Common Drug Review
Combination Product Submission

August 2016

Drug	canagliflozin and metformin hydrochloride (Invokamet)
Indication	To improve glycemic control as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus inadequately controlled on a sulfonylurea in combination with metformin or in patients already being treated and achieving glycemic control with a sulfonylurea in combination with metformin and canagliflozin as separate tablets.
Listing request	For the treatment of patients who are already stabilized on therapy with metformin, a sulfonylurea and canagliflozin, to replace the individual components of canagliflozin and metformin in these patients.
Dosage form(s)	50 mg/500 mg, 50 mg/850 mg, 50 mg/1,000 mg, 150 mg/500 mg, 150 mg/850 mg, and 150 mg/1,000 mg tablets
NOC date	June 1, 2016
Manufacturer	Janssen Inc.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

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

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

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ABBREVIATIONS

AE	adverse event
AUC	area under the curve
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CI	confidence interval
CSR	Clinical Study Report
DB	double-blind
FDC	fixed-dose combination
RCT	randomized controlled trial
SAE	serious adverse event
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Diabetes mellitus (DM) is a metabolic disease and characterized by persistent elevations in blood glucose. There are two main types of DM: type 1 (T1DM) and type 2 (T2DM). T1DM is primarily due to lack of adequate insulin secretion from pancreatic beta cells whereas T2DM occurs when the body is unresponsive to insulin. Clinically, T2DM is often associated with hypertension, dyslipidemia, and abdominal obesity. T2DM is a progressive disease. Inadequate glycemic control causes microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (peripheral vascular disease, cardiovascular disease, and cerebrovascular disease) disease. T2DM needs a stepwise approach treatment in order to meet glycemic targets, and reduce the risk of long-term complications.[1-4]
A complex medication regimen (e.g., polypharmacy) is often associated with a high pill burden and various dosing frequencies, which frequently cause patients' poor adherence to treatment.[5-9] Non-adherence has been associated with outcomes such as loss of glycemic control, increased risk of hospitalization and mortality, and increased costs associated with T2DM morbidity and mortality.[10-12]
A treatment strategy to address non-adherence related to polypharmacy and treatment complexity is to utilize fixed-dose combination (FDC) dosage formats to combine individual components into one tablet, thereby reducing pill burden.[12-14]

Canagliflozin/metformin FDC exhibits its efficacy in T2DM through complementary mechanisms of action of its individual components. Canagliflozin is a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, and provides an anti-hyperglycemic effect by inhibiting the glucose transporter in the kidney independent on insulin. Canagliflozin also has an effect on the reduction in systolic blood pressure (SBP) and body weight.[15] Metformin acts to lower basal and postprandial plasma glucose by reducing hepatic glucose production and increasing insulin sensitivity in muscle, thereby improving peripheral glucose uptake and by delaying intestinal glucose absorption.[16] Canagliflozin/metformin FDC is available in the following six FDC regimens: 50 mg/500 mg, 50 mg/850 mg, 50 mg/1,000 mg, 150 mg/500 mg, 150 mg/850 mg and 150 mg/1,000 mg.[17] One of the clinical indications of canagliflozin/metformin FDC is to replace canagliflozin and metformin given separately in patients who are already stabilized on canagliflozin and metformin.[17-20]

Indication under review
To improve glycemic control as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus inadequately controlled on a sulfonylurea in combination with metformin or in patients already being treated and achieving glycemic control with a sulfonylurea in combination with metformin and canagliflozin as separate tablets.[17]
Listing criteria requested by sponsor
Patients who are already stabilized on therapy with metformin, a sulfonylurea and canagliflozin, to replace the individual components of canagliflozin and metformin in these patients.

Note: This is a pre-Notice of Compliance (NOC) submission; the target date for final NOC is June 1, 2016.

The objective of this systematic review is to evaluate of the beneficial and harmful effects of canagliflozin/metformin FDC for the treatment of the patients with T2DM who are already stabilized on triple therapy with metformin, a sulfonylurea, and canagliflozin; and to evaluate the bioequivalence of individual components (i.e., canagliflozin and metformin) in canagliflozin/metformin FDC to canagliflozin and metformin given in separate tablets concurrently.

Results and Interpretation

Clinical efficacy and safety

Included Studies

The clinical efficacy and safety data for supporting the use of canagliflozin/metformin FDC to replace canagliflozin + metformin used concurrently in separate tablets was based on two pivotal phase 3 clinical studies for canagliflozin, which were the key evidence of a previous review by the CADTH Common Drug Review (CDR) for canagliflozin as a third-line therapy added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea.[21,22] In January 2015, canagliflozin received a CADTH Canadian Drug Expert Committee (CDEC) recommendation for the treatment of T2DM as added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea and for whom insulin is not an option.[23] Therefore, the two phase 3 studies mentioned above are not included as part of the present submission.

In addition to the two previously reviewed pivotal phase 3 clinical studies for canagliflozin, and the supplied pivotal bioequivalence trials for canagliflozin/metformin FDC, the manufacturer also submitted an 18-week supportive phase 2, placebo-controlled randomized control trial (RCT), DIA2003. Study DIA2003 assessed the efficacy and safety of canagliflozin (50 mg or 150 mg, twice daily) in T2DM patients who were inadequately controlled on metformin monotherapy. The findings from this trial showed that canagliflozin twice daily regimen statistically significantly reduced glycated hemoglobin (A1C) compared with placebo in patients with T2DM inadequately controlled with metformin. The potential limitations of study DIA2003 were as follows:

- Canagliflozin was not used in patients who were inadequately controlled with metformin and sulfonylurea combination therapy (i.e., as a triple therapy, as specified in the indication under this review and the listing request criteria for this submission).
- It was not designed to evaluate the clinical efficacy and safety of canagliflozin/metformin FDC compared with other third-line antidiabetic agents in the treatment of patients with T2DM who failed in the combination therapy of metformin and sulfonylurea.
- It was not designed to investigate the clinical and safety for canagliflozin once daily compared with the canagliflozin twice-daily dose regimen.

Efficacy

The primary source of efficacy data for canagliflozin/metformin FDC was based on two pivotal phase 3 clinical trials for canagliflozin previously reviewed by CDR (data not provided in this report, as mentioned). For this review, the phase 2 study (DIA2003)[22] provided additional efficacy data for canagliflozin/metformin FDC:

- A1C: In study DIA2003, at the end of 18 weeks, A1C decreased by 0.44% ($P < 0.001$) and 0.60% ($P < 0.001$) for patients treated with canagliflozin 50 mg and 150 mg twice daily, respectively, as compared with placebo. A greater proportion of patients achieved an A1C < 7.0% at week 18 when

treated with canagliflozin 50 mg and 150 mg twice daily versus placebo (47.8% [$P < 0.05$], 57.1% [$P < 0.001$], and 31.5%, respectively).
- Body weight: Statistically significant reductions in body weight (as measured by least squares mean [LSM] per cent change from baseline) were observed with canagliflozin 50 mg and 150 mg twice daily compared with placebo at the end of 18 weeks (LSM difference [standard error (SE)]: –2.2% [–2.1] and –2.6% [–2.6], respectively; $P < 0.001$ for both dose regimens).
- SBP: Treatment with canagliflozin 50 mg or 150 mg (twice daily) was also associated with reductions in SBP compared with placebo (LSM difference [95% confidence interval (CI)], [mm Hg]: –5.4 [–8.4 to –2.3] and –5.7[–8.7 to –2.6], respectively).[22]

Harms

The primary source of safety data for canagliflozin/metformin FDC was based on two pivotal phase 3 clinical trials for canagliflozin previously reviewed by CDR[21] (data not provided in this report, as mentioned). For this review, the phase 2 study (DIA2003)[22] provided additional safety data for canagliflozin/metformin FDC. Overall, study DIA2003 did not raise any new signals that were not reported by previous clinical studies reviewed by CDR for canagliflozin.[21] The canagliflozin/metformin FDC regimens appear to have tolerability and safety profiles similar to the individually coadministered components.[24,25] Furthermore, study DIA1032[26] found that canagliflozin was well tolerated in both once-daily and twice-daily treatment arms (either 100 mg or 300 mg total daily doses) with no meaningful differences between either dosing regimens or total daily doses; study DIA1037[27] reported that canagliflozin/metformin FDC 150 mg/1,000 mg was generally well tolerated in both a fed and fasted state. Due to study DIA1032 and study 1037 being conducted in healthy volunteers, it is unknown whether the findings of the safety outcomes in these studies can be generalizable to T2DM patients.

Bioequivalence

Findings from six phase 1 studies indicated that all six strengths of canagliflozin/metformin FDC appeared to be bioequivalent to its individual components given concurrently in separate tablets.[28-34] Results from studies DIA1070[35] and DIA1071[36] [redacted] between the metformin component in canagliflozin/metformin FDC tablets and the Canadian formulation of metformin immediate-release (IR) in fed and fasted healthy participants. The predefined criteria to [redacted]; namely, the 90% CI of the geometric mean ratio of AUC_{last} (or AUC_{0-t}) and C_{max} of the test to reference product was within the bioequivalence limits of 80% to 125%. Furthermore, the bioequivalence of canagliflozin/metformin FDC was validated in two more studies (studies DIA1032[24,26] and DIA1037[25,27] which demonstrated that the bioequivalence of canagliflozin dosed at 100 mg or 300 mg a day as either a twice-daily or once-daily format was comparable[26] and the bioequivalence of canagliflozin/metformin FDC was not affected by the administration of a high-fat meal.

Other Considerations

Patient adherence to medications for diabetes is often suboptimal. The canagliflozin/metformin FDC tablet may improve adherence by simplifying the medication regimen, which may result in better outcomes. According to the clinical expert involved in this review, metformin is usually given twice daily or three times daily; therefore, a canagliflozin/metformin twice-daily regimen is not a concern.

Overall, the number of pills will be reduced by using canagliflozin/metformin FDC compared with canagliflozin and metformin given concurrently in separate tablets. However, no study has formally assessed adherence with canagliflozin/metformin FDC compared with canagliflozin plus metformin administered individually.

Conclusion

The clinical efficacy and safety of canagliflozin used in patients with T2DM inadequately controlled with the combination therapy of metformin and sulfonylurea have been previously reviewed by CDR. Canagliflozin has previously received a CDEC Recommendation for the treatment of T2DM as an add-on therapy to metformin and a sulfonylurea for patients inadequately controlled on metformin and a sulfonylurea. The canagliflozin and metformin components in canagliflozin/metformin FDC appeared to be bioequivalent to the canagliflozin and metformin given concurrently in separate tablets. The twice-daily regimen of canagliflozin added to metformin showed greater efficacy in reduction of A1C, body weight, and SBP compared with placebo in patients inadequately controlled with metformin monotherapy. However, no direct evidence on the comparative clinical efficacy and safety of canagliflozin when administered as a twice-daily dose regimen versus the previously reviewed once-daily dose regimen was available.

1. PRODUCT INFORMATION

1.1 Health Canada–Approved Indications

Please note that as this is a pre–Notice of Compliance (NOC) submission, the anticipated or proposed Health Canada indication to be reviewed by the CADTH Common Drug Review (CDR) is noted in the table below.

Indication(s) to be Reviewed by the CADTH Common Drug Review
To improve glycemic control as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus inadequately controlled on a sulfonylurea in combination with metformin or in patients already being treated and achieving glycemic control with a sulfonylurea in combination with metformin and canagliflozin as separate tablets.

1.2 Requested Listing Criteria

Requested Listing Criteria
Patients who are already stabilized on therapy with metformin, a sulfonylurea and canagliflozin, to replace the individual components of canagliflozin and metformin in these patients.

1.3 Manufacturer's Rationale and Place in Therapy for the Combination

1.3.1 Rationale

a) Therapeutic Rationale

Type 2 diabetes mellitus (T2DM) is a progressive disease that is treated via a stepwise approach with dose adjustments and/or add-on therapies in order to meet glycemic targets. [1-3] T2DM is also often associated with a broader constellation of abnormalities such as hypertension, dyslipidemia, and abdominal obesity — all of which also require treatment in order to reduce the risk for long-term complications.[3-5] The end result is a potentially complex medication regimen associated with a high pill burden and various dosing frequencies.

