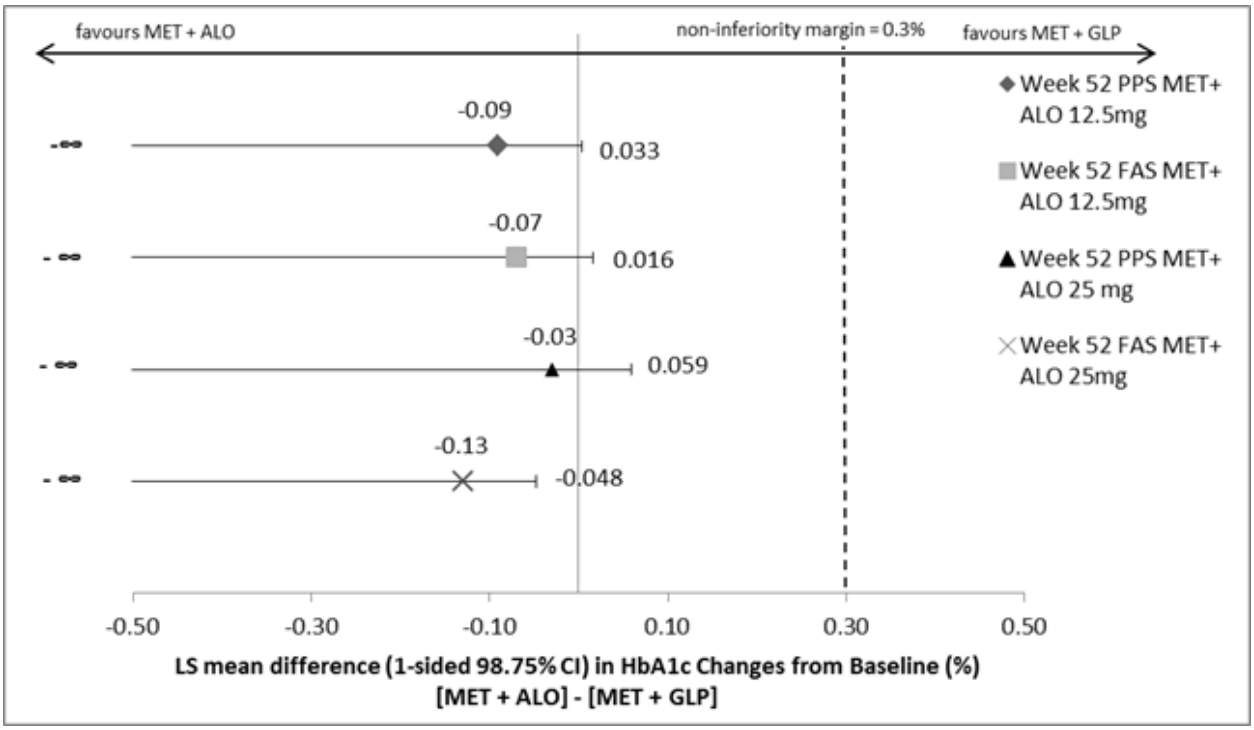
A1C = glycated hemoglobin; ALO = alogliptin; CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; MET = metformin; NA = not applicable; PL = placebo; SD = standard deviation; SE = standard error; vs. = versus.
[a] $P < 0.001$.
Note: Data from Clinical Study Report for Study 008.[20]

TABLE 19: 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 in baseline, LSM (SE)	–0.8 (0.0)	–0.9 (0.0)	–0.8 (0.0)
LSMD vs. GLZ (95% CI)	0.0 (–0.07, 0.08)	0.01 (–0.07, 0.08)	NA
Week 52 change in baseline, LSM (SE)	–0.8 (0.0)	–0.8 (0.0)	–0.7 (0.0)
LSMD vs. GLZ[a] (1-sided 98.75% CI)	–0.1[b] (0.00)	–0.03[b] (0.06)	NA
Week 104 change in baseline, LSM (SE)	–0.7 (0.037)	–0.7 (0.037)	–0.6 (0.039)
LSMD vs. GLZ[a] (1-sided 98.75% CI)	–0.1[c] (0.04)	–0.1[c] (–0.01)	NA

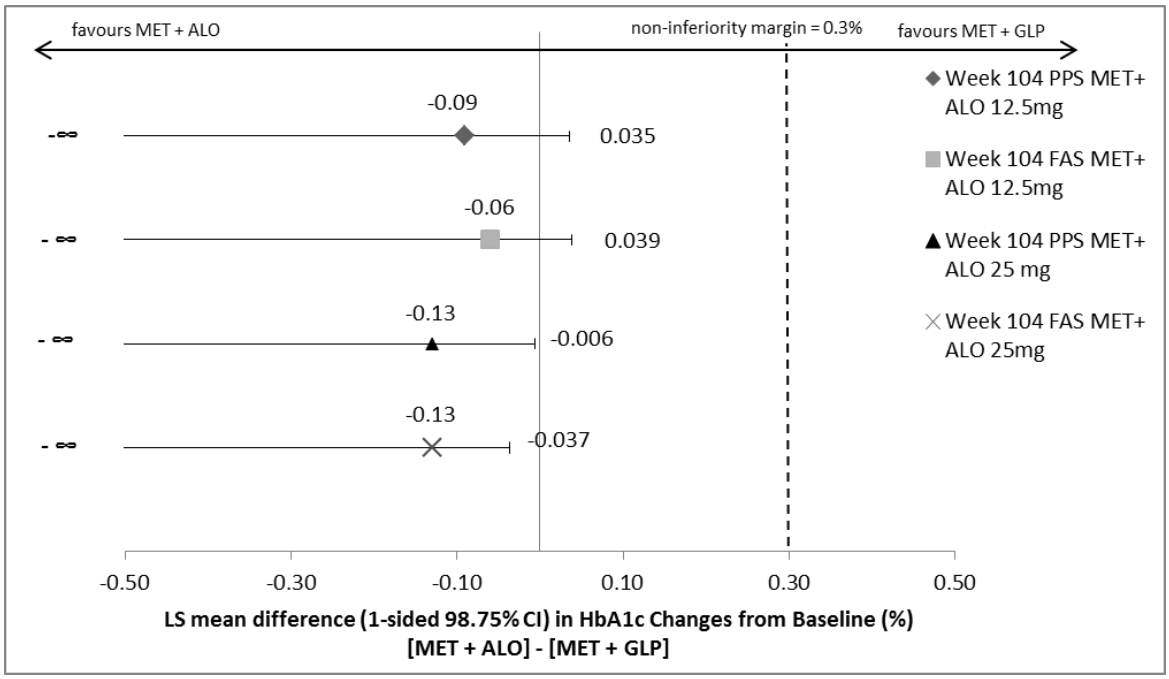
A1C = glycated hemoglobin; ALO = alogliptin; CI = confidence interval; GLZ = glipizide; LSM = least squares mean; LSMD = least squares mean difference; MET = metformin; NA = not applicable; PPS = per-protocol set; vs = versus.
[a] The non-inferiority margin was set at 0.3%, difference in A1C.
[b] In Study 305, a non-inferiority margin of 0.3% difference in A1C was tested with a 1-sided significance of 0.0125.
[c] Non-inferiority was confirmed.

FIGURE 4: LEAST SQUARES MEAN DIFFERENCES IN A1C CHANGES FROM BASELINE AT WEEK 52 IN STUDY 305



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

FIGURE 5: LEAST SQUARES MEAN DIFFERENCES IN A1C CHANGES FROM BASELINE AT WEEK 104 IN STUDY 305



A1C = glycated hemoglobin; ALO = alogliptin; CI = confidence interval; FAS = full analysis set; GLP = glipizide; Hb = hemoglobin; LS = least squares; MET = metformin; PPS = per-protocol set.
Source: Figure from Clinical Study report 305.[25]

TABLE 20: CHANGES FROM BASELINE IN A1C (FULL ANALYSIS SET) AT 26 WEEKS IN STUDY 302

Parameter		MET 500 mg b.i.d. (N = 114)	MET 1,000 mg b.i.d. (N = 111)	ALO/MET 12.5 mg/500 mg b.i.d. (N = 111)	ALO/MET 12.5 mg/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 in baseline, LSM (SE)	–0.7 (0.1)	–1.1 (0.1)	–1.2 (0.1)	–1.6 (0.1)	0.2 (0.1)
	Change in baseline, LSMD (97.5% CI) vs. MET 500 mg	NA	NA	–0.6 (–0.9 to –0.3)[a]	NA	NA
	Change in baseline, LSMD (97.5% CI) vs. MET 1,000 mg	NA	NA	NA	–0.4 (–0.7 to –0.2)[a]	NA
	Change in baseline, LSMD (95% CI) vs. PL	NA	NA	–1.4 (–1.6 to –1.1)[a]	–1.7 (–2.0 to –1.5)[a]	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; vs. = versus.
[a] $P < 0.001$.
Note: Data from Clinical Study Reports for Study 009[32] and Study 011.[33]

b) Fasting plasma glucose

In Study 008, baseline FPG values were similar among treatment groups, ranging from 9.34 to 9.96 mmol/L. The adjusted changes from baseline at 26 weeks were similar for ALO 12.5 mg and ALO 25 mg (–0.97 and –1.04 mmol/L, respectively) compared with placebo (0.0 mmol/L). At 26 weeks, ALO 12.5 mg and ALO 25 mg demonstrated statistically significantly greater decreases in FPG when compared with placebo (LSMD = –1.04 mmol/L; 95% CI, –1.51 to –0.57 mmol/L, and LSMD = –0.97 mmol/L; 95% CI, –1.44 to –0.49 mmol/L, respectively) (Table 21).