Inadequate glycemic control can often be attributed to poor adherence to medical interventions, including diet and medications.[6] A systematic review of 15 retrospective and five prospective studies on adherence to oral antihyperglycemic agents in T2DM patients noted that adherence rates ranged from 36 to 93%.[7] The reasons for non-adherence may be multifactorial; however, there is evidence that polypharmacy and the ensuing complexities play a significant role.[3, 7-10] Non-adherence has been associated with outcomes such as loss of glycemic control, increased risk of hospitalization and mortality, and increased costs associated with T2DM morbidity and mortality.[3, 11-13]

A treatment strategy to address non-adherence related to polypharmacy and treatment complexity is to utilize fixed-dose combination (FDC) dosage formats to combine individual components into one tablet, thereby reducing pill burden.[10, 13-15] Two systematic reviews have demonstrated that FDC formulations are associated with significant improvements in adherence (as measured by the Medication Possession Ratio) in T2DM patients.[16, 17] One systematic review also reported that a significant reduction in glycated hemoglobin (A1C) was associated with FDC formulations versus regimens composed of individual components (mean difference = –0.53% [95% confidence interval (CI), –0.78 to –0.28]; $P < 0.0001$).[16] Moreover, a recent retrospective cohort study of 23,361 patients with T2DM demonstrated that patients on FDC formulations had a significantly greater rate of adherence compared with patients on the equivalent individual component regimen (57% versus 50.7%, $P < 0.0001$, respectively).[18] Patients on

the FDC formulation also had significantly lower rates of nonpersistence and a longer time-to-nonpersistence.[18] The evidence from literature therefore supports the notion that there is a therapeutic need for FDC formulations in order to maximize adherence rates and improve clinical and economic outcomes.

b) Pharmacologic Rationale

Invokamet (canagliflozin and metformin hydrochloride [canagliflozin/metformin]) is a FDC consisting of two molecules that exhibit their efficacy in T2DM through complementary mechanisms of action. Canagliflozin is a sodium-glucose cotransporter-2 (SGLT-2) inhibitor that provides glycemic control through an insulin independent pathway. Through inhibition of SGLT-2, renal reabsorption of glucose is decreased and a reduction in renal threshold for glucose excretion subsequently increases urinary glucose excretion — providing a reduction in plasma glucose.[19] Urinary excretion of glucose also translates to an osmotic diuresis effect, resulting in a reduction in systolic blood pressure (SBP), and caloric loss resulting in a reduction in body weight.[19] Metformin hydrochloride is a biguanide that acts to lower basal and postprandial plasma glucose.[20] This is achieved by reducing hepatic glucose production and increasing insulin sensitivity in muscle, thereby improving peripheral glucose uptake and by delaying intestinal glucose absorption. [20]

Together, this combination provides glycemic control and reductions in SBP and body weight through complementary mechanisms of action.

Use of FDC formulations allows patients to overcome the barrier of treatment complexity and high pill burden associated with medication regimens composed of individual components.[21]

1.3.2 Place in Therapy

The appropriate place in therapy for canagliflozin/metformin FDC is for patients who are already stabilized on canagliflozin and metformin or are being treated with metformin and are looking to add an SGLT-2 inhibitor.

Canagliflozin recently received a CDEC recommendation that it be added on to T2DM patients with inadequate glycemic control on metformin and a sulfonylurea and for whom insulin is not an option.[22] Metformin is recognized as a first-line drug in treating T2DM and is typically initiated along with lifestyle interventions (diet and exercise), or after those have failed to bring the patient to glycemic targets.[2]

Canagliflozin/metformin FDC is available in six strengths: 50 mg/500 mg, 50 mg/850 mg, 50 mg/1,000 mg, 150 mg/500 mg, 150 mg/850 mg, and 150 mg/1,000 mg — dosed twice daily. Canagliflozin is commercially available in a 100 mg or 300 mg tablet and is taken once daily.[19] Metformin (immediate-release [IR] formulation) is commercially available as a 500 mg or 850 mg tablet and is dosed at 500 mg three to four times daily or 850 mg two or three times daily — however, in practice it is typically dosed twice daily, irrespective of tablet strength.[20, 21] Thus, the six strengths of the FDC allow patients to be treated at the commonly prescribed daily doses of canagliflozin/metformin.

Therapy may be initiated in patients who are being treated with metformin and wish to add an SGLT-2 inhibitor to their regimen or in patients already stabilized on canagliflozin/metformin.

1.3.3 Dosing Considerations

Canagliflozin/metformin FDC may be initiated in patients who are being treated with metformin and wish to add an SGLT-2 inhibitor to their regimen — titration is not necessary.

Canagliflozin/ metformin FDC is available in six strengths to allow patients to titrate doses of both canagliflozin and metformin throughout the full range of possible doses.

Increasing dose of one component can be achieved while maintaining the same dose of the second component, if desired.

2. CLINICAL EVIDENCE

The primary source of clinical efficacy data supporting the use of canagliflozin/metformin FDC comes from the pivotal CANagliflozin Treatment And Trial Analysis (CANTATA) phase 3 clinical trial program for canagliflozin (trade name: Invokana). These pivotal phase 3 trials were the focus of a previous CDR review for canagliflozin and are therefore not part of the present submission.[22]

Canagliflozin/metformin FDC is supported by an additional 11 studies, noted in Table 1.
The bioequivalence of canagliflozin/metformin FDC to its individual components (canagliflozin and metformin IR) is supported by eight pivotal bioequivalence trials (DIA1038, DIA1039, DIA1046, DIA1050, DIA105, DIA1052, DIA1070, and DIA1071). In addition, supportive phase 1 trials assess the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of once- versus twice-daily dosing of canagliflozin (DIA1032) and the impact of food on PK parameters on canagliflozin/metformin FDC (DIA1037). Lastly, a supportive phase 2, randomized, placebo-controlled trial evaluates the efficacy and safety of twice-daily dosing of canagliflozin (50 mg or 150 mg twice daily) in T2DM patients on metformin monotherapy (DIA2003).

The following studies will be discussed in the designated sections below:

- Section 2.1 (Pivotal Clinical Studies): DIA2003
- Section 2.3 (Safety): all 11 studies
- Section 2.4 (Bioequivalence): summary of the eight pivotal bioequivalence studies.

2.1 Pivotal Clinical Studies

As noted above, this section will provide details regarding the supportive phase 2 clinical trial, DIA2003.

TABLE 1: SUMMARY OF KEY TRIALS FOR CANAGLIFLOZIN AND METFORMIN HYDROCHLORIDE FIXED-DOSE COMBINATION

Study Name	Design	Objectives	Population
DIA1038[23, 24]	Phase 1, randomized, open-label, single-centre, single-dose, 2-treatment, 2-way crossover study	Primary: Evaluate the bioequivalence of canagliflozin/metformin FDC (150 mg/1,000 mg), taken as 2 tablets, to equal doses of the individual components of canagliflozin (1 × 300 mg tablet) and metformin IR (2 × 1,000 mg tablets). Secondary: Assess the safety and tolerability of canagliflozin/metformin FDC and the individual components.	Healthy, fed adult participants
DIA1039[24, 25]	Phase 1, randomized, open-label, single-centre, single-dose, 2-treatment, 2-way crossover study	Primary: Evaluate the bioequivalence of canagliflozin/metformin FDC (50 mg/850 mg), taken as 2 tablets, to equal doses of the individual components of canagliflozin (1 × 100 mg tablet) and metformin IR (2 × 850 mg tablets). Secondary: Assess the safety and tolerability of canagliflozin/metformin FDC and the individual components.	Healthy, fed adult participants
DIA1046[24, 26]	Phase 1, randomized, open-label, single-centre, single-dose, 2-treatment, 2-way crossover study	Primary: Evaluate the bioequivalence of canagliflozin/metformin FDC (50 mg/500 mg), taken as 2 tablets, to equal doses of the individual components of canagliflozin (1 x 100 mg tablet) and metformin IR (2 x 500 mg tablets). Secondary: Assess the safety and tolerability of canagliflozin/metformin FDC and the individual components.	Healthy, fed adult participants
DIA1050[24, 27]	Phase 1, randomized, open-label, single-centre, single-dose, 2-treatment, 2-way crossover study	Primary: Evaluate the bioequivalence of canagliflozin/metformin FDC (150 mg/ 500 mg), taken as 2 tablets, to equal doses of the individual components of canagliflozin (1 × 300 mg tablet) and metformin IR (2 × 500 mg tablets). Secondary: Assess the safety and tolerability of canagliflozin/metformin FDC and the individual components.	Healthy, fed adult participants
DIA1051[24, 28]	Phase 1, randomized, open-label, single-centre, single-dose, 2-treatment, 2-way crossover study	Primary: Evaluate the bioequivalence of canagliflozin/metformin FDC (50 mg/1,000 mg), taken as 2 tablets, to equal doses of the individual components of canagliflozin (1 × 100 mg tablet) and metformin IR (2 × 1,000 mg tablets).	Healthy, fed adult participants

Study Name	Design	Objectives	Population
		Secondary: Assess the safety and tolerability of canagliflozin/metformin FDC and the individual components.	
DIA1052[24, 29]	Phase 1, randomized, open-label, single-centre, single-dose, 2-treatment, 2-way crossover study	Primary: Evaluate the bioequivalence of canagliflozin/metformin FDC (150 mg/ 850 mg), taken as 2 tablets, to equal doses of the individual components of canagliflozin (1 × 300 mg tablet) and metformin IR (2 × 850 mg tablets). Secondary: Assess the safety and tolerability of canagliflozin/metformin FDC and the individual components.	Healthy, fed adult participants
DIA1070[30]	Phase 1, randomized, open-label, single-centre, single-dose, 4-treatment, 4-way crossover study	Primary: Evaluate the bioequivalence of the metformin component in canagliflozin/metformin FDC (50 mg/500 mg), taken as 1 tablet, to the Canadian reference product for metformin IR (Glucophage 1 × 500 mg), coadministered with canagliflozin (1 × 50 mg). Secondary: Assess the safety and tolerability of canagliflozin/metformin FDC and the individual components.	Healthy, fed and fasted adult participants
DIA1071[31]	Phase 1, randomized, open-label, single-centre, single-dose, 4-treatment, 4-way crossover study	Primary: Evaluate the bioequivalence of the metformin component in canagliflozin/metformin FDC (150 mg/ 500 mg), taken as 1 tablet, to the Canadian reference product for metformin IR (Glucophage 1 × 500 mg), coadministered with canagliflozin (1 × 50 mg and 1 x 100 mg). Secondary: Assess the safety and tolerability of canagliflozin and metformin hydrochloride FDC and the individual components.	Healthy, fed and fasted adult participants
DIA2003[32, 33]	Phase 2, randomized, double-blind, placebo-controlled, 3-arm, 18-week trial	Primary: Change in baseline A1C at week 18 with canagliflozin 50 mg or 150 mg or placebo twice daily. Secondary: Change in FPG, body weight (%), and proportion of patients achieving A1C < 7%.	T2DM adult patients with inadequate glycemic control (A1C ≥ 7% and ≤ 10.5%) on metformin monotherapy.
DIA1032[34, 35]	Phase 1, open-label, multiple-dose, 2-cohort, 2-way crossover study	Primary: Assess the steady-state pharmacokinetic and pharmacodynamic of once-daily versus twice-daily dosing of canagliflozin at the same total daily dose of 100 mg and 300 mg.	Healthy adult participants

Study Name	Design	Objectives	Population
		Secondary: Assess the safety and tolerability of canagliflozin administered once or twice daily.	
DIA1037[36, 37]	Phase 1, randomized, open-label, single-dose, 2-period crossover study	Primary: Assess the effect of coadministration of a high-fat meal on the oral bioavailability of canagliflozin/metformin FDC (150 mg/1,000 mg) Secondary: Assess the safety and tolerability of canagliflozin/metformin FDC 150 mg/1,000 mg	Healthy adult participants

A1C = glycated hemoglobin; canagliflozin/metformin = canagliflozin and metformin hydrochloride; FDC = fixed-dose combination; FPG = fasting plasma glucose; IR = immediate-release; T2DM = type 2 diabetes mellitus.

2.1.1 DIA2003[32, 33]

a) Study Characteristics

DIA2003 was an 18-week, phase 2, randomized, placebo-controlled double-blind trial evaluating the efficacy and safety of canagliflozin dosed 50 mg or 150 mg twice daily in T2DM patients on a background therapy of metformin monotherapy (see Table 2 for a summary of study characteristics). In conjunction with pivotal bioequivalence data (summarized in Table 9 in section 2.4), the results from this trial provide further validation that the incorporation of canagliflozin and metformin into an FDC format is not expected to result in changes to the efficacy and safety profile established for canagliflozin when administered concurrently with metformin to treat T2DM.

TABLE 2: SUMMARY OF STUDY CHARACTERISTICS FOR DIA2003

Characteristics		Details for *DIA2003*
STUDY DESIGN	**Objective**	Efficacy and safety study
	Blinding	Double-blind
	Study Period	2011-06 to 2012-04
	Study Centres	60 study centres in 7 countries: – 23 centres = US – 7 centres = Canada – 4 centres = Mexico – 5 centres = Czech Republic – 5 centres = Romania – 6 centres = Slovakia – 10 centres = Russia
	Design	Superiority
STUDY POPULATION	**Randomized (N)**	279
	Inclusion Criteria	– Men and women with T2DM between 18 and 80 years of age – Inadequate glycemic control (A1C ≥ 7.0% and ≤ 10.5%) – Metformin monotherapy (≥ 2,000 mg per day or ≥ 1,500 mg per day if unable to tolerate higher doses) for ≥ 8 weeks prior to screening
	Exclusion Criteria	– History of T1DM or DKA – History of cardiovascular disease (including myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident) within 3

Characteristics		Details for *DIA2003*
		months before screening – Uncontrolled hypertension – Treatment with a PPAR gamma agonist, insulin, SGLT-2 inhibitor, or any other antihyperglycemic drug (other than metformin monotherapy) within 12 weeks before screening – eGFR < 55 mL/min/1.73m^2 (or < 60mL/min/1.73m^2 if based on restriction in local metformin label) or serum creatinine ≥ 124 µmol/L (male) or ≥ 115 µmol/L (female)
DRUGS	**Intervention**	– Canagliflozin, 50 mg, oral, twice-daily – Canagliflozin, 150 mg, oral, twice-daily
	Comparator(s)	– Placebo, oral, twice-daily
DURATION	**Run-in**	2 weeks
	Treatment	18 weeks
	Follow-up	30 days
OUTCOMES	**Primary End Point(s)**	– Change in baseline A1C at week 18
	Other End Points	– Week 18 assessments: – Change in FPG – Per cent change in body weight – Proportion of patients achieving A1C < 7.0% – Change in SBP and DBP – Per cent change in fasting plasma lipids – Safety
NOTES	**Publications**	– Qiu R, Capuano G, Meininger G. Efficacy and safety of twice-daily treatment with canagliflozin, a sodium glucose co-transporter 2 inhibitor, added on to metformin monotherapy in patients with type 2 diabetes mellitus. Journal of Clinical & Translational Endocrinology. 2014;1(2):54-60. doi: doi:10.1016/j.jcte.2014.04.001. – NCT01340664[32, 33]

A1C = glycated hemoglobin; DBP = diastolic blood pressure; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; PPAR = peroxisome proliferator-activated receptor; SBP = systolic blood pressure; SGLT-2 = sodium-glucose cotransporter-2; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Intervention and Comparators

The test intervention in the trial was either canagliflozin 50 mg or 150 mg administered orally twice daily over the 18-week study period. The comparator arm was placebo administered orally twice daily over the 18-week study period.

A double-blind method was employed in this trial. [redacted] Moreover, placebo capsules were supplied as capsules matching the appearance of canagliflozin capsules in both size and appearance.

[redacted]

[redacted]

Outcomes

The primary efficacy outcome of DIA2003 was change in baseline A1C (measured as a percentage) after 18 weeks.

Secondary efficacy outcomes at week 18 included:

- Change in fasting plasma glucose (FPG) (mmol/L)
- Change in body weight (kg)
- Proportion of patients achieving A1C < 7.0%
- Change in SBP and diastolic blood pressure (DBP) (mm Hg)
- Per cent change in fasting plasma lipids (mmol/L)

Safety end points were assessed based on type, incidence, and severity of treatment-emergent adverse events (TEAEs) as well as laboratory tests, vital sign measurements, physical examinations, and 12-lead electrocardiogram (ECG) measurements.

Statistical Analyses

The primary objective of the study was to establish the superiority of canagliflozin dosed twice daily versus placebo. All statistical tests were interpreted at a two-sided significance level of 0.05 and CIs at a two-sided confidence level of 95%. Efficacy analyses were performed using the modified intention-to-treat (mITT) population, which included all randomized patients who received at least one dose of study drug. The last observation carried forward (LOCF) methodology was employed to populate missing efficacy data. Safety analyses were conducted according to the predominant treatment received; in this study, the safety analysis set was identical to the mITT analysis set.

b) Results

Baseline Characteristics

Table 3 summarizes selected baseline characteristics of patients enrolled in the trial. Patients were generally similar across treatment groups (i.e., similarities noted in age, baseline A1C, body mass index [BMI], duration of diabetes, etc.). A slightly higher proportion of women were enrolled in the trial overall (53.4% female versus 46.6% male). Mean daily dose of metformin across treatment groups was similar, ranging from 2,128 mg to 2,137 mg per day.

TABLE 3: SUMMARY OF BASELINE CHARACTERISTICS FOR DIA2003

Characteristic	Placebo (n = 93)	Canagliflozin 50 mg b.i.d. (n = 93)	Canagliflozin 150 mg b.i.d. (n = 93)	Total (n = 279)
Sex, n (%)				
Male	46 (49.5)	40 (43)	44 (47.3)	130 (46.6)
Female	47 (50.5)	53 (57)	49 (52.7)	149 (53.4)
Age — years, mean (SD)	57 (9.3)	58.6 (8.9)	56.7 (10.3)	57.4 (9.5)
Race, n (%)[a]				
Caucasian	73 (78.5)	75 (80.6)	83 (89.2)	231 (82.8)
Black, African-American	4 (4.3)	5 (5.4)	1 (1.1)	10 (3.6)
Asian	9 (9.7)	3 (3.2)	6 (6.5)	18 (6.5)
Other	7 (7.5)	10 (10.8)	3 (3.2)	20 (7.2)
Baseline A1C, mean (SD)	7.7 (0.9)	7.6 (0.9)	7.6 (0.9)	7.6 (0.9)
Body weight — kg, mean (SD)	90.5 (18.1)	91.2 (23.9)	90.2 (19.1)	90.6 (20.4)
BMI — kg/m^2, mean (SD)	32.3 (5.7)	33 (7)	32.3 (6.8)	32.5 (6.5)
Mean duration of diabetes, years (SD)	7 (6.4)	6.7 (4.9)	7.3 (6)	7 (5.8)
Mean daily dose of metformin, mg/day (SD)	2,131 (343.1)	2,137 (304.1)	2,128 (341.6)	2,132 (328.9)
Baseline eGFR — mL/min/1.73m^2, mean (SD)	84.8 (16.5)	86.9 (18)	85.9 (15.3)	85.9 (16.6)

A1C = glycated hemoglobin; b.i.d. = twice daily; eGFR = estimated glomerular filtration rate; SD = standard deviation.
Source: DIA2003[32]

Patient Disposition

A total of 480 patients were screened and 279 were randomized 1:1:1 in DIA2003. Overall, approximately 90% (251 of 279) of patients completed 18 weeks of treatment where a slightly higher discontinuation rate was noted for the canagliflozin 150 mg twice-daily treatment arm versus canagliflozin 50 mg twice daily and placebo treatment arms (14%, 8.6% and 7.5%, respectively). Patients in the mITT and safety analysis sets were identical. The most common reason for study withdrawal was adverse events resulting in eight patients discontinuing, and a greater proportion withdrawing from the canagliflozin 150 mg twice-daily treatment arm (seven patients). See Table 4 for more information.

TABLE 4: SUMMARY OF PATIENT DISPOSITION FOR DIA2003

Disposition	DIA2003		
	Placebo b.i.d. (n = 93)	Canagliflozin 50 mg b.i.d. (n = 93)	Canagliflozin 150 mg b.i.d. (n = 93)
Screened, N[a]	480		
Randomized, N	93	93	93
Discontinued, N (%)	7 (7.5)	8 (8.6)	13 (14)
WDAEs, N (%)	0	1 (1.1)	7 (7.5)
Withdrawal due to SAEs, N (%)	0	0	3 (3.2)
Death	0	0	1 (1.1)[b]
Creatinine/eGFR withdrawal criteria	0	1 (1.1)	2 (2.2)
Lost to follow-up, N (%)	2 (2.2)	0	2 (2.2)
Withdrawal of consent	2 (2.2)	4 (4.3)	0
Glycemic withdrawal criteria	2 (2.2)	0	0
Other[c]	1 (1.1)	2 (2.2)	2 (2.2)
mITT, N	93	93	93
Per-protocol, N	[redacted]	[redacted]	[redacted]
Safety, N	93	93	93

b.i.d. = twice-daily; eGFR = estimated glomerular filtration rate; mITT = modified intention-to-treat; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] A total of 480 patients were screened prior to randomization.

[b] Colon cancer — not considered related to study drug.

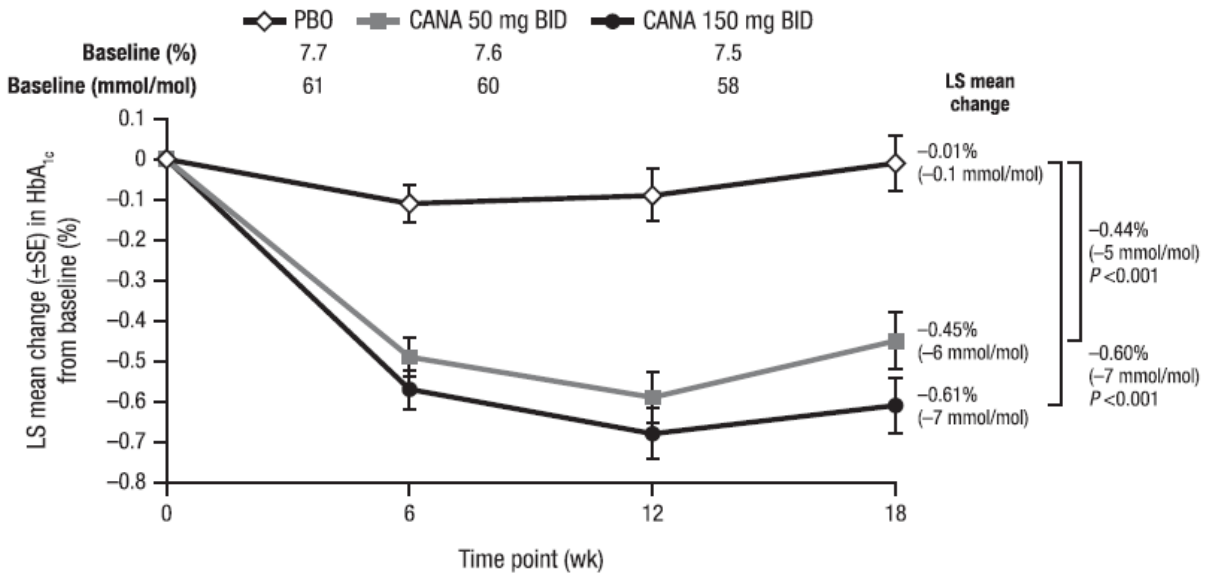
[c] Includes reasons related to relocation, extended travel, and poor compliance with study visits.