In Study 305, baseline FPG values were similar among treatment groups ranging from 8.19 to 8.29 mmol/L. The adjusted mean change from baseline at 52 weeks for ALO 12.5 mg and ALO 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, ALO 12.5 mg and ALO 25 mg were associated with higher adjusted mean reductions in FPG within groups (least squares mean [LSM] = –0.05 mmol/L and –0.48 mmol/L, respectively) compared with placebo (LSM = 0.30 mmol/L). At both 52 and 104 weeks, ALO 12.5 mg and 25 mg demonstrated statistically significantly greater reductions in FPG compared with placebo (Table 22).

In Study 302, baseline FPG values were similar among the treatment groups, ranging from 9.76 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 ALO/MET 12.5 mg/500 mg twice-daily and ALO/MET 12.5 mg/1,000 mg twice-daily groups, respectively) compared with all other treatment groups with the exception of MET 1,000 mg twice daily (–1.77 mmol/L). Both ALO/MET 12.5 mg/500 mg twice daily and ALO/MET 12.5 mg/1,000 mg twice daily were associated with statistically significant reductions in FPG compared with the respective MET monotherapy regimens (LSMD = –0.78 mmol/L; 95% CI, –1.45 to –0.10, and LSMD = –1.12 mmol/L; 95% CI, –1.81 to –0.43, respectively) (Table 23).

TABLE 21: CHANGES FROM BASELINE FASTING PLASMA GLUCOSE AT 26 WEEKS IN STUDY 008 (FULL ANALYSIS SET)

Parameter		008		
		ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
FPG (mmol/L)	Baseline, mean (SD)	9.34 (2.44)	9.54 (2.54)	9.96 (2.79)
	End, mean (SD)	8.38 (2.50)	8.57 (2.46)	9.82 (2.96)
	Change in baseline, LSM (SE)	–1.04 (0.14)	–0.97 (0.14)	0.0 (0.20)
	Change in baseline, LSMD (95% CI) vs. PL	–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; LSM = least squares mean; LSMD = least squares mean difference; MET = metformin; NA = not applicable; PL = placebo; SD = standard deviation; SE = standard error; vs = versus.
[a] $P < 0.001$.
Note: Data from Clinical Study Report for Study 008.[20]

TABLE 22: 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 in baseline, LSM (SE) LSMD vs. 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 in baseline, LSM (SE) LSMD vs. 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 in baseline, LSM (SE) LSMD vs. 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

A1C = glycated hemoglobin; 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; vs. = versus.
[a] $P < 0.001$.
Note: Data from Clinical Study Report for Study 305.[25]

TABLE 23: WITHIN-GROUP CHANGES IN FASTING PLASMA GLUCOSE (FULL ANALYSIS SET) AT 26 WEEKS IN STUDY 302

Parameter		MET 500 mg b.i.d. (N = 114)	MET 1,000 mg b.i.d. (N = 111)	ALO/MET 12.5 mg/500 mg b.i.d. (N = 111)	ALO/MET 12.5 mg/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 in baseline, LSM (SE)	–0.64 (0.25)	–1.77 (0.24)	–1.76 (0.25)	–2.55 (0.24)	0.69 (0.25)
	Change in baseline, LSMD (97.5% CI) vs. MET 500 mg		NA	–1.12 (–1.81 to –0.43)[a]	NA	NA
	Change in baseline, LSMD (97.5% CI) vs. MET 1,000 mg	NA		NA	–0.78 (–1.45 to –0.10)[a]	NA
	Change in baseline, LSMD (95% CI) vs. PL	NA	NA	–2.45 (–3.15 to –1.75)[c]	–3.24 (–3.92 to –2.55)[c]	NA

A1C = glycated hemoglobin; 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; vs. = versus.
[a] $P < 0.01$.
[b] $P < 0.05$.
[c] $P < 0.001$.
Note: Data from Clinical Study Report for Study 302.[23]

3.6.3 Changes in body weight

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 to –0.7 kg and –0.4 kg for the ALO 12.5 mg, ALO 25 mg and placebo groups, respectively. There were no significant differences

between ALO 12.5 mg and placebo (LSMD = 0.0 kg; 95% CI, –0.7 to 0.7), and ALO 25 mg and placebo (LSMD = –0.3 kg; 95% CI, –0.9 to 0.4) (Table 24).

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 to –0.71 kg and 0.86 kg for the ALO 12.5 mg, ALO 25 mg, and GLZ groups, respectively. Adjusted mean differences between ALO 12.5 mg and 25 mg versus GLZ were statistically significant (LSMD = –1.51; 95% CI, –1.79 to –1.231, and LSMD = –1.58 kg; 95% CI, –1.86 to –1.30, respectively). At 104 weeks, adjusted mean changes from baseline body weight were –0.64 kg to –0.91 kg and –0.89 for ALO 12.5 mg, ALO 25 mg, and GLZ, respectively. Adjusted mean differences between ALO 12.5 and 25 mg versus GLZ were statistically significant (LSMD = –1.52 kg; 95% CI, –1.85 to –1.20, and LSMD = –1.80 kg; 95% CI, –2.12 to –1.47, respectively) (Table 25).

In Study 302, 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 twice-daily ALO/MET 12.5 mg/1,000 mg and twice-daily ALO/MET 12.5 mg/500 mg were –1.2 kg and 0.6 kg, respectively. This compared with values of –1.2 kg for the MET 1,000 mg twice-daily group to –0.8 kg for the MET 500 mg twice-daily group and –0.9 kg for the placebo group. The mean differences between ALO/MET 12.5 mg/500 mg versus MET 500 mg twice daily, and ALO/MET 12.5 mg/1,000 mg twice daily versus MET 1,000 mg twice daily, were not statistically significant (LSMD = –0.2 kg; 95% CI, –0.6 to 1.0, and LSMD = 0.1 kg; 95% CI, –0.7 to 0.8, respectively) (Table 26).

TABLE 24: CHANGES IN BODY WEIGHT FROM BASELINE AT 26 WEEKS IN STUDY 008

Change in Body Weight	008		
	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
Baseline (kg), mean (SD)	87.7 (18.4)	88.1 (19.5)	89.3 (20.4)
End (kg), mean (SD)	85.6 (17.4)	87.3 (19.2)	86.2 (20.1)
Change from baseline, LSM (SE)	–0.4 (0.2)	–0.7 (0.2)	–0.39 (0.3)
Change from baseline, LSMD (95% CI) vs. PL	0.0 (–0.7 to 0.7)	–0.3 (–0.9 to 0.4)	NA

ALO = alogliptin; 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; vs. = versus.
Note: Data from Clinical Study Report for Study 008.[20]

TABLE 25: 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 in baseline, LSM (SE)	–0.65 (0.101)	–0.71 (0.101)	0.86 (0.101)
Week 26 LSMD (95% CI) vs. MET + GLZ	–1.51[a] (–1.79 to –1.23)	–1.58[a] (–1.857 to –1.296)	NA
Week 52 change in baseline, LSM (SE)	–0.64 (0.117)	–0.91 (0.117)	0.89 (0.117)
LSMD (95% CI) vs. MET + GLZ	–1.52[a] (–1.846 to –1.198)	–1.80[a] (–2.122 to –1.473)	NA
Week 104 change in baseline, LSM (SE)	NR	NR	NR
Change in 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] $P < 0.001$.
Note: Data from Clinical Study Report for Study 305.[25]

TABLE 26: CHANGES IN BODY WEIGHT FROM BASELINE IN STUDY 302

Change in Body Weight	302				
	MET 500 mg b.i.d. (N = 109)	MET 1,000 mg b.i.d. (N = 111)	ALO/MET 12.5 mg/ 500 mg b.i.d. (N = 106)	ALO/MET 12.5 mg/ 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) vs. MET 500 mg		NA	0.2 (–0.6 to 1.0)	NA	NA
Change from baseline, LSMD (95% CI) vs. MET 1,000 mg	NA		NA	0.1 (–0.7 to 0.8)	NA
Change from baseline, LSMD (95% CI) vs. 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; vs. = versus.
Note: Data from Clinical Study Report for Study 302.[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 below (see 2.2.1, Protocol). (For detailed harms data, see APPENDIX 3: DETAILED OUTCOME DATA.) A summary of harms data from the included studies is displayed in Table 27, Table 28, and Table 29.