Source: DIA2003[32, 33]

Efficacy

A1C decreased by 0.44% ($P < 0.001$) and 0.60% ($P < 0.001$) at 18 weeks for patients treated with canagliflozin 50 mg and 150 mg twice daily, respectively, as compared with placebo (Figure 1. A greater proportion of patients achieved an A1C < 7.0% at week 18 when treated with canagliflozin 50 mg and 150 mg twice daily versus placebo (47.8%, 57.1%, and 31.5%, respectively; $P < 0.05$ and $P < 0.001$ versus placebo, respectively).

Figure 1: Change in Baseline Glycated Hemoglobin Over 18 Weeks (Last Observation Carried Forward) — DIA2003

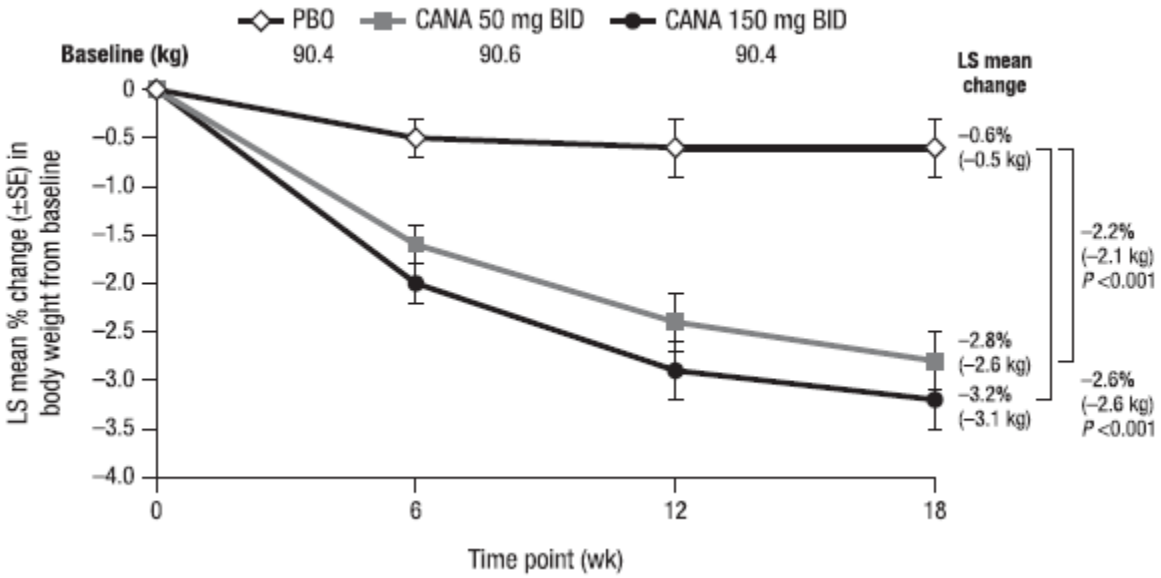


$HbA1_C$ = glycated hemoglobin; BID = twice daily; CANA = canagliflozin; LS = least squares; PBO = placebo; SE = standard error; wk = week.

Source: DIA2003[32]

Statistically significant reductions in body weight (as measured by least squares (LS) mean per cent change from baseline) were observed with canagliflozin 50 mg and 150 mg twice daily compared with placebo over the 18-week study period (difference versus placebo: –2.2% [–2.1 kg] and –2.6% [–2.6 kg], respectively; $P < 0.001$ for both doses) (Figure 2).

Figure 2: Change From Baseline in Body Weight Over 18 Weeks (Last Observation Carried Forward) — DIA2003[32]



BID = twice-daily; CANA = canagliflozin; LS = least squares; PBO = placebo; SE = standard error; wk = week.

Treatment with canagliflozin 50 mg and 150 mg twice daily was also associated with reductions in SBP compared with placebo (difference in LS mean change versus placebo: –5.4 mm Hg and –5.7 mm Hg, respectively) (Table 5).

Source: DIA2003[32]

TABLE 5: CHANGE FROM BASELINE IN SYSTOLIC BLOOD PRESSURE AT WEEK 18 (LAST OBSERVATION CARRIED FORWARD) —DIA2003

	Placebo (n = 92)	Canagliflozin 50 mg b.i.d. (n = 90)	Canagliflozin 150 mg b.i.d. (n = 91)
Mean (SD) baseline, mm Hg	128.6 (11.0)	131.1 (12.4)	128.2 (12.0)
LS mean (SE) change	3.3 (1.1)	–2.1 (1.1)	–2.4 (1.1)
Difference versus placebo (95% CI)	-	–5.4 (–8.4 to –2.3)	–5.7 (–8.7 to –2.6)

b.i.d. = twice daily; CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error.
Source: DIA2003[32]

Twice-daily dosing of canagliflozin 50 mg or 150 mg offers greater efficacy in A1C, body weight, and SBP reduction compared with placebo. The overall efficacy findings from DIA2003 are similar to results from trials in the CANTATA phase 3 clinical trial program (previously reviewed by CDR), thus providing further validation of the efficacy profile of twice-daily canagliflozin/metformin FDC.

2.1.2 All Other Studies

2.2 Critical Appraisal of Pivotal Clinical Studies

2.2.1 Internal Validity

The 10 phase 1 bioequivalence studies were randomized, open-label, single-centre, crossover studies in healthy adults. All randomized controlled trials (RCTs) were based on a single dose, except one RCT,[26] which was based on multiple doses.[24] The bioequivalent criteria were predefined when the 90% CI of geometric mean ratio for primary PK parameters (AUC_{0-t} [AUC_{last}] and C_{max}) were entirely contained within 80% and 125%.

Study DIA2003 was a multi-centre, double-blind, phase 2 RCT conducted in seven countries including Canada. The randomization and blinding procedure was well described. [redacted] Matched placebo was used for maintaining the treatment blinding. A1C and FPG values were masked to the study centres. Clinical efficacy and safety outcomes were also well defined and assessed. The primary and major secondary outcomes were tested in a predefined hierarchical testing sequence and the type I error was controlled at 5%. The primary and secondary efficacy analyses were based on the mITT analysis set, in which an analysis of covariance (ANCOVA) model was used with treatment and the stratification factor related to glycemic control prior to randomization. Per-protocol analysis was conducted as a supporting analysis. No concerning internal validity issues on the included studies were identified.

2.2.2 External Validity

In addition to the study of bioequivalence of canagliflozin/metformin FDC to its individual components of canagliflozin and metformin given concurrently in separate tablets,[28-32] the bioequivalence studies also showed that [redacted] of metformin in canagliflozin/metformin FDC compared with the Canadian reference product for metformin (Glucophage) in both fed and fasted conditions.[35,36] Furthermore, it was also reported the bioequivalence of the canagliflozin twice-daily regimen was comparable with the once-daily regimen based on the same total daily dose.[26] Finally, it also showed no meaningful impact of a high-fat meal on the bioequivalence of canagliflozin/metformin FDC.[27] Therefore, there are no obvious generalizability concerns for canagliflozin/metformin FDC for use in Canadian settings.

The supportive study DIA2003 did not use the FDC under review in this submission. While bioequivalence between twice-daily and once-daily canagliflozin has been demonstrated, no comparisons were provided that evaluate the clinical efficacy and safety of twice-daily dosing of canagliflozin used in this FDC to the existing once-daily formulation of canagliflozin that is currently used in practice and was previously reviewed by CDR.

It is worth mentioning that the supportive study DIA2003 was conducted in patients with T2DM inadequately controlled with metformin monotherapy (i.e., canagliflozin was used in the dual therapy), but not in the patients inadequately controlled with metformin + sulfonylurea (i.e., not used in triple therapy, which was indicated in the manufacturer's listing request criteria for this submission and the indication previously reviewed by CDR). Therefore, the clinical efficacy and safety profile was not directly established for the canagliflozin twice-daily regimen in patients with T2DM inadequately controlled with the combination therapy of metformin + sulfonylurea, although the main clinical efficacy and safety evidence of the triple therapy of canagliflozin (once daily) + metformin + sulfonylurea were reviewed in the previous CDR review of canagliflozin, and are the primary source of efficacy and safety data for canagliflozin/metformin FDC.

2.3 Summary of Safety

The primary source of safety and tolerability data supporting the use of canagliflozin/metformin FDC is the pivotal CANTATA phase 3 clinical trial program for canagliflozin (trade name: Invokana). These pivotal phase 3 trials were the focus of a previous CDR review for canagliflozin and are therefore not part of the present submission.[22]

The following section summarizes new safety data from key trials (see Table 1) supporting the regulatory filing of canagliflozin/metformin FDC.

2.3.1 Safety Evaluation Plan

As previously noted, the primary source of safety data for canagliflozin/metformin FDC is the pivotal CANTATA phase 3 clinical trial program (which was the focus of a previous CDR review). Those trials evaluated once-daily canagliflozin as an adjunct to diet and exercise in monotherapy and in combination with various antihyperglycemic drugs (including both insulin and non-insulin drugs) in approximately 10,285 patients. Building on phase 3 clinical trial data are additional phase 1 and phase 2 data from key

trials supporting the regulatory filing of canagliflozin/metformin FDC (see Table 1). The data from these trials validate the known safety profile of canagliflozin when used in combination with metformin.

2.3.2 Safety Populations Evaluated

Incremental safety data supporting the regulatory filing of canagliflozin/metformin FDC comes in the form of additional phase 1 and phase 2 studies (see Table 1). The largest additional controlled data source is a phase 2 randomized placebo-controlled trial (DIA2003) evaluating the efficacy and safety of twice-daily dosing of canagliflozin (50 mg or 150 mg twice daily) in T2DM patients with a background therapy of metformin monotherapy.[32] In this study, safety data on 279 patients over 18 weeks provides further validation that the safety profile of canagliflozin dosed twice daily (consistent with how canagliflozin/metformin FDC will be dosed in practice) is similar to once-daily dosing of canagliflozin (consistent with the currently marketed format, Invokana).