3.7.1 Adverse events

In Study 008, the proportion of patients who experienced an AE during the 26-week treatment period was lower in the ALO 12.5 mg and 25 mg groups (62.9% and 57.0%, respectively) compared with placebo (66.3%). The most common AEs in the ALO 12.5 mg were UTI (6.6%), nasopharyngitis (5.6%), and upper

respiratory tract infection (4.7%). The most common AEs in the ALO 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 36).

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 ALO 12.5 mg, 25 mg, and GLZ groups, respectively). The most frequent AEs in the ALO 12.5 mg groups were nasopharyngitis (8.9%), diarrhea (6.9%), and UTI (4.8%) (Table 37), while hypertension (7.7%), nasopharyngitis (7.6%), and headache (6.9%) were the most frequent AEs in the ALO 25 mg group. The most frequent AEs in the GLZ group were hypoglycemia (10.5%), nasopharyngitis (7.5%), and diarrhea (7.2%). Pancreatitis was categorized as acute pancreatitis, pancreatitis, and chronic pancreatitis in Study 305. There were two cases of acute pancreatitis (one each in the ALO 25 mg and GLZ groups), one case of pancreatitis in the GLZ group, and one patient who experienced chronic pancreatitis in the GLZ group.

In Study 302, the proportions of patients who experienced an AE in the ALO/MET 12.5 mg/500 mg twice-daily and ALO/MET 12.5 mg/1,000 mg twice-daily groups were similar (63.2% and 64.0%, respectively). The proportions in the twice-daily MET 500 mg, 1,000 mg, and placebo groups were 68.8%, 62.2%, and 71.7%), respectively.

The most frequently reported AEs in the ALO/MET 12.5 mg/500 mg twice-daily group were hyperglycemia (7.5%) and headache (6.6%). The most frequently reported AEs in the ALO/MET 12.5 mg/1,000 mg twice-daily group were reduced creatine renal clearance (7.9%), dyspepsia (7.0%), and diarrhea (7.0%). The most frequently reported AEs in the MET 500 mg twice-daily group were dyslipidemia (6.4%), headache (6.4%), and back pain (5.5%). The most frequently reported AEs in the MET 1,000 mg twice-daily group were diarrhea (9.0%) and hyperglycemia (8.1%). One patient (0.9%) experienced pancreatitis in the twice-daily ALO/MET 12.5 mg/1,000 mg group (Table 38).

TABLE 27: SUMMARY OF HARMS FROM STUDY 008

Summary of AEs, n (%)	008		
	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 207)	PL + MET (N = 104)
Any AEs	134 (62.9)	118 (57.0)	69 (66.3)
SAEs	6 (2.8)	8 (3.9)	4 (3.8)
WDAEs	7 (3.3)	4 (1.9)	1 (1.0)
Deaths	1 (0.5)	0	0
Hypoglycemia	2 (0.9)	0	3 (2.9)

AE = adverse event; ALO = alogliptin; MET = metformin; PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Note: Data from Clinical Study Report for Study 008.[20]

TABLE 28: SUMMARY OF HARMS FROM STUDY 305

Summary of AEs, 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.
Note: Data from Clinical Study Report for Study 305.[25]

TABLE 29: SUMMARY OF HARMS FROM STUDY 302

Summary of AEs, n (%)	MET 500 mg b.i.d. (N = 109)	MET 1,000 mg b.i.d. (N = 111)	ALO/MET 12.5 mg/500 mg b.i.d. (N = 106)	ALO/MET 12.5 mg/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; 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 PI (due to hyperglycemia).
Note: Data from Clinical Study Report for Study 302.[23]

3.7.2 Serious adverse events

In Study 008, similar proportions of patients experienced SAEs among the treatment groups. Eight patients in the ALO 12.5 mg group (3.9%), six patients in the ALO 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 ALO 12.5 mg group. The cause of death was hypertensive heart disease, which was considered unrelated to the study drug (Table 27).

In Study 305, 11% of patients in the ALO 25 mg group, 9.9% in the ALO 12.5 mg group, and 9.3% in the GLZ group experienced an SAE. There were 11 deaths in Study 305, three in the ALO 12.5 group (0.3%), three in the ALO 25 mg group (0.3%), and five in the GLZ group (0.6%). However, only one death, caused by pulmonary edema in the ALO 25 mg group, was determined to have possibly been related to the study drug (Table 28).

In Study 302, the proportions of patients with a SAE were similar among the dual therapy and MET monotherapy groups. Two patients in the ALO/MET 12.5 mg/500 mg twice-daily group (1.9%), two patients in the ALO/MET 12.5 mg/1,000 mg twice-daily group (1.8%), two patients in the MET 500 mg group (1.8%), two patients in the MET 1,000 mg group (1.8%), and three patients (2.8%) in the placebo group experienced an SAE. There were no deaths in Study 302 (Table 29).

3.7.3 Withdrawal due to adverse events

In Study 008, seven (3.3%) patients discontinued due to AEs in the ALO 12.5 mg group compared with four patients (1.9%) in the ALO 25 mg group and one patient (1.0%) in the placebo group. No single AE resulted in discontinuation of ≥ 3% of the safety set population in any of the treatment groups (Table 30).

In Study 305, fewer patients discontinued due to AEs in the ALO 12.5 mg and 25 mg groups (6.8% and 8.4%, respectively) versus the GLZ group (9.4%). No single AE resulted in discontinuation of ≥ 3% of the ALO 12.5 mg group safety set. However, in the ALO 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 GLZ group discontinued due to metabolism or nutrition disorders (3.2%), the most frequent cause of discontinuation due to AEs in this group (Table 31).

In Study 302, there was a higher incidence of discontinuation due to AEs in the co-administration groups, with five patients (4.7%) in the ALO/MET 12.5 mg/500 mg twice-daily group and 11 patients (9.6%) in the ALO/MET 12.5 mg/1,000 mg twice-daily group, compared with three patients in the MET 500 mg twice-daily (2.8%) and two patients in the MET 1,000 mg twice-daily groups (1.8%). Five patients (4.7%) discontinued due to AEs in the placebo group. No single AE resulted in discontinuation of ≥ 3% of the safety population, except in the ALO/MET 12.5 mg/1,000 mg twice-daily group, in which six patients (5.3%) discontinued due to investigations (Table 32).

TABLE 30: SUMMARY OF WITHDRAWALS DUE TO ADVERSE EVENTS FROM STUDY 008 (SAFETY SET)

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

ALO = alogliptin; MET = metformin; NR = not reported; PL = placebo; SOC = system organ class; WDAE = withdrawal due to adverse event

[a] ≥ 3% patients.

Note: Data from Clinical Study Report for Study 008.[20]

TABLE 31: SUMMARY OF WITHDRAWALS DUE TO ADVERSE EVENTS FROM STUDY 305 (SAFETY SET)

WDAEs[a] by SOC, 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 and 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; NR = not reported; SOC = system organ class; WDAE = withdrawal due to adverse event.
[a] ≥ 2 patients.
Note: Data from Clinical Study Report for Study 305.[25]

TABLE 32: SUMMARY OF WITHDRAWALS DUE TO ADVERSE EVENTS FROM STUDY 302 (SAFETY SET)

WDAEs by SOC, n (%)	MET 500 mg b.i.d. (N = 109)	MET 1,000 mg b.i.d. (N = 111)	ALO/MET 12.5 mg/ 500 mg b.i.d. (N = 106)	ALO/MET 12.5 mg/ 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)
Respiratory, thoracic, and mediastinal disorders	1 (0.9)	0	0	0	0

ALO = alogliptin; b.i.d. = twice daily; MET = metformin; PL = placebo; SOC = system organ class; WDAEs = withdrawal due to adverse event.
Note: Data from Clinical Study Report for Study 302.[23]

3.7.4 Hypoglycemia

In Study 008, two patients (0.9%) in the ALO 12.5 mg group, no patients in the ALO 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 33).

In Study 305, 22 patients (2.5%) in the ALO 12.5 mg group, 12 patients (1.4%) in the ALO 25 mg group, and 202 patients (23.2%) in the GLZ group experienced at least one episode of hypoglycemia. Severe hypoglycemia occurred in one patient (0.1%) in the ALO 12.5 mg group, and five patients in the GLZ (0.6%) group (Table 34).

In Study 302, hypoglycemia occurred in two patients (1.9%), six patients (5.3%), seven patients (6.3%), two patients (1.8%), and one patient (1.8%) in the twice-daily ALO/MET 12.5 mg/500 mg, ALO/MET 12.5 mg/1,000 mg, MET 1,000 mg, MET 500 mg, and placebo groups, respectively (Table 35). No patients experienced severe hypoglycemia in this study.

TABLE 33: HYPOGLYCEMIC EVENTS IN STUDY 008 (SAFETY SET)

Hypoglycemia	008		
	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 210)	PL + MET (N = 104)
Any hypoglycemia, n (%)	2 (0.9)	0	3 (2.9)
Severe hypoglycemia, n (%)	0	0	0

ALO = alogliptin; MET = metformin; PL = placebo.
Note: Data from Clinical Study Report for Study 008.[20]

TABLE 34: 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.
Note: Data from Clinical Study Report for Study 305.[25]

TABLE 35: HYPOGLYCEMIC EVENTS IN STUDY 302 (SAFETY SET)

Hypoglycemia	302				
	MET 500 mg b.i.d. (N = 109)	MET 1,000 mg b.i.d. (N = 111)	ALO/MET 12.5 mg/ 500 mg b.i.d. (N = 106)	ALO/MET 12.5 mg/ 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.
Note: Data from Clinical Study Report for Study 302.[23]

4. DISCUSSION

4.1 Summary of Available Evidence

The manufacturer originally requested that alogliptin be listed "equivalent to other DPP-4 inhibitors and metformin fixed-dose combinations currently available in Canada." Recommendations from CEDAC/CDEC for other DPP-4 inhibitors (sitagliptin, linagliptin, and saxagliptin) and DPP-4 inhibitor/MET FDCs have been consistent in recommending these drugs in combination with metformin and a sulfonylurea when insulin is not an option.[8-13] While many publicly funded drug plans have listing criteria for the DPP-4 inhibitor/MET FDCs that are in alignment with these recommendations, some exceptions exist. ALO/MET FDC is unique among the other DPP-4 inhibitor/MET FDCs in that it does not have an approved indication for use in combination with a sulfonylurea. Upon consideration of these factors, and in consultation with the manufacturer, it was determined that the approved indication for ALO/MET FDC of greatest relevance for review by CDR was as an adjunct to diet and exercise in patients inadequately controlled on metformin or in patients already treated with the combination of alogliptin and metformin. Subsequently, the manufacturer revised the requested listing criteria to align with the indication under review.

Three double-blind, phase 3 RCTs were identified for inclusion in this review. Study 008 was a 26-week, placebo-controlled trial of patients who had inadequate glycemic control when treated with metformin. Study 302 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. There were no studies that employed ALO/MET FDC. The population and trial design of these RCTs was consistent with current advice from the US FDA and European Medicines Agency (EMA) regarding registration trials for new anti-hyperglycemic 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.[29,30]

4.2 Interpretation of Results

4.2.1 Efficacy

Similar to RCTs of most other anti-hyperglycemic drugs, the primary end point in the reviewed alogliptin studies was change from baseline in A1C. While the results of major trials of intensive glucose lowering conducted in the past few years have generated some degree of controversy regarding the relationship between A1C lowering and cardiovascular outcomes,[34,35] A1C is considered an appropriate primary outcome in clinical trials of anti-hyperglycemic drugs. NICE and the US FDA have indicated that reductions from baseline in A1C as small as –0.5% and –0.7%, respectively, have clinical importance.[29,30] In Study 008, alogliptin 12.5 mg and 25 mg added to metformin was associated with A1C reductions of 0.5% compared with addition of placebo. Similarly, in Study 302, dual therapy with alogliptin and metformin was associated with reductions in A1C of 0.4% to 0.6% compared with metformin monotherapy. In Study 305, alogliptin 12.5 mg and 25 mg demonstrated non-inferiority to glipizide on A1C when added to metformin; mean reductions from baseline A1C 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 metformin appear to satisfy the conventional thresholds of clinical importance. The EMA and FDA both came to similar conclusions, describing the A1C effect sizes associated with alogliptin add-on therapy as modest but clinically relevant.[26,31]

Given the availability of three previous DPP-4 inhibitors/MET FDCs on the Canadian market (i.e., sitagliptin/MET, saxagliptin/MET, and linagliptin/MET), the central issue in the evaluation of ALO/MET FDC is its comparative efficacy and safety versus these drugs. Unfortunately, no direct comparative trials of ALO/MET FDC versus other DPP-4 inhibitor/MET FDCs 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 and/or sulfonylureas (SUs) (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.[36] 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 between alogliptin and the other DPP-4 inhibitors available in Canada on A1C, 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 7: SUMMARY AND CRITICAL APPRAISAL OF MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS — TOLLEY ET AL. (2014)).[37] 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 between-study heterogeneity. As dual therapy with either metformin or sulfonylurea, there were no statistically significant differences for change from baseline in adjusted mean A1C at 24 weeks between alogliptin and linagliptin, saxagliptin, and sitagliptin. The authors also reported a high probability (between 64% and 100%, depending upon 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. An 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. The included trials did not directly address the issue of daily fluctuations in blood glucose. However, alogliptin in combination with metformin was associated with statistically significant reductions in FPG compared with metformin alone in Studies 008 and 302. 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 to 0.48 mmol/L).

Patient group input received by CADTH demonstrated concerns regarding the weight gain associated with some antidiabetic 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 TZDs were associated with weight gain (range: 1.9 to 5.0 kg). 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. 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 sulfonylureas. The original manufacturer-submitted NMA (by Craddy et al.) assessed weight gain between 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 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/metformin.

Cardiovascular risk is an area of concern for anti-hyperglycemic drugs for patients with T2DM. Regulatory agencies require a comprehensive evaluation of the cardiovascular safety profile of new antidiabetic therapies.[38] The Examination of Cardiovascular Outcomes With Alogliptin (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 syndrome.[39] EXAMINE was a phase 3, multi-centre, randomized, double-blind, placebo-controlled study (APPENDIX 8: 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 (MI), and non-fatal stroke). Patients were eligible for study participation if they were older than 18 years of age, had a diagnosis of T2DM, were receiving antidiabetic 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 ACS within 15 to 90 days prior to randomization. Patients were randomized to receive either alogliptin once daily or placebo once daily, in addition to standard of care for T2DM 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 MI, or non-fatal ischemic stroke (hazard ratio = 1.00; 95% CI, 0.89 to 1.12).[40]

Diabetes may have a substantial impact on quality of life. Patient group 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, DTSQ) as an end point, but no data were reported.

4.2.2 Harms

Overall, the proportions of patients experiencing AEs when treated with alogliptin with metformin were similar to the metformin monotherapy groups during a 26-week treatment period. The proportion 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 glipizide/metformin group. In all cases, 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 proportions of patients experiencing SAEs with alogliptin/metformin dual therapy compared with placebo/metformin, glipizide/metformin, and placebo. In addition, there was no apparent pattern in the type of SAEs.[31] WDAE proportions were similar between alogliptin and glipizide in Study 305. However, combinations of alogliptin with metformin tended to be associated with more WDAEs than metformin alone: in Study 302, proportions experiencing WDAE were 4.7% in the twice-daily alogliptin 12.5 mg + 500 mg metformin group and 9.6% in the alogliptin 12.5 mg + 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. Study 008 did not suggest the potential for an increased risk of hypoglycemia alogliptin/metformin dual therapy compared with metformin monotherapy. Not surprisingly, given the well-established propensity for sulfonylureas 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 (Craddy et al.), odds ratios for all DPP-4 inhibitors as dual therapy with metformin versus metformin monotherapy were statistically non-significant. However, in the second NMA (Tolley et al.), 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 the authors noted that hypoglycemia definitions were heterogeneous 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 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]

All of the DPP-4 inhibitors approved for use in Canada carry a warning regarding the risk of pancreatitis in their respective product monographs.[15-18,41-44] There were no cases of pancreatitis reported in Study 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.[45]

4.3 Other Considerations

4.3.1 Bioequivalence

A key consideration in the assessment of ALO/MET FDC is its comparative bioavailability with ALO and MET administered as separate dosage forms. The pharmacokinetic characteristics of ALO/MET FDC were compared with co-administration of the single-drug tablets in two phase 1 studies of healthy volunteers (MET-103 and MET-101) (APPENDIX 5: SUMMARY OF BIOEQUIVALENCE STUDIES OF ALOGLIPTIN/METFORMIN).[21] Both bioequivalence studies were open-label, randomized, two-cohort, four-sequence, four-period crossover studies with the same dosing schedule. The first cohort in each study received ALO/MET FDC 6.25 mg/500 mg, ALO/MET FDC 6.25 mg/1,000 mg, co-administered ALO 6.25 mg + MET 500 mg, and co-administered ALO 6.25 mg + MET 1,000 mg. The second cohort received ALO/MET FDC 12.5 mg/500 mg, ALO/ MET FDC 12.5 mg/1,000 mg, co-administered ALO 12.5 mg + MET 500 mg, and co-administered ALO 12.5 mg + MET 1,000 mg. Frequency of administration was not specified (although it is assumed to be twice daily), and study duration was not reported. The 90% confidence intervals for the area under the curve (AUC) and maximum concentration (C_{max}) for ALO/MET FDC, ALO 12.5 mg, and MET administered separately were within the EMA-specified bioequivalence range of 80% to 125% for all studied doses. Hence, ALO/MET FDC was shown to be bioequivalent to ALO and MET co-administered as individual dosage forms in healthy patients according to the EMA standards for bioequivalence.