2.3.3 Overview of Safety

The bioequivalence trials demonstrated that the safety and tolerability profile of canagliflozin/metformin FDC are similar to the individual components or free form treatment formulations (see Table 6 and Table 7). Gastrointestinal (GI) adverse events were the most commonly reported adverse event throughout all trials. Nearly all GI adverse events were deemed to be possibly, probably, or very likely related to metformin, as it is a known adverse event associated with metformin therapy.[24]

TABLE 6: SUMMARY OF SELECTED ADVERSE EVENTS FOR DIA1038, DIA1039, DIA1046, DIA1050, DIA1051 AND DIA1052

	DIA1038[a]		DIA1039[b]		DIA1046[c]		DIA1050[d]		DIA1051[e]		DIA1052[f]	
	Free form (n = 74)	FDC (n = 71)	Free form (n = 73)	FDC (n = 72)	Free form (n = 63)	FDC (n = 60)	Free form (n = 61)	FDC (n = 63)	Free form (n = 61)	FDC (n = 63)	Free form (n = 63)	FDC (n = 63)
Any AE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths, n	0	0	0	0	0	0	0	0	0	0	0	0
Hypoglycemia, n	0	0	0	0	0	0	0	0	0	0	0	0
GI AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; CANA = canagliflozin; FDC = fixed-dose combination; GI = gastrointestinal; MET = metformin.
[a] Compared 2 × CANA/MET FDC 150 mg/1,000 mg to 1 × CANA 300 mg + 2 × MET 1,000 mg.
[b] Compared 2 × CANA/MET FDC 50 mg/850 mg to 1 × CANA 100 mg + 2 × MET 850 mg.
[c] Compared 2 × CANA/MET FDC 50 mg/500 mg to 1 × CANA 100 mg + 2 × MET 500 mg.
[d] Compared 2 × CANA/MET FDC 150 mg/500 mg to 1 × CANA 300 mg + 2 × MET 500 mg.
[e] Compared 2 × CANA/MET FDC 50 mg/1,000 mg to 1 × CANA 100 mg + 2 × MET 1,000 mg.
[f] Compared 2 × CANA/MET FDC 150 mg/850 mg to 1 × CANA 300 mg + 2 × MET 850 mg.
Source: [23, 25-29]

TABLE 7: SUMMARY OF SELECTED ADVERSE EVENTS FOR DIA1070 AND DIA1071

	DIA1070 Treatments				DIA1071 Treatments			
	Fed		Fasted		Fed		Fasted	
	CANA/MET FDC 50 mg/ 500 mg (n = [redacted])	CANA 50 mg + MET 500 mg (n = [redacted])	CANA/MET FDC 50 mg/ 500 mg (n = [redacted])	CANA 50 mg + MET 500 mg (n = [redacted])	CANA/MET FDC 150 mg/ 500 mg (n = [redacted])	CANA 150 mg + MET 500 mg (n = [redacted])	CANA/MET FDC 150 mg/ 500 mg (n = [redacted])	CANA 150 mg + MET 500 mg (n = [redacted])
Any AE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycemia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GI AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AEs = adverse events; CANA = canagliflozin; FDC = fixed-dose combination; GI = gastrointestinal; MET = metformin.
Source: DIA1070 and DIA1071[30, 31]

The safety profile of canagliflozin dosed 50 mg or 150 mg twice daily, as compared with placebo, was examined in the phase 2 randomized controlled trial DIA2003.[32] The overall incidence of adverse events was 35.5%, 40.9%, and 36.6% with canagliflozin 50 mg twice daily, canagliflozin 150 mg twice daily, and placebo, respectively (Table 8). Canagliflozin treatment was generally well tolerated and was associated with an increase in mild to moderate urinary tract infections (UTIs), female genital mycotic infections (GMIs), and adverse events related to osmotic diuresis. One death was reported in the canagliflozin 150 mg twice-daily treatment arm, but this was not considered related to study drug (colon cancer). Rates of hypoglycemia were similar across all treatment arms. The safety profile is similar to results obtained from the CANTATA phase 3 clinical trial program, which examined canagliflozin as an individual component in various lines of therapy and was the focus of a previous CDR review.[22]

TABLE 8: SUMMARY OF OVERALL SAFETY AND SELECTED ADVERSE EVENTS AT WEEK 18 FOR DIA2003

	PBO (n = 93)	CANA 50 mg b.i.d. (n = 93)	CANA 150 mg b.i.d. (n = 93)
Any AE, n (%)	34 (36.6)	33 (35.5)	38 (40.9)
AEs leading to discontinuation	0	1 (1.1)	7 (7.5)
AEs related to study drug	2 (2.2)	11 (11.8)	15 (16.1)
Serious AEs	1 (1.1)	0	3 (3.2)
Deaths	0	0	1 (1.1)
UTI	2 (2.2)	4 (4.3)	4 (4.3)
GMI			
Male[a,b]	1 (2.2)	1 (2.5)	0
Female[c,d]	2 (4.3)	6 (11.3)	1 (2.0)
Osmotic diuresis-related AEs[e]	0	0	7 (7.5)
Volume depletion AEs	0	0	0
Hypoglycemia	3 (3.2)	4 (4.3)	3 (3.2)

AEs = adverse events; b.i.d. = twice-daily; CANA = canagliflozin; GMI = genital mycotic infection; PBO = placebo; UTI = urinary tract infection.

[a] PBO n = 46; CANA 50 mg b.i.d. n = 40; CANA 150 mg b.i.d. n = 44.

[b] Including balanitis candida and fungal genital infection.

[c] PBO n = 47; CANA 50 mg b.i.d. n = 53; CANA 150 mg b.i.d. n = 49.

[d] Including vaginal infection, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis.

[e] Including dry mouth, micturition urgency, pollakiuria, and thirst.

Source: DIA2003[32]

Additional supportive phase 1 studies highlight the following:

- **DIA1032:** Canagliflozin is well tolerated in both once-daily and twice-daily treatment arms (either 100 mg or 300 mg total daily doses) with no meaningful differences between either dosing regimens or total daily doses (see Table 5.3 and Table 5.4 in the Clinical Summary document, the Clinical Study Report, and the publication for more information).[34, 35]
- **DIA1037:** Canagliflozin/metformin FDC 150 mg/1,000 mg was generally well tolerated in both a fed and fasted state with no meaningful differences between either treatment arms (see Table 5.5 in the Clinical Summary document, the Clinical Study Report, and the publication for more information).[36, 37]

Canagliflozin/metformin FDC tablets are expected to result in a similar safety profile to canagliflozin and metformin as individual components, as demonstrated in the robust CANTATA phase 3 clinical trials. Overall, canagliflozin/metformin FDC tablets are a safe, tolerable, and convenient treatment option, with limited risk of hypoglycemia for patients living with T2DM.

2.4 Bioequivalence

The bioequivalence of canagliflozin/metformin FDC to its individual components (canagliflozin and metformin IR) is supported by eight pivotal bioequivalence trials. Six trials (DIA1038, DIA1039, DIA1046, DIA1050, DIA1051, and DIA1052) were conducted to establish bioequivalence of the FDC to its individual components for each of its six strengths. In these six trials, however, a US formulation of metformin IR (as an individual component) was utilized. In order to attain Health Canada approval, an additional two bioequivalence studies were conducted (DIA1070 and DIA1071) to demonstrate that the metformin component in the FDC was bioequivalent to the Canadian formulation of metformin IR (as an individual component). The results of DIA1070 and DIA1071 validate the results from DIA1038, DIA1039, DIA1046, DIA1050, DIA1051, and DIA1052 and make it applicable to the Canadian setting.

DIA1038, DIA1039, DIA1046, DIA1050, DIA1051, and DIA1052 were phase 1, randomized, open-label, single-dose, two-way crossover studies conducted in healthy, fed participants aged 18 to 55 years that consisted of three phases: a screening phase (approximately three weeks), a treatment phase (up to 20 days, including a 10- to 15-day washout period between day 1 of each treatment period) and a follow-up phase of seven to 10 days.[24] A total of 64 to 83 participants were randomized 1:1 in each study to receive either the reference treatment first, followed by the test treatment or vice versa.[24] DIA1070 and DIA1071 were phase 1, randomized, open-label, single-dose, four-way crossover studies conducted in healthy fed and fasted participants aged 18 to 55 years that consisted of three phases: a screening phase (approximately three weeks), a treatment phase (up to 20 days, including a six- to eight-day washout period between day 1 of each treatment period) and a follow-up phase of five to seven days.[30, 31] A total of [redacted] participants were randomized in each study to one of four treatment groups, with each group comprising four treatments (i.e., canagliflozin/metformin FDC in the fed or fasted state or canagliflozin and metformin as individual components in the fed or fasted state) in varying sequences.[30, 31]

2.4.1 Pharmacokinetic Characteristics of Individual Components

As an individual component, canagliflozin possesses uncomplicated PK characteristics. Metformin hydrochloride, as an individual component, has non-linear PK characteristics.

2.4.2 Bioequivalence Data Summary

All strengths of canagliflozin/metformin FDC were bioequivalent to treatment with its individual components across six studies (see Table 9).[24] Moreover, results from DIA1070 and DIA1071 [redacted] between the metformin component in canagliflozin/metformin FDC tablets to the Canadian formulation of metformin IR (see Table 9). The predefined criteria to [redacted]; namely, the 90% CI of the geometric mean ratio of AUC_{last} (or AUC_{0-t}) and C_{max} of the test to reference product was within the bioequivalence limits of 80% to 125%. This is consistent with Health Canada guidance on bioequivalence standards.[38]

TABLE 9: BIOEQUIVALENCE PROFILE SUMMARY FOR CANAGLIFLOZIN AND METFORMIN HYDROCHLORIDE FIXED-DOSE COMBINATION — CANAGLIFLOZIN AND METFORMIN COMPONENTS ACROSS 8 PIVOTAL TRIALS

Study DIA1038	**CANA as 2 x CANA/MET FDC 150 mg/1,000 mg**	**CANA as 1 x CANA 300 mg + 2 x MET 1,000 mg[a]**	**MET as 2 x CANA/MET FDC 150 mg/1,000 mg**	**MET as 1 x CANA 300 mg + 2 x MET 1,000mg[a]**
$AUC_{(0-t)}$ (ng·h/mL)	n = 62	n = 62	n = 62	n = 62
Geometric mean	27560.10	26960.48	16873.75	18256.73
Coefficient of variance	7		11	
Geometric mean ratio (90% CI)	102.22 (100.00 to 104.50)		92.42 (89.42 to 95.54)	
C_{max} (ng/mL)	n = 62	n = 62	n = 62	n = 62
Geometric mean	2225.02	2099.09	2099.46	2309.04
Coefficient of variance	27		15	
Geometric mean ratio (90% CI)	106.00 (97.90 to 114.77)		90.92 (87.03 to 94.99)	
T_{max} (h)	n = 68	n = 68	n = 68	n = 68
Median (range)	3.00 (0.98 to 16.00)	4.00 (0.98 to 24.00)	4.00 (1.00 to 10.00)	4.00 (1.00 to 6.00)
Study DIA1039	**CANA as 2 x CANA/MET FDC 50 mg/850 mg**	**CANA as 1 x CANA 100mg + 2 x MET 850mg[a]**	**MET as 2 x CANA/MET FDC 50 mg/850 mg**	**MET as 1 x CANA 100 mg + 2 x MET 850 mg[a]**
$AUC_{(0-t)}$ (ng·h/mL)	n = 62	n = 62	n = 62	n = 62
Geometric mean	8487.99	8370.97	16098.88	16322.17
Coefficient of variance	6		10	
Geometric mean ratio (90% CI)	101.40 (99.73 to 103.10)		98.63 (95.85 to 101.50)	
C_{max} (ng/mL)	n = 62	n = 62	n = 62	n = 62
Geometric mean	740.96	705.28	2145.93	2181.83
Coefficient of variance	24		11	
Geometric mean ratio (90% CI)	105.06 (97.89 to 112.76)		98.35 (95.31 to 101.49)	
T_{max} (h)	n = 68	n = 66	n = 68	n = 66
Median (range)	3.00 (1.00 to 10.00)	3.52 (1.00 to 10.00)	4.00 (1.50 to 6.00)	4.00 (1.00 to 6.23)
Study DIA1046	**CANA as 2 x CANA/MET FDC 50 mg/500 mg**	**CANA as 1 x CANA 100 mg + 2x MET 500 mg[a]**	**MET as 2 x CANA/MET FDC 50 mg/500 mg**	**MET as 1 x CANA 100 mg + 2 x MET 500mg[a]**
$AUC_{(0-t)}$ (ng·h/mL)	n = 58	n = 58	n = 58	n = 58
Geometric mean	8561.16	8523.60	11300.29	11436.06
Coefficient of variance	7		9	
Geometric mean ratio (90% CI)	100.44 (98.27 to 102.66)		98.81 (96.07 to 101.63)	
C_{max} (ng/mL)	n = 58	n = 58	n = 58	n = 58
Geometric mean	679.01	722.50	1471.39	1507.20
Coefficient of variance	29		11	

Geometric mean ratio (90% CI)	93.98 (86.10 to 102.58)		97.62 (94.32 to 101.05)	
T_{max} (h)	n = 59	n = 63	n = 59	n = 63
Median (range)	3.00 (1.00 to 16.00)	3.00 (0.98 to 12.00)	4.00 (1.00 to 8.00)	4.00 (0.98 to 6.00)
Study DIA1050	**CANA as 2 x CANA/MET FDC 150 mg/500 mg**	**CANA as 1 x CANA 300 mg + 2 x MET 500 mg[a]**	**MET as 2 x CANA/MET FDC 150 mg/500 mg**	**MET as 1 x CANA 300 mg + 2 x MET 500 mg[a]**
$AUC_{(0-t)}$ (ng·h/mL)	n = 60	n = 60	n = 60	n = 60
Geometric mean	28125.42	27679.43	9256.26	9292.72
Coefficient of variance	5		12	
Geometric mean ratio (90% CI)	101.61 (99.94 to 103.31)		99.61 (96.17 to 103.17)	
C_{max} (ng/mL)	n = 60	n = 60	n = 60	n = 60
Geometric mean	2673.78	2558.49	1178.57	1195.92
Coefficient of variance	20		12	
Geometric mean ratio (90% CI)	104.51 (98.47 to 110.92)		98.55 (94.91 to 102.33)	
T_{max} (h)	n = 63	n = 61	n = 63	n = 61
Median (range)	3.00 (1.50 to 10.03)	4.00 (1.00 to 12.00)	4.00 (1.50 to 7.98)	4.00 (0.98 to 6.03)
Study DIA1051	**CANA as 2 x CANA/MET FDC 50 mg/1,000 mg**	**CANA as 1 x CANA 100 mg + 2 x MET 1,000 mg[a]**	**MET as 2 x CANA/MET FDC 50 mg/1,000 mg**	**MET as 1 x CANA 100 mg + 2 x MET 1,000mg[a]**
$AUC_{(0-t)}$ (ng·h/mL)	n = 57	n = 57	n = 58	n = 58
Geometric mean	8752.70	8609.25	15899.55	16828.48
Coefficient of variance	7		9	
Geometric mean ratio (90% CI)	101.67 (99.33 to 104.06)		94.48 (91.90 to 97.13)	
C_{max} (ng/mL)	n = 57	n = 57	n = 58	n = 58
Geometric mean	775.90	803.00	2141.21	2274.31
Coefficient of variance	26		11	
Geometric mean ratio (90% CI)	96.62 (89.12 to 104.77)		94.15 (91.00 to 97.40)	
T_{max} (h)	n = 60	n = 57	n = 60	n = 58
Median (range)	3.00 (1.00 to 10.00)	4.00 (1.00 to 10.00)	3.98 (1.50 to 6.00)	3.00 (1.00 to 6.00)
Study DIA1052	**CANA as 2 x CANA/MET FDC 150 mg/850 mg**	**CANA as 1 x CANA 300 mg + 2 x MET 850 mg[a]**	**MET as 2 x CANA/MET FDC 150 mg/850 mg**	**MET as 1 x CANA 300 mg + 2 x MET 850 mg[a]**
$AUC_{(0-t)}$ (ng·h/mL)	n = 61	n = 61	n = 61	n = 61
Geometric mean	30344.32	30037.82	14537.47	15013.95
Coefficient of variance	5		10	
Geometric mean ratio (90% CI)	101.02 (99.60 to 102.47)		96.83 (93.92 to 99.83)	
C_{max} (ng/mL)	n = 61	n = 61	n = 61	n = 61
Geometric mean	2606.24	2527.63	1910.31	2042.38
Coefficient of variance	24		13	

Geometric mean ratio (90% CI)	103.11 (95.91 to 110.86)		93.53 (90.00 to 97.20)	
T_{max} (h)	n = 62	n = 63	n = 62	n = 63
Median (range)	3.00 (1.00 to 12.00)	3.00 (1.50 to 12.02)	4.00 (0.98 to 6.00)	3.00 (0.98 to 6.00)
Study DIA1070	**MET as 1 x CANA/MET FDC 50 mg/500 mg (Fed)**	**MET as 1 x CANA 50 mg + 1x MET 500 mg[a] (Fed)**	**MET as 1 x CANA/MET FDC 50 mg/500 mg (Fasted)**	**MET as 1 x CANA 50 mg + 1x MET 500 mg[a] (Fasted)**
$AUC_{(0-t)}$ (ng·h/mL)	n=	n=	n=	n=
Geometric mean				
Coefficient of variance				
Geometric mean ratio (90% CI)				
C_{max} (ng/mL)				
Geometric mean				
Coefficient of variance				
Geometric mean ratio (90% CI)				
T_{max} (h)				
Median (Range)				
Study DIA1071	**MET as 1 x CANA/MET FDC 150 mg/500 mg (Fed)**	**MET as 1 x CANA 150 mg + 1 x MET 500 mg[a] (Fed)**	**MET as 1 x CANA/MET FDC 150 mg/500 mg (Fasted)**	**MET as 1 x CANA 150 mg + 1 x MET 500 mg[a] (Fasted)**
$AUC_{(0-t)}$ (ng·h/mL)	n=	n=	n=	n=
Geometric mean				
Coefficient of variance				
Geometric mean ratio (90% CI)				
C_{max} (ng/mL)				
Geometric mean				
Coefficient of variance				
Geometric mean ratio (90% CI)				
T_{max} (h)				
Median (range)				

$AUC_{(0-t)}$ = area under the plasma concentration-time curve from time 0 to the time of the last observed quantifiable concentration; CANA = canagliflozin; C_{max} = maximum observed plasma concentration; CI = confidence interval; FDC = fixed-dose combination; MET = metformin; NA = not available; T_{max} = time to reach the maximum observed plasma concentration.

[a] Canagliflozin plus metformin, given concurrently.

SOURCE:DIA1038, DIA1039, DIA1046, DIA1050, DIA1051, DIA1052, DIA1070, AND DIA1071[24, 30, 31]

Canagliflozin/metformin FDC is further validated by two supportive PK trials that demonstrate that canagliflozin dosed at 100 mg or 300 mg a day as either a twice-daily or once-daily format was comparable and met the criteria for bioequivalence; and the FDC was not meaningfully affected by the administration of food as measured by PK parameters. [34, 35, 36, 37]

3. PHARMACOECONOMIC EVALUATION

3.1 Manufacturer-Submitted Cost Information

TABLE 10: COST COMPARISON OF INVOKAMET (CANAGLIFLOZIN AND METFORMIN HYDROCHLORIDE) AND INDIVIDUAL COMPONENTS — DAILY DRUG COST (NO MARKUP OR DISPENSING FEES)

Drug/Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Daily Use[b]	Daily Drug Cost ($)[c]
Canagliflozin and metformin hydrochloride (Invokamet) FDC	**50 mg/500 mg** **50 mg/850 mg** **50 mg/1,000 mg** **150 mg/500 mg** **150 mg/850 mg** **150 mg/1,000 mg**	**IR tablet** **IR tablet** **IR tablet** **IR tablet** **IR tablet** **IR tablet**	**$1.5338** **$1.5338** **$1.5338** **$1.5338** **$1.5338** **$1.5338**	**1 tab b.i.d.** **1 tab b.i.d.** **1 tab b.i.d.** **1 tab b.i.d.** **1 tab b.i.d.** **1 tab b.i.d.**	**$3.0676** **$3.0676** **$3.0676** **$3.0676** **$3.0676** **$3.0676**
Canagliflozin (Invokana)[d]	100 mg 300 mg	IR tablet IR tablet	$2.6177 $2.6177	1 tab o.d. 1 tab o.d.	$2.6177 $2.6177
Metformin (Glucophage, and generics)[d]	500 mg 850 mg	IR tablet IR tablet	$0.0444 $0.0610	1 tab b.i.d. to q.i.d. 1 tab b.i.d.	$0.0888 to $0.1776 $0.1220
Total (Canagliflozin + Metformin)					**$2.7065 to $2.7953**

b.i.d. = twice daily; FDC = fixed-dose combination; IR = immediate-release; o.d. = once daily; q.i.d. = four times daily; t.i.d. = three times daily.

[a] Cost of Invokamet (canagliflozin and metformin hydrochloride) FDC provided by manufacturer. Price of canagliflozin and metformin sourced from the Régie de l'assurance maladie Quebec (RAMQ) List of Medications February 8, 2016.

[b] Sourced from Invokamet (canagliflozin and metformin hydrochloride) FDC, Invokana, and Glucophage product monographs and CDR Komboglyze FDC Review Report.

[c] Does not include markup or dispensing fee; drug cost only.

[d] Invokana has patents expiring in 2024 and 2027 (see section 3.2 for more information) — the patents for metformin have already expired.

The submitted anticipated market price of Invokamet (canagliflozin and metformin hydrochloride) FDC tablets is $1.5338 per tablet. Taken twice a day, the daily cost of canagliflozin/metformin FDC is $3.0676 (see Table 10). The daily cost of therapy with canagliflozin and metformin taken as individual components ranges from $2.7065 to $2.7953 and is dependent on the daily dose of metformin (see Table 10). Therefore, the potential daily price difference of the FDC product compared with the individual components ranges from $0.2723 to $0.3611. The daily dose of metformin in Table 10 is based on recommended doses from the manufacturer product monograph but also takes into consideration that in practice it is typically dosed twice daily, irrespective of tablet strength.[20, 21]

A cost-minimization analysis (CMA) comparing canagliflozin/metformin FDC with its individual components was undertaken from the perspective of the Ontario Public Drug Programs. The analysis assumed a one-year time horizon and to be conservative, utilized the lowest Canadian list prices derived from the Régie de l'assurance maladie Quebec list of medications (Ontario specific dispensing fees [$8.83] and markups [8%] were applied).[39, 40] Prescriptions were assumed to be filled at a 100-day supply. Utilization weights (based on IMS Brogan PharmaStat public claims data)41 were applied to produce a weighted average price that appropriately reflects variability in pricing of dosage regimens associated with canagliflozin and metformin as individual components (see Table 11). Over one year, the cost associated with treatment with canagliflozin and metformin hydrochloride FDC was $1,241.48

versus $1,157.95 for the cost of therapy using the individual components (see Table 12). Therapy with the FDC format is associated with a modest incremental annual cost of $83.53 per patient. Results of sensitivity analyses, which included lowering the prescription day supply from 100 days to 30 days as well as both lowering and increasing dispensing fees by 25%, suggest that the incremental annual cost of the FDC format can range from $8.45 to $91.71 per patient.

TABLE 11: UTILIZATION BREAKDOWN OF CANAGLIFLOZIN AND METFORMIN AS INDIVIDUAL COMPONENTS

Regimen of Canagliflozin and Metformin as Individual Components (Canagliflozin Dose + Metformin Dose)	Utilization (%)[a]
100 mg q.d. + 500 mg b.i.d.	6%
100 mg q.d.+ 500 mg q.i.d.	28%
100 mg q.d.+ 850 mg b.i.d.	6%
300 mg q.d.+ 500 mg b.i.d.	9%
300 mg q.d.+ 500 mg q.i.d.	42%
300 mg q.d.+ 850 mg b.i.d.	9%

b.i.d. = twice daily; q.d. = once daily; q.i.d. = four times daily.
[a] Based on IMS Brogan PharmaStat public claims data (all Canadian provinces).