4.3.2 Alogliptin triple therapy with metformin and a sulfonylurea

The manufacturer has requested that alogliptin be listed in accordance with the indication under review. Alogliptin is not indicated for use in combination with metformin and sulfonylurea, [redacted]. The manufacturer did, however, provide some evidence related to the efficacy of alogliptin as triple therapy with metformin and sulfonylurea in the form of a post hoc exploratory subgroup analysis of patients from the EXAMINE study (N = 1,398). In the subgroup of patients receiving metformin and a sulfonylurea at baseline, the adjusted mean difference on A1C between alogliptin and placebo [redacted]. The alogliptin and placebo groups [redacted] with respect to the incidence of overall adverse events [redacted] in the metformin/sulfonylurea 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

Three double-blind, placebo- or active-controlled randomized controlled trials (RCTs) were included in this review of alogliptin/metformin (ALO/MET) FDC. In all trials, the addition of alogliptin to metformin was associated with modest but clinically relevant improvements in glycated hemoglobin (A1C) ranging from 0.4% to 0.6%. In the only active-controlled trial in the dual therapy setting, 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 was weight-neutral versus placebo when added to metformin, and associated with lower weight gain than a sulfonylurea when either was added to metformin. Alogliptin was not associated with a higher risk of hypoglycemia than placebo when added to either metformin, but was associated with lower hypoglycemia versus a sulfonylurea. 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.

None of the included trials employed ALO/MET FDC. However, the FDC was shown to be bioequivalent to ALO and MET co-administered as individual dosage forms in healthy patients, according to European Medicines Association standards for bioequivalence. There was no direct comparative evidence for alogliptin versus other DPP-4 inhibitors available in Canada in the context of metformin dual therapy. The manufacturer-submitted NMA suggested that there are no differences across dipeptidyl peptidase-4 (DPP-4) inhibitors on A1C, body weight, and hypoglycemia, and that alogliptin as dual therapy with metformin 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 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, and these are listed in the 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 DPP4 use had taken DPP4 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, interactions with friends and family, and cause stress and worry, as well as ability to participate in normal activities of daily living. 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) in addition to 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, cost of expensive supplies and medication.” Maintaining control of diabetes has the potential to reduce anxiety and avoid or delay complications as well as improve overall quality of life.

Diabetes requires considerable self-management, including healthy eating, 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 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 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 through 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 dipeptidyl peptidase-4 (DPP-4) inhibitor experience reported being mostly satisfied with drug therapy (similar to overall response) and that their blood sugar levels were kept at target although some indicated lack of control. Many patients indicated frustration with having to take multiple medications, including drugs to maintain blood sugar, hypertension, cholesterol-lowering drugs, and others. Several respondents identified previous prescribed drugs as having intolerable side effects — mostly 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, alogliptin (with a sulfonylurea [SU] or insulin) and thereby reduces pill burden and promotes adherence. Of all respondents, 95% had little or no knowledge of Nesina; 86% of respondents had little or no knowledge of Kazano. Most with no exposure to the DDP-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 the expectation of 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 co-morbid conditions such as hypertension, heart failure, depression, renal disease, and others. Simplifying the drug regimen is a serious and important issue for this patient population and when asked if 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 during the course of their disease. Their preference and tolerance of therapy is 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 6: ORGANIZATIONS AND FOUNDATIONS THAT MADE DONATIONS TO THE CANADIAN DIABETES ASSOCIATION BETWEEN SEPTEMBER 2012 AND AUGUST 2013

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

Source: Canadian Diabetes Association, Annual Report, 2013.[46]

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.

MULTI-DATABASE STRATEGY	
#	**Searches**
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, metformin, 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 36: SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS FROM STUDY 008 OCCURRING IN ≥ 3% OF PATIENTS IN ANY TREATMENT GROUP

AEs by SOC, n (%)	Study 008		
	ALO 12.5 mg + MET (N = 213)	ALO 25 mg + MET (N = 207)	PL + MET (N = 104)
Any AEs	**134 (62.9)**	**118 (57.0)**	**69 (66.3)**
Diarrhea	6 (2.8)	7 (3.4)	6 (5.8)
Oedema peripheral	NR	NR	NR
Urinary tract infection	14 (6.6)	6 (2.9)	4 (3.8)
Nasopharyngitis	12 (5.6)	7 (3.4)	6 (5.8)
Upper respiratory tract infection	10 (4.7)	5 (2.4)	7 (6.7)
Influenza	NR	NR	NR
Bronchitis	9 (4.2)	6 (2.9)	2 (1.9)
Sinusitis	5 (2.3)	4 (1.9)	5 (4.8)
Hypertriglyceridemia	NR	NR	NR
Hyperuricemia	NR	NR	NR
Arthralgia	4 (1.9)	3 (1.4)	5 (4.8)
Back pain	NR	NR	NR
Pain in extremity	5 (2.3)	3 (1.4)	4 (3.8)
Headache	8 (3.8)	4 (1.9)	2 (1.9)
Dizziness	NR	NR	NR
Pruritus	NR	NR	NR
Hypertension	4 (1.9)	6 (2.9)	5 (4.8)

AE = adverse event; ALO = alogliptin; MET = metformin; NR = not reported; PL = placebo; SOC = system organ class.
Note: Data from Clinical Study Report for Study 008.[20]

TABLE 37: SUMMARY OF ADVERSE EVENTS FROM STUDY 305 ≥ 3% OF PATIENTS IN ANY TREATMENT GROUP

AEs by SOC, 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)

AEs by SOC, n (%)	305		
	MET + ALO 12.5 mg (N = 873)	MET + ALO 25 mg (N = 878)	MET + GLZ (N = 869)
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; SOC = system organ class.
Note: Data from Clinical Study Report for Study 305.[25]

TABLE 38: SUMMARY OF ADVERSE EVENTS FROM STUDY 302 ≥ 3% OF PATIENTS IN ANY TREATMENT GROUP

AEs, n (%)	302						
	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.
Note: Data from Clinical Study Report for Study 302.[23]

APPENDIX 4: EXCLUDED STUDIES

TABLE 39: 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-PL-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 hyperglycemia: 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 [Internet]. 2012 May [cited 2014 Aug 21];97(5):1615-22. Available from: http://press.endocrine.org/doi/pdf/10.1210/jc.2011-2243	
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-4 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 [Internet]. 2010 Nov [cited 2014 Aug 21];33(11):2406-8.	
Clinical study report: SYR-322-SULF-007	
Pratley RE, Kipnes MS, Fleck PR, Wilson C, Mekki Q, Alogliptin Study 007 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes inadequately controlled by glyburide monotherapy. Diabetes Obes Metab. 2009 Feb;11(2):167-76.	

APPENDIX 5: SUMMARY OF BIOEQUIVALENCE STUDIES OF ALOGLIPTIN/METFORMIN FIXED-DOSE COMBINATION

Objective

To summarize the available data supporting the bioequivalence of alogliptin/metformin (ALO/MET) fixed-dose combination (FDC) with ALO and MET co-administered as individual dosage forms.

Findings

The pharmacokinetic characteristics of ALO/MET FDC were compared against co-administration of the single tablets in two phase 1 studies of healthy volunteers. The pivotal bioequivalence study (MET-103) compared ALO/MET FDC with individual doses of ALO and EU-marketed MET, while an additional bioequivalence study (MET-101) used US-sourced MET. Both bioequivalence studies were open-label, randomized, two-cohort, four-sequence, four-period crossover studies with the same dosing schedule. The first cohort in each study received ALO/MET FDC 6.25 mg/500 mg, ALO/MET FDC 6.25 mg/1,000 mg, co-administered ALO 6.25 mg + MET 500 mg and co-administered ALO 6.25 mg + MET 1,000 mg. The second cohort received ALO/MET FDC 12.5 mg/500 mg, ALO/MET FDC 12.5 mg/1,000 mg, co-administered ALO 12.5 mg + MET 500 mg and co-administered ALO 12.5 mg + MET 1,000 mg. Only results from the second cohort are summarized here. Frequency of administration was not specified (although it is assumed to be twice daily), and study duration was not reported. Ninety-six patients were enrolled in MET-101 (48 per cohort enrolled, 87 completed) and 72 patients were enrolled in MET-103 (36 per cohort enrolled, 66 completed); patients were randomized equally to one of four treatment sequence groups. The studies were designed in accordance with the European Medicines Agency (EMA) Guideline on the Investigation of Bioequivalence.[47] Details of the studies are provided in Table 40. Studies MET-101 and MET-103 are unpublished. The information presented below was provided in the Health Canada module; full study results were not available in any of the materials available to CDR.