3.2 Cost Comparison Table/Summary of Cost-Minimization Analysis

TABLE 12: SUMMARY OF CMA RESULTS OF CANAGLIFLOZIN AND METFORMIN HYDROCHLORIDE FIXED-DOSE COMBINATION COMPARED WITH INDIVIDUAL COMPONENTS — DAILY AND ANNUAL DRUG COST (INCLUDES MARKUPS AND DISPENSING FEE)

Drug / Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Daily Use[b]	Average Daily Drug Cost ($)	Annual Drug Cost ($)[c,d,e]
Canagliflozin/ Metformin (Invokamet) FDC	**50 mg/500 mg** **50 mg/850 mg** **50 mg/1,000 mg** **150 mg/500 mg** **150 mg/850 mg** **150 mg/1,000 mg**	**IR tablet** **IR tablet** **IR tablet** **IR tablet** **IR tablet** **IR tablet**	**$1.5338** **$1.5338** **$1.5338** **$1.5338** **$1.5338** **$1.5338**	**1 tab b.i.d.** **1 tab b.i.d.** **1 tab b.i.d.** **1 tab b.i.d.** **1 tab b.i.d.** **1 tab b.i.d.**	**$3.0676** **$3.0676** **$3.0676** **$3.0676** **$3.0676** **$3.0676**	**$1,241.48**
Canagliflozin (Invokana) + Metformin (Glucophage, and generics)	100 mg 300 mg	IR tablet IR tablet	$2.6177 $2.6177	**Canagliflozin/Metformin** 100 mg q.d./500 mg b.i.d. 100 mg q.d./500 mg q.i.d. 100 mg q.d./850 mg b.i.d. 300 mg q.d./500 mg b.i.d. 300 mg q.d./500 mg q.i.d. 300 mg q.d./850 mg b.i.d.	 $2.7065 $2.7953 $2.7397 $2.7065 $2.7953 $2.7397	**$1,157.83**
	500 mg 850 mg	IR tablet IR tablet	$0.0444 $0.0610			
Annual Incremental Cost						**$83.65**

b.i.d. = twice daily; CMA = cost-minimization analysis; FDC = fixed-dose combination; IR = immediate-release; q.d. = once daily; q.i.d. = four times daily.
Note: Annual Drug Costs were originally reported by the manufacturer as $1,224.91 and $1,142.85 with an incremental cost for canagliflozin/metformin FDC of $82.06; however, these figures contained a calculation error resulting from including only 360 days of therapy per year while dispensing fees were based on a 365-day year.

[a] Cost of Invokamet provided by manufacturer. Price of canagliflozin and metformin sourced from the Régie de l'assurance maladie Quebec (RAMQ) List of Medications, February 8, 2016.
[b] Sourced from Invokamet (canagliflozin and metformin hydrochloride) FDC, Invokana, Glucophage product monographs and CADTH Common Drug Review Komboglyze FDC Review Report.
[c] Assumes a dispensing fee of $8.83 and 8% markup — based on the Ontario Drug Benefit (ODB) Program (September 2015).
[d] Assumes prescriptions are dispensed with a 100-day supply.
[e] Total annual cost of individual components based on weighted utilization (see Table 10).

3.3 Manufacturer-Submitted Information Regarding Current Patent Status

Please refer to Table 13 for the current patent status of canagliflozin.

TABLE 13: PATENT STATUS FOR INVOKANA (CANAGLIFLOZIN)

Patent	Granted	Expiry Date
2534024	June 2, 2009	July 30, 2024
2671357	November 1, 2011	December 3, 2027

The patent for metformin has already expired.

3.4 Critical Appraisal of Cost Information

At a cost of $3.07 per patient per day, the manufacturer submitted canagliflozin/metformin FDC at a 9.7% to 13.3% price premium over the combined costs for the individual components ($2.71 to $2.80 per patient per day, based on the list prices shown in Table 10). The annual premium for the FDC, without taking into account markup or dispensing fees, ranges from $99 to $132 per patient per year. This premium is not entirely mitigated by the reduced dispensing fees associated with the FDC (i.e., one fee per dispensing interval is required for the FDC rather than two for the individual components). When an 8% markup and $8.83 dispensing fee per 100-day supply are applied, the FDC costs $75 to $110 more per patient per year than the individual components.

Patients using metformin may take a variable number of tablets daily; therefore, it is not possible to directly estimate the proportion of patients on each daily dose from metformin utilization data. The manufacturer estimated the proportion of patients on each dose of metformin based on the observed distribution of use of Janumet (sitagliptin [a DPP-4]/metformin FDC, offered at similar doses of metformin). This estimate was then multiplied by utilization data for each dose of canagliflozin (Invokana) to estimate the proportion of patients that would use each combination of individually-dosed canagliflozin and metformin (see Table 11). These proportions were then used to estimate a weighted average annual per-patient cost for using the individual components. This estimate was then subtracted from the cost of canagliflozin/metformin FDC, leading to an incremental cost for using the FDC rather than the components of $83.65 per patient per year (see Table 12).

The approach used to estimate the dose distribution likely to be used for the FDC and the individual components appeared reasonable according to the clinical expert consulted by CDR, who did not anticipate significant differences in the metformin doses used by patients receiving a DPP-4 (i.e., sitagliptin) versus canagliflozin. While CDR was able to arrive at results similar to those of the manufacturer using 2015 public claims data from IMS Brogan's PharmaStat database, the dose distribution was found to vary across individual jurisdictions (see Table 3.5 with Ontario data used as an example). Furthermore, when linagliptin plus metformin FDC (Jentadueto) utilization data were

compared with the sitagliptin plus metformin FDC data, the estimated proportion of patients using each metformin dose was quite different (Table 14). This suggests that the distribution of metformin doses varies even within the DPP-4 inhibitor class; therefore, it is questionable whether the dose distribution data for either are transferable to canagliflozin/metformin FDC. Nevertheless, the assumed dose distributions for metformin have little impact on the weighted average annual per patient cost, due to the low cost of individual component metformin (and thus small differences in costs between metformin doses).

Table 14: CADTH Common Drug Review Reanalysis Exploring Dose Utilization Transferability Assumption

Daily regimen of CANA and MET as taken individually (CANA + MET)	Estimated from sitagliptin/MET FDC for MET use		Estimated from linagliptin/MET FDC for MET use	
	National public data 2015	Ontario public data 2015	National public data	Ontario public data
100 mg + 2 × 500 mg	6%	6%	12%	14%
100 mg + 4 × 500 mg	29%	33%	24%	24%
100 mg + 2 × 850 mg	5%	1%	5%	2%
300 mg + 2 × 500 mg	9%	9%	17%	20%
300 mg + 4 × 500 mg	43%	49%	35%	37%
300 mg + 2 × 850 mg	8%	2%	7%	3%
Weighted average annual cost of individual components	**$1,158**	**$1,160**	**$1,154**	**$1,153**
Incremental cost of CANA/MET FDC (annual FDC cost = $1,241)	**$83**	**$81**	**$88**	**$88**

CANA = canagliflozin; FDC = fixed-dose combination; MET = metformin.
Source: National and Ontario public plan utilization data from IMS Brogan PharmaStat, accessed April 21, 2016.

While it may be argued that the convenience and potential for increased adherence with the FDC warrants a price premium, another SGLT-2 plus metformin FDC, XigDuo (dapagliflozin/metformin), which is already on the Canadian market but not yet on public formularies at the time of this review, is priced (based on wholesale prices) identically to that of dapagliflozin alone (Forxiga); i.e., the cost of metformin is saved when using FDC. Both dapagliflozin alone and the dapagliflozin/metformin FDC are marketed at a price of $2.62 daily in most provinces and $2.45 daily in Quebec (Delta PA wholesale prices, accessed April 21, 2016), lower than the submitted price of the canagliflozin/metformin FDC ($3.07 daily) or the list price of canagliflozin alone.

At the submitted price of $1.53 per tablet regardless of strength, substitution with canagliflozin/metformin FDC in patients who are stabilized on the individual components costs an additional $99 to $132 (10% to 13%) per patient per year based solely on drug costs.

4. DISCUSSION

Clinical Efficacy and Safety

The clinical efficacy and safety data for supporting the use of canagliflozin/metformin FDC to replace canagliflozin + metformin used concurrently in two separate tablets was based on two pivotal phase 3 clinical studies for canagliflozin, which were the key evidence reviewed in a previous CDR review for canagliflozin as a third-line therapy added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea.[21] In January 2015, canagliflozin received a CDEC recommendation for the treatment of type 2 diabetes for add-on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea and for whom insulin is not an option.[23] Therefore, the two phase 3 studies mentioned above are not included as part of the present submission.

In addition to the two previously reviewed pivotal phase 3 clinical studies for canagliflozin, and the supplied pivotal bioequivalence trials for canagliflozin/metformin FDC, the manufacturer also submitted an 18-week supportive phase 2, placebo-controlled RCT, DIA2003.[22] Study DIA2003 assessed the efficacy and safety of canagliflozin (50 mg or 150 mg twice daily) in T2DM patients who were inadequately controlled on metformin monotherapy. The findings from this trial showed that the canagliflozin twice-daily regimen resulted in greater A1C reduction compared with placebo in patients with T2DM inadequately controlled with metformin monotherapy. The potential limitations of study DIA2003 were as follows:

- Canagliflozin was not used in patients who were inadequately controlled with metformin and sulfonylurea combination therapy (i.e., as a triple therapy specified in the indication under this review and the list request criteria.
- It was not designed to evaluate the clinical efficacy and safety of canagliflozin/metformin FDC compared with other third-line antidiabetic drugs in the treatment of patients with T2DM who failed in the combination therapy of metformin and sulfonylurea.
- It was not designed to investigate the clinical efficacy and safety for canagliflozin dosed twice daily compared with the previously reviewed once-daily formulation.
- Study duration was relatively short for assessing the clinical important outcomes such as mortality, quality of life, and health care resource utilization.
- Baseline A1C level was relatively lower compared with those in phase 3 studies previously reported.[21] Therefore, the population evaluated in study DIA2003 is slightly different from those evaluated in the third-line therapy studies previously reviewed by CDR. It is uncertain how this may affect the application of the results of the twice-daily studies to patients on triple therapy (metformin + sulfonylurea + canagliflozin) with the once-daily formulation.

Efficacy

Reported in study DIA2003:

- A1C: at the end of 18 weeks, A1C decreased by 0.44% ($P < 0.001$) and 0.60% ($P < 0.001$) for patients treated with canagliflozin 50 mg and 150 mg twice daily, respectively, as compared with placebo. A greater proportion of patients achieved an A1C < 7.0% at week 18 when treated with canagliflozin 50 mg and 150 mg twice daily versus placebo (47.8% [$P< 0.05$], 57.1% [$P < 0.001$], and 31.5%, respectively).

- Body weight: Statistically significant reductions in body weight (as measured by LSM per cent change from baseline) were observed with canagliflozin 50 mg and 150 mg twice daily compared with placebo over the 18-week study period (LSM difference [SE]: –2.2% [–2.1] and –2.6% [–2.6], respectively; $P < 0.001$ for both dose regimens).
- SBP: Treatment with canagliflozin 50 mg and 150 mg twice daily was also associated with reductions in SBP compared with placebo (LSM difference [95% CI] [mm Hg], –5.4 [–8.4 to –2.3] and –5.7[–8.7 to –2.6], respectively).

Harms

For this review, 10 phase 1 bioequivalence studies (in healthy adults) and study DIA2003 provided additional safety data for canagliflozin/metformin FDC. Overall, these new studies did not raise any new safety signals that were not reported by previous clinical studies reviewed in CDR review for canagliflozin.[21] The FDC regimens appear to have similar tolerability and safety profiles as the individually co-administered components. Furthermore, study DIA1032[24,26] found that canagliflozin was well tolerated in both once-daily and twice-daily treatment arms (either 100 mg or 300 mg total daily doses) with no meaningful differences between either dosing regimens or total daily doses; study DIA1037[25,27] reported that canagliflozin/metformin FDC 150 mg/1000 mg was generally well tolerated in both a fed and fasted state.

Bioequivalence

Findings from six phase 1 bioequivalence studies indicated that all strengths of canagliflozin/metformin FDC were bioequivalent to its individual components.[28-34] Moreover, results from DIA1070[35] and DIA1071[36] [redacted] between the metformin component in canagliflozin/metformin FDC tablets to the Canadian formulation of metformin IR in fed and fasted healthy participants. The predefined criteria to [redacted];[28-33,35,36] namely, the 90% CI of the geometric mean ratio of AUC_{last} (or AUC_{0-t}) and C_{max} of the test to reference product was within the bioequivalence limits of 80% to 125%.[34] Furthermore, the bioequivalence of canagliflozin/metformin FDC was validated in two more studies (studies DIA1032[26] and DIA1037[27]) that demonstrate the bioequivalence of canagliflozin dosed at 100 mg or 300 mg a day as either a twice-daily or once-daily format was comparable and met the criteria for bioequivalence[26] and the bioequivalence of canagliflozin/metformin FDC was not affected by the administration of a high-fat meal.[24,25,27]

Other Considerations

Patient adherence to medications for diabetes is often suboptimal. The canagliflozin/metformin FDC tablet may improve adherence by simplifying the medication regimen, which may result in better outcomes. According to the clinical expert involved in this review, metformin is usually given twice daily or three times daily; therefore, a canagliflozin/metformin twice-daily regimen is not a concern. Overall, the number of pills will be reduced by using canagliflozin/metformin FDC compared with canagliflozin and metformin given separately. In addition to canagliflozin and metformin being combined, this formulation reduces the number of metformin tablets taken, as metformin doses are usually administered in 500 mg tablets when it is administered separately. However, no study formally assessed adherence with canagliflozin/metformin FDC compared with canagliflozin plus metformin administered individually.

Conclusion

The clinical efficacy and safety of canagliflozin used in patients with T2DM inadequately controlled with the combination therapy of metformin and sulfonylurea has been previously reviewed by CDR. Canagliflozin has previously received a CDEC Recommendation for the treatment of type 2 diabetes as added-on therapy to metformin and a sulfonylurea for patients inadequately controlled on metformin and a sulfonylurea. The canagliflozin and metformin components in canagliflozin/metformin FDC appeared to be bioequivalent to the canagliflozin and metformin given concurrently in separate tablets. The twice-daily regimen of canagliflozin added to metformin showed greater efficacy in reduction of A1C, body weight, and SBP compared with placebo in patients inadequately controlled with metformin monotherapy. However, no direct evidence on the comparative clinical efficacy and safety of canagliflozin when administered as a twice-daily dose regimen versus the previously reviewed once-daily dose regimen is available.

At the submitted price of $1.53 per tablet regardless of strength, substitution with canagliflozin plus metformin FDC in patients who are stabilized on the individual components costs an additional $99 to $132 (10% to 13%) per patient per year based solely on drug costs. Based on an 8% markup, $8.83 dispensing fee, and dispensing of 100-day supply, the annual incremental cost per patient for the FDC is between $75 and $110.

APPENDIX 1: DRUG PLAN LISTING STATUS FOR INDIVIDUAL COMPONENTS

Abbreviation	Description
EX	Exception item for which coverage is determined on a case-by-case basis
FB	Full benefit
NB	Not a benefit
RES	Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit)
UR	Under review
–	Information not available

TABLE 15: LISTING STATUS FOR INDIVIDUAL COMPONENTS OF THE NEW COMBINATION PRODUCT

Components	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Canagliflozin	**NB**	**RES**	**RES**	**RES**	**FB**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**RES**	**NB**	**RES**
Metformin (IR)	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**

AB = Alberta, BC = British Columbia; CDR = CADTH Common Drug Review; DND = Department of National Defence; IR = immediate-release; MN = Manitoba; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

TABLE 16: RESTRICTED BENEFIT CRITERIA FOR CANAGLIFLOZIN FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

Drug Plan	Criteria for Restricted Benefit
AB	As add-on therapy for the treatment of type 2 diabetes in patients with intolerance to and/or inadequate glycemic control on: – a sufficient trial (i.e., a minimum of 6 months) of metformin, *and* – a sulfonylurea, *and* – for whom insulin is not an option. *or* for whom these products are contraindicated.
SK	For treatment of patients with type 2 diabetes who have concurrent prescriptions for metformin and a sulfonylurea. This product should not be used in combination with dipeptidyl peptidase-4 inhibitors. Please note: This product should be used in patients with diabetes who are not adequately controlled on or are intolerant to metformin and/or a sulfonylurea, and for whom insulin is not an option.
MB	For the treatment of patients with type 2 diabetes who have previously been treated with metformin and a sulfonylurea. Should be used in patients with diabetes who are not adequately controlled on or are intolerant to metformin and a sulfonylurea, and for whom insulin is not an option.
NB	For the treatment of type 2 diabetes mellitus, in addition to metformin and a sulfonylurea, in patients with inadequate glycemic control on

	metformin and a sulfonylurea and for whom insulin is not an option.
NS	For the treatment of type 2 diabetes for patients with: - inadequate glycemic control on metformin and a sulfonylurea; and - for whom insulin is not an option. Note: 200 mg is not a recognized dose; as such, a dose of two 100 mg tablets will not be funded.
PE	For the treatment of type 2 diabetes as a third drug added on to metformin and a sulfonylurea for patients with inadequate glycemic control on optimal doses of metformin and a sulfonylurea, and for whom insulin is not an option.
NL	For the treatment of type 2 diabetes as a third drug added to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea *and* in whom insulin is not an option.
YK	In addition to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea *and* for whom insulin is not an option.
NT	For the treatment of patients with type 2 diabetes mellitus who did not achieve glycemic control *or* who demonstrated intolerance to an adequate trial of metformin *and* a sulfonylurea.
NIHB	For the treatment of patients with type 2 diabetes mellitus who did not achieve glycemic control *or* who demonstrated intolerance to an adequate trial of metformin *and* a sulfonylurea.
VAC	NA – not specified; pharmacist or physician must contact VAC.

AB = Alberta, BC = British Columbia; CDR = CADTH Common Drug Review; DND = Department of National Defence; IR = immediate-release; MN = Manitoba; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan; VAC =Veterans Affairs Canada; YK = Yukon

APPENDIX 2: SUMMARY OF PATIENT INPUT

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input
Two patient groups, the Canadian Diabetes Association (CDA) and BC & Yukon Branch, Kidney Foundation of Canada (KFC), provided input.

CDA helps people with diabetes live healthy lives and find a cure. The CDA is supported by a network of volunteers, employees, health care professionals, researchers, and partners. It provides education and services, advocates on behalf of patients with diabetes, supports research, and translates research into practical applications. The CDA receives unrestricted educational grants from multiple manufacturers and vendors of pharmaceuticals, supplies, and devices for diabetes. These funds are used to help the CDA support community programs and services for patients with diabetes and to fund research and advocacy across Canada. The CDA reported no conflicts of interest in the preparation of this submission.

The KFC's mission is to fund and stimulate innovative research, provide education and support, and promote access to high-quality health care. The KFC BC & Yukon Branch is supported by volunteers (patients, caregivers, and family members) and health care professionals. KFC estimated that there has been a 148% increase in chronic kidney disease (CKD) in British Columbia since 2005. Patients with CKD often have diabetes (such as kidney disease or kidney failure as a result of diabetes). The KFC encourages patients with diabetes, their families, and their caregivers to manage their chronic disease effectively in order to lower glycated hemoglobin (A1C) and promote the health of their kidneys in order to avoid or delay kidney failure. The KFC BC & Yukon Branch receives unrestricted educational grants from pharmaceutical industries including Alexion, Amgen, Aspreva, Astellas, Baxter, Boehringer Ingelheim, Eli Lilly, Fresenius, GSK, Janssen, Johnson & Johnson, Otsuka, Pfizer, Sanofi, Takeda, and Vifor Pharma. The KFC BC & Yukon Branch reported no conflicts of interest in the preparation of this submission.

2. Condition-Related Information
The CDA's submission was derived from a survey (March 2016) from 1,198 Canadians. Of these respondents, 988 were patients with type 2 diabetes and 61 respondents were caregivers. The KFC's submission was also based on a survey (January 2016) from 20 patients with diabetes and kidney disease.

Type 2 diabetes is a chronic and progressive condition that occurs when the pancreas does not produce enough insulin or when the body does not effectively use the insulin. Common symptoms of diabetes include fatigue, thirst, and weight change. High blood glucose levels can cause long-term complications such as blindness, heart disease, kidney problems, nerve damage, and erectile dysfunction. The goal of diabetes management is to keep glucose levels within the target range to minimize symptoms and avoid or delay the complications. Diabetes requires considerable self-management, including healthy eating, regular physical activity, healthy body weight, taking diabetes medications as prescribed, monitoring blood glucose, and managing stress. The majority of patients indicated that self-management of diabetes, including taking multiple medications, and constantly monitoring food intake, activity, and

blood sugar, is very challenging, unrelenting, and overwhelming. Poor glucose control can result in acute crises, serious long-term complications, and reduced quality of life. It was indicated that 35% of the patients in the KFC database were living with or had had diabetes-related kidney disease. The patients and their caregivers also indicated that diabetes had a psychological and emotional impact on their lives (stress, anxiety, adjusting to changes in diet and lifestyle, medication and treatment management, and relationships with family). Respondents also described fatigue, and lack of energy. Some quotes were as follows: "…diabetes management…is exhausting and relentless…" "It affects all aspects of life from work to travel to everyday meal planning…it is depressing to have to monitor every bit of food…"

3. Current Therapy-Related Information

Many people with type 2 diabetes fail to achieve optimal glycemic control and are therefore at risk for both acute and chronic diabetes complications. The initial therapy they receive is most often metformin, but over time, most people will require the addition of a second or third agent 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. A total of 616 patients with type 2 diabetes and their caregivers indicated experience with taking diabetes medications. Approximately 20% stated they were very unsatisfied or unsatisfied with their current therapies. Patients indicated that current therapies resulted in better blood glucose and A1C levels. However, a significant number of patients have found that it is not easier to avoid low blood glucose ("the same," "worse," or "much worse" for 38%), weight gain (≥ 40%) or gastrointestinal (GI) adverse effects (60%). Overall, patients were more satisfied than dissatisfied with their medications in terms of the ability to manage their blood glucose levels. However, there were issues with side effects. Patients mentioned that taking multiple medications not only reminds them that they have a life-threatening disease — diabetes — but is also challenging on busy days. Fewer medications will be easier for compliance. The majority of patients and caregivers indicated the following benefits of therapy were "quite" or" very important":

- Blood glucose kept at satisfactory levels in the morning/after fasting (93%), and during the day after meal (94%)
- Avoiding adverse events such as weight gain (87%), low blood glucose during the day/overnight (84%), GI effects (84%), high blood pressure (82%), fluid retention (82%), or urinary tract infection (81%).

4. Expectations About the Drug Being Reviewed

Canagliflozin belongs to a new class of drugs to lower blood glucose through inhibition of subtype 2 sodium-glucose cotransporter-2 protein (SGLT-2). The SGLT2 inhibition also causes a reduction in blood pressure and weight loss. As the fixed-dose combination (FDC) of canagliflozin and metformin (canagliflozin/metformin FDC) is not yet available on the market, very few patients have had experience with this FDC medication. However, many patients indicated they currently have used canagliflozin plus metformin.

A total of 574 patients with type 2 diabetes and caregivers indicated they had experience taking canagliflozin (with or without metformin). They highlighted its effectiveness in lowering blood glucose compared with other medications. The improvement in blood glucose levels ("fasting and throughout the day") and the accompanying weight loss was broadly described as follows: "life is better" and "I feel my diabetes is under control." Many respondents noted less dependency on other drugs such as insulin as a result of canagliflozin, and this — less or no insulin treatment — was considered to be a desirable

outcome. In addition, respondents generally did not describe serious side effects, although some did experience side effects such as frequent urination, dehydration, or increased appetite. These were described as "manageable." Other quotes from patients and caregivers on using canagliflozin with or without metformin include:

- "I am feeling better, more in control mentally as well."
- "I feel more energetic and better in control of myself."
- "Invokana has helped me to lose weight and meet blood glucose targets. I am very happy with it."
- "… Would be great if only one pill for diabetes would solve the problem…"

KFC submitted the patient input for this review from the perspective of preventing kidney disease by managing diabetes effectively. Both of the patient groups believed that canagliflozin/metformin FDC is convenient for patients with type 2 diabetes in their self-management, which is a critical step to achieve the optimal glycemic control. The availability of canagliflozin/metformin FDC would serve the purpose of offering effective therapy while reducing pill burden and promoting adherence to prescribed therapy. This would offer a significant advantage for physicians and patients working together to achieve optimal treatment with the lowest effective dose.

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