Mean plasma concentrations of ALO and MET were measured during time following administration of study treatments. For both ALO/MET FDC 12.5 mg/500 mg and ALO/MET FDC 12.5 mg/1,000 mg compared with the respective individual doses, the 90% confidence intervals for the area under the curve (AUC) and maximum concentration (C_{max}) of ALO and MET were within the EMA-specified bioequivalence range of 80% to 125%. Therefore, both FDCs met the criteria for bioequivalence with the respective individual doses. Administration of the two drugs as an FDC did not materially affect the pharmacokinetics of either drug.

TABLE 40: PHASE 1 STUDIES EVALUATING THE BIOEQUIVALENCE OF ALOGLIPTIN/METFORMIN FDC WITH CO-ADMINISTRATION OF SINGLE DRUGS

Study Identifier	Study Design	Population	Treatment (mg)	Results
MET-103	Randomized, open-label, 2-cohort, single-centre, 4-sequence, 4-period crossover	72 healthy volunteers under fasted conditions (36 per cohort)	Cohort 2 (n = 9 per treatment sequence group): FDC ALO 12.5/MET 500 ALO 12.5 + MET 500 FDC ALO 12.5/MET 1,000 ALO 12.5 + MET 1,000	90% CIs for AUC and C_{max} were within the bioequivalence range of 80% to 125% for both FDCs versus individual drugs
MET-101	Randomized, open-label, 2-cohort, single-centre, 4-sequence, 4-period crossover	96 healthy volunteers under fasted conditions (48 per cohort)	Cohort 2 (n = 12 per treatment sequence group): FDC ALO 12.5/MET 500 ALO 12.5 + MET 500 FDC ALO 12.5/MET 1,000 ALO 12.5 + MET 1,000	90% CIs for AUC and C_{max} were within the bioequivalence range of 80% to 125% for both FDC versus individual drugs

ALO = alogliptin; AUC = area under the curve; CI = confidence interval; C_{max} = maximum concentration; FDC = fixed-dose combination; MET = metformin.
Source: Kazano Health Canada Module 2.7.1.[21]

Conclusion

ALO/MET FDC was shown to be bioequivalent to ALO and MET co-administered as individual dosage forms in healthy patients, according to EMA standards for bioequivalence.

APPENDIX 6: SUMMARY AND CRITICAL APPRAISAL OF MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS — 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)[36] 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 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 as there are currently limited head-to-head comparative efficacy data between DPP-4 inhibitors.

Methods

TABLE 41: 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 co-transporter 2 inhibitors • pioglitazone Dual therapy comparisons were between the above drugs combined with metformin, sulfonylurea, pioglitazone, or insulin. Triple therapy comparisons were between the above 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 = dipeptidylpeptidase-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 control trials (RCTs) investigating DPP-4 inhibitors as mono-, dual, or triple therapy compared with other oral and injectable antidiabetic pharmacologic interventions, including insulin, in the treatment of patients with type 2 diabetes with inadequate glycemic control (Table 38). 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,[48] by the checklist criteria recommended in its guide to the literature and grading of recommendations,[49] and the quality-assessment criteria recommended by the National Institute for Health and Care Excellence (NICE, UK) in its single-technology appraisal template.[50] Included trials were also assessed as to whether they had been reported according to the Consolidated Standards of Reporting Trials (CONSORT).[51]

Random-effects meta-analyses employing 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).

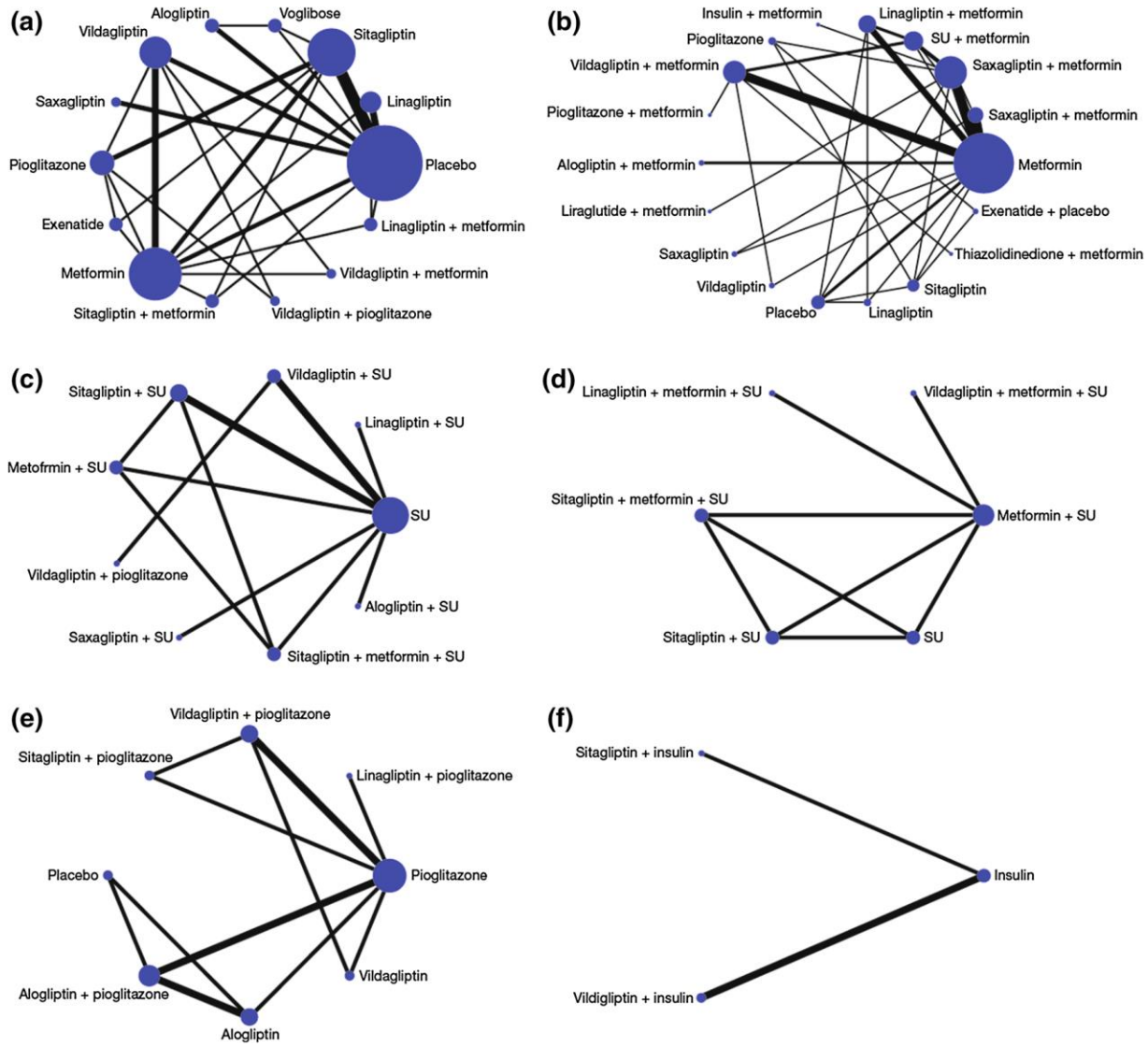
Bayesian meta-analytical techniques were employed for the NMAs using the WinBUGS software. Separate NMAs were conducted for DPP-4 inhibitors as monotherapy compared with placebo, and for dual and triple therapy combinations compared with the backbone monotherapy and dual-therapy regimens, respectively. 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 from baseline in A1C and body weight 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 hyperglycemic 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 across 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 7: NETWORK OF ELIGIBLE COMPARISONS FOR A1C MEAN CHANGE FROM BASELINE



a = DPP-4 monotherapy; b = DPP-4 + metformin; c = DPP-4 + SU; d = DPP-4 plus metformin + SU; e = DPP-4 + pioglitazone; f = DPP-4 + insulin.
Source: Figure 2 in Craddy et al. 2014.[36]

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 the numbers do not add up to 83 as each RCT could be used in multiple sets analyses): 24 RCTs for monotherapy,

38 RCTs for DPP-4 + metformin, 8 RCTs for DPP-4 + SU, 3 RCTs for DPP-4 + metformin + SU, 9 RCTs for DPP-4 + pioglitazone, 1 RCT for DPP-4 + metformin + pioglitazone, 4 RCTs for DPP-4 + insulin, and 1 RCT for DPP-4 + metformin + insulin (Table 42). 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% to 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 post-prandial glucose, BMI, body weight, fasting lipids, fasting plasma insulin, fasting insulin, fasting C-peptide, vital signs, and number or proportion of patients with adverse events.

TABLE 42: NUMBER OF RANDOMIZED CONTROLLED TRIALS INCLUDED IN NETWORK META-ANALYSIS BY TREATMENT

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

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 43 the greatest mean (95% confidence interval [CI]) reduction in A1C from baseline among the DPP-4 inhibitors was with alogliptin –0.797 % (–0.943% to –0.651%). Mean increases in weight from baseline only reached statistical significance versus placebo for linagliptin and sitagliptin; mean (95% CI) weight changes from baseline were 0.431 kg (0.004 kg to 0.86 kg) and 0.717 kg (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 42), 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 (95% CI) body weight relative to placebo of 0.70 kg (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 the odds ratios were statistically non-significant for the other DPP-4 inhibitors. Absolute treatment effects are presented in Table 45.

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 41). 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 + metformin versus saxagliptin + 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 (95% CI) change in A1C from baseline was 0.09% (–0.01% to 0.20%), and within the study's predefined criterion (< 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 44). Results from the analysis of absolute treatment effects are presented in Table 45.

DPP-4 Inhibitor/Sulfonylurea 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, though results for linagliptin and saxagliptin were based solely on one study (Table 43). 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 with sitagliptin combined with SU compared with SU alone.

In the NMA analysis (Table 44), 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 45.

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 43). 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 44), 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 + pioglitazone was associated with a statistically significant increase in body weight (1.20 kg; 95% CI, 0.06 to 2.34) 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 45.

DPP-4 Inhibitor/Insulin Dual Therapy

In the direct comparison analysis, data for dual therapy with DPP-4 + 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 43). Due to 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/Sulfonylurea 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 43). However, a trial of saxagliptin versus placebo in combination with metformin and sulfonylurea has in fact been conducted, and was previously reviewed by CDR.[8] The mean (95% CI) differences versus placebo in change from baseline A1C for sitagliptin and linagliptin were –0.89% (–2.41% to 0.63%) and –0.20% (–0.73% to –0.51%) respectively, and mean (95% CI) differences in change from baseline body weight were 0.33 kg (–0.30 kg to 0.69 kg) and 0.70 kg (–0.22 kg to 1.62 kg), respectively. The odds ratios (95% CI) of a hypoglycemic event versus placebo were 1.69 (1.16 to 2.47) and 8.70 (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] As seen in Table 44 and Table 45, MTC results for relative and absolute treatment effects for linagliptin or sitagliptin triple therapy versus metformin/sulfonylurea dual therapy were not statistically significant.

TABLE 43: RESULTS FROM DIRECT COMPARISONS OF DPP-4 INHIBITORS VERSUS COMPARATORS

End Point	Monotherapy Versus Placebo			
	Alogliptin 25 mg PO daily	**Linagliptin 5 mg PO daily**	**Saxagliptin 5 mg PO daily**	**Sitagliptin 100 mg PO 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] (0.37,1.06) 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
End Point	**Dual Therapy Versus Respective Monotherapy**			
	Alogliptin 25 mg PO daily + metformin	**Linagliptin 5 mg PO daily + metformin**	**Saxagliptin 5 mg PO daily + metformin**	**Sitagliptin 100 mg PO 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 PO daily + SU	**Linagliptin 5 mg PO daily + SU**	**Saxagliptin 5 mg PO daily + SU**	**Sitagliptin 100 mg PO 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

End Point	Dual Therapy Versus Respective Monotherapy (Continued)			
	Alogliptin 25 mg PO daily + pioglitazone	**Linagliptin 5 mg PO daily + pioglitazone**	**Saxagliptin 5 mg PO daily + pioglitazone**	**Sitagliptin 100 mg PO 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 PO daily + insulin	**Linagliptin 5 mg PO daily + insulin**	**Saxagliptin 5 mg PO daily + insulin**	**Sitagliptin 100 mg PO 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 PO daily + metformin + SU	**Linagliptin 5 mg PO daily + metformin + SU**	**Saxagliptin 5 mg PO daily + metformin + SU**	**Sitagliptin 100 mg PO 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; PO = oral administration; SU = sulfonylurea.
[a] Statistically significant versus comparator.

TABLE 44: NETWORK META-ANALYSIS RESULTS FOR RELATIVE EFFECTS OF DPP-4 INHIBITORS VERSUS COMPARATORS

End Point	Monotherapy Versus Placebo			
	Alogliptin 25 mg PO daily	**Linagliptin 5 mg PO daily**	**Saxagliptin 5 mg PO daily**	**Sitagliptin 100 mg PO 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 (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% CrI)				
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 PO daily + metformin	**Linagliptin 5 mg PO daily + metformin**	**Saxagliptin 5 mg PO daily + metformin**	**Sitagliptin 100 mg PO 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 (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 PO daily + SU	**Linagliptin 5 mg PO daily + SU**	**Saxagliptin 5 mg PO daily + SU**	**Sitagliptin 100 mg PO 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 (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 PO daily + pioglitazone	**Linagliptin 5 mg PO daily + pioglitazone**	**Saxagliptin 5 mg PO daily + pioglitazone**	**Sitagliptin 100 mg PO 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 (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 PO daily + insulin	Linagliptin 5 mg PO daily + insulin	Saxagliptin 5 mg PO daily + insulin	Sitagliptin 100 mg PO daily + insulin
Weighted mean difference (95% CrI)				
A1C change from baseline %	-	-	-	–0.41 (–5.07 to 4.25)
Weight change from baseline (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 PO daily + metformin + SU	**Linagliptin 5 mg PO daily + metformin + SU**	**Saxagliptin 5 mg PO daily + metformin + SU**	**Sitagliptin 100 mg PO 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 (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; CrI = credible interval; PO = oral administration; SU = sulfonylurea.
[a] Statistically significant versus comparator.

TABLE 45: NETWORK META-ANALYSIS RESULTS FOR ABSOLUTE TREATMENT EFFECTS OF DPP-4 INHIBITORS

End Point	Monotherapy			
	Alogliptin 25 mg PO daily	**Linagliptin 5 mg PO daily**	**Saxagliptin 5 mg PO daily**	**Sitagliptin 100 mg PO 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 (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 PO daily + metformin	**Linagliptin 5 mg PO daily + metformin**	**Saxagliptin 5 mg PO daily + metformin**	**Sitagliptin 100 mg PO daily + metformin**
Weighted mean difference (95% CrI)				
Pioglitazone 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 (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 PO daily + SU	**Linagliptin 5 mg PO daily + SU**	**Saxagliptin 5 mg PO daily + SU**	**Sitagliptin 100 mg PO 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 (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)
	Dual Therapy (Continued)			
	Alogliptin 25 mg PO daily + pioglitazone	**Linagliptin 5 mg PO daily + pioglitazone**	**Saxagliptin 5 mg PO daily + pioglitazone**	**Sitagliptin 100 mg PO 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 (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 PO daily + insulin	Linagliptin 5 mg PO daily + insulin	Saxagliptin 5 mg PO daily + insulin	Sitagliptin 100 mg PO daily + insulin
Weighted mean difference (95% CrI)				
A1C change from baseline %	-	-	-	–0.56 (–5.22 to 4.09)
Weight change from baseline (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 PO daily + Metformin + SU	**Linagliptin 5 mg PO daily + Metformin + SU**	**Saxagliptin 5 mg PO daily + Metformin + SU**	**Sitagliptin 100 mg PO 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 (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; PO = 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) + 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 46.

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 are 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 Institute for Quality and Efficiency in Health Care (Germany) guidelines on methods for conducting systematic reviews,[48] checklist criteria recommended by l'Agence nationale d'accreditation et d'evaluation en santé (France),[49] and quality-assessment criteria recommended by the National Institute for Health and Care Excellence (NICE) (UK) in its single-technology appraisal template.[50] Study reporting in accordance with the CONSORT was also determined.[51]

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 utilized 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 affect the overall findings for mean change from baseline in A1C. 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 setting 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," above, the analysis of absolute treatment effects was considered to have limitations arising from the need to make assumptions regarding comparator treatment effects. The main focus of this summary, therefore, is 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.[52]

Summary

The manufacturer-submitted NMA demonstrated numerically similar efficacy between DPP-4 inhibitors either as monotherapy or combination therapy for mean change from baseline in A1C. The relative treatment effect results for mean change from baseline in body weight and hyperglycemic events 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 to show that there are 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 46: 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 clearly stated • Search strategy, study selection process, and data extraction 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%) was 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 — 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 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)[37] 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[36]), 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 doses. 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 NMA if they consisted of adult patients with type 2 diabetes mellitus (T2DM) and inadequate glycemic control despite treatment with metformin or SU. The primary efficacy outcome of interest was mean change from baseline glycated hemoglobin (A1C) at the final visit. Mean change in body weight from baseline and proportion of patients with A1C < 7% (results not shown or discussed in this summary) were exploratory outcomes. Safety outcomes included occurrence of ≥ 1 hypoglycemic events 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) 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 approach where possible based on the deviance information criterion and residual deviance statistics. Heterogeneity was assessed using chi-squared and I-squared statistics for direct pair-wise 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 A1C change from baseline outcome, 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 antidiabetic 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 were deemed to be of poor quality (all metformin dual therapy studies).

Metformin Dual Therapy

In the metformin dual therapy analyses, there were no statistically significant differences for change from baseline in adjusted mean A1C at 24 weeks using the random- or fixed-effects model for comparisons of alogliptin with linagliptin, saxagliptin, and sitagliptin (Table 47).

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 for alogliptin 25 mg were seen for the comparisons with saxagliptin 5 mg with a mean difference of 1.18 kg (95% credible interval [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 ≥ 1 hypoglycemic episode with both the fixed- and random-effects models.

TABLE 47: 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 PO daily	**Saxagliptin 5 mg PO daily**	**Sitagliptin 100 mg PO 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 PO daily	**Saxagliptin 5 mg PO daily**	**Sitagliptin 100 mg PO 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)*	3.94 (0.00 to 9.97)*

A1C = glycated hemoglobin; CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; PO = orally; NA = not applicable; 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 OR 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 from baseline in mean A1C 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 hyperglycemic events for any of the comparisons (Table 47).

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

End Point	DPP-4 Inhibitor Versus Alogliptin (Fixed-Effects Model)		
	Linagliptin 5 mg PO daily	**Saxagliptin 5 mg PO daily**	**Sitagliptin 100 mg PO daily**
A1C change from baseline, WMD (95% CI)	0.06 (–0.25, 0.37)	–0.19 (–0.44, 0.06)	–0.04 (–0.36, 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, 0.42)	NA	0.22 (–0.83, 1.27)
Patients with ≥ 1 hypoglycemic event, log odds ratio (95% CrI)	0.39 (–1.07, 1.93)	0.20 (–2.19, 2.60)	1.29 (–0.29, 3.04)

A1C = glycated hemoglobin; CI = confidence interval; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; PO = orally; SU = sulfonylurea; 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 OR for hypoglycemia AE 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 SU compared with other available DPP-4 inhibitors. Both fixed- and random-effects modelling were performed based on model fit statistics. Unlike the NMA by Craddy et al.[36] 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. With wide CrIs, there was a considerable amount of uncertainty seen within the random-effects models. 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 A1C change from baseline when alogliptin combined with metformin or SU was compared with other DPP-4 inhibitors. There was a high probability that alogliptin was similar to other DPP-4 inhibitors on change from baseline in A1C 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 compared with saxagliptin and for the outcome of hypoglycemic events compared with saxagliptin and sitagliptin. Limitations of the Tolley analysis were the relatively small number of included studies and high between-study heterogeneity.

APPENDIX 8: 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[53] in which alogliptin (ALO) once daily was compared with placebo once daily in combination with standard of care among individuals with type 2 diabetes mellitus (T2DM) and acute coronary syndrome (ACS).

Study Characteristics

EXAMINE was a phase 3, multi-centre, randomized, double-blind, placebo-controlled study. The primary objective of this study was to demonstrate non-inferiority of ALO versus placebo with respect to a composite of major adverse cardiac events (MACE) in high-risk T2DM patients. A total of 8,033 patients were screened, and 5,380 patients were randomized to either ALO (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 T2DM, were receiving antidiabetic 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 to 90 days prior to 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 dialysis within 14 days prior to screening.

Patients were randomized to receive either ALO once daily or placebo once daily, in addition to standard of care for T2DM and prophylaxis for cardiovascular comorbidities that patients were already receiving. Investigators were allowed to modify concomitant medications for T2DM 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 ALO 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 (MI), and non-fatal stroke). The secondary end point was time to an event within a secondary MACE composite (cardiovascular death, non-fatal MI, 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 (hsCRP). Incidence and severity of adverse events were assessed. Study visits were performed at the time of screening, 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 ALO 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 ALO 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 in Table 49. 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 ALO and placebo groups. The proportion of patients within each category of renal disease severity and concomitant medication use were similar between treatment groups.

TABLE 49: 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)	8.8 (3.2) (n = 2,680)	8.8 (3.1) (n = 2,655)
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; ACS = acute coronary syndrome; ALO = alogliptin; BMI = body mass index; CABG = coronary artery bypass graft; FPG = fasting plasma glucose; MI = myocardial infarction; PCI = percutaneous coronary intervention; PL = placebo; SD = standard deviation; T2DM = type 2 diabetes mellitus.
Source: EXAMINE Clinical Study Report.[53]

A total of 2,701 patients and 2,679 patients were randomized to the ALO and placebo groups, respectively. The disposition of patients is summarized in Table 50. A total of 564 patients (20.9%) in the ALO group and 606 patients (22.6%) in the PL group discontinued the study drug for any reason, the most common of which were due to adverse events (10.1% overall) and voluntary withdrawal (6.7% overall). The median time of drug exposure was 17.5 months in the ALO group and 17.1 months in the PL group. The proportion of patients receiving therapy for greater than one, two, and three years was similar for both groups.

TABLE 50: 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)

ALO = alogliptin; NR = not reported; PL = placebo; PP = per-protocol.
Source: EXAMINE Clinical Study Report.[53]

Results

Cardiovascular Outcomes

As seen in Table 51, the complete analysis demonstrated that ALO 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. ALO was not shown to be statistically superior to placebo with respect to cardiovascular outcomes. A1C levels in the ALO group were consistently significantly lower than in the placebo group during the course of the study. There was a significant difference between the least squares mean difference values of the ALO and placebo groups for both A1C and FPG values at the last study visit.

TABLE 51: CARDIOVASCULAR AND EFFICACY OUTCOMES

End Point	ALO (N = 2,701) n (%)	PL (N = 2,679) n (%)	Hazard Ratio for ALO (95% CI)
Primary and secondary end points			
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 to 1.04)
Non-fatal MI	187 (6.9)	173 (6.5)	1.08 (0.88 to 1.33)
Non-fatal stroke	29 (1.1)	32 (1.2)	0.91 (0.55 to 1.50)
Secondary MACE composite[c]	344 (12.7)	359 (13.4)	0.95 (≤ 1.14)[b]

End Point		ALO (N = 2,701) n (%)	PL (N = 2,679) n (%)	Hazard Ratio for ALO (95% CI)
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 in baseline, LSM (SE)	–0.3 (0.03)	0.03 (0.03)	NA
	Change in baseline, LSMD (95% CI) vs. PL	–0.4 (–0.4 to –0.3)[d]	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 in baseline, LSM (SE)	0.1 (0.1)	0.5 (0.1)	NA
	Change in baseline, LSMD (95% CI) vs. PL	–0.3 (–0.5 to –0.1)[d]	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; PL = placebo; SD = standard deviation; SE = standard error; vs = versus.
[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.[53]

Harms

The rates of on-study adverse events, serious adverse events, and withdrawals due to adverse events are summarized in Table 52. A summary of adverse events occurring with a frequency greater than 3% in either study group is presented in Table 53. The overall safety profile of ALO was similar to placebo during the course of the study, and there were no apparent differences in the rates of serious adverse events between the two groups.

TABLE 52: 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 53: ON-STUDY ADVERSE EVENTS OCCURRING IN ≥ 3% 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 creatine 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)
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-blinded 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. The blind 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 FDA guidelines.[38] The study appeared to be powered appropriately (91%) with a sufficient sample size to determine non-inferiority of ALO to placebo with respect to the initial (1.8) and final (1.3) hazard ratios. The baseline demographics between the two groups were generally well balanced.

The results showing non-inferiority of ALO 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 ALO treatment on cardiovascular risk beyond this time point cannot be extrapolated. The EXAMINE study enrolled patients with a relatively long duration of T2DM and existing atherosclerotic disease. Hence, the results may not be applicable to other subgroups of patients with T2DM such as those who are recently diagnosed.

Summary

ALO 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 T2DM and recent ACS. These findings suggest no increased risk of cardiovascular death, non-fatal MI, or non-fatal stroke with ALO 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.

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