Common Drug Review
Fixed-Dose Combination Report

July 2016

Drug	dapagliflozin/metformin hydrochloride (XigDuo) fixed-dose combination (FDC)
Indication	Indicated for use: 1. as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already being treated with dapagliflozin and metformin as separate tablets and achieving glycemic control 2. in combination with insulin as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already achieving glycemic control with dapagliflozin, metformin, and insulin. 3. in combination with a sulfonylurea as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already achieving glycemic control with dapagliflozin, metformin, and a sulfonylurea 4. in combination with sitagliptin as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already achieving glycemic control with dapagliflozin, metformin, and sitagliptin
Listing request	• XigDuo is indicated for use as an adjunct to diet and exercise in adults with type 2 diabetes who are already being treated with dapagliflozin and metformin as separate tablets and achieving glycemic control. • XigDuo is indicated for use in combination with insulin as an adjunct to diet and exercise in adults with type 2 diabetes who are already achieving glycemic control with dapagliflozin, metformin, and insulin. • XigDuo is indicated for use in combination with a sulfonylurea as an adjunct to diet and exercise in adults with type 2 diabetes who are already achieving glycemic control with dapagliflozin, metformin, and a sulfonylurea.
Dosage form(s)	5 mg /850 mg or 5 mg /1,000 mg
NOC date	Issued December 10, 2015 for indications 1 and 2 Issued April 12, 2016 for indications 3 and 4
Manufacturer	AstraZeneca Canada Inc.

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

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ABBREVIATIONS

A1C	glycated hemoglobin
AE	adverse event
AUC	area under the curve (total exposure)
$AUC_{(0-t)}$	area under curve from 0 to t
BE	bioequivalence
b.i.d.	twice daily
CADTH	Canadian Agency for Drugs and Technologies in Health
CDA	Canadian Diabetes Association
CDR	CADTH Common Drug Review
CI	confidence interval
CL_{Cr}	creatinine clearance
C_{max}	maximum concentration (peak exposure)
DAPA	Dapagliflozin
eGFR	estimated glomerular filtration rate
FDC	fixed-dose combination
FPG	fasting plasma glucose
IR	immediate release
LOCF	last observation carried forward
Met	metformin
q.d.	once daily
XR	extended release

EXECUTIVE SUMMARY

Introduction

Diabetes is a metabolic disease, characterized by persistent elevations in blood glucose (hyperglycemia). This persistent elevated blood glucose causes damage to blood vessels, on both a microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (peripheral vascular disease, cardiovascular disease) level. There are two main subtypes of DM — type 1 diabetes, where the primary problem is a lack of adequate insulin secretion from pancreatic beta cells, and type 2 diabetes, where cells are unresponsive to insulin. Dapagliflozin is a sodium-dependent glucose co-transporter inhibitor, and by inhibiting the glucose transporter in the kidney, increases the excretion of glucose, having an antihyperglycemic effect. Secondary effects may include weight loss secondary to reduced glucose absorption and a lowering of blood pressure. XigDuo is a fixed-dose combination (FDC) product containing dapagliflozin and metformin hydrochloride, a biguanide antidiabetic drug. The objective of this review was to evaluate the manufacturer-submitted evidence for the efficacy and safety of dapagliflozin and metformin hydrochloride twice daily dosing (b.i.d.), as well as the bioequivalence (BE), safety, and costs of XigDuo 5 mg /850 mg and 5 mg /1,000 mg as an adjunct to diet and exercise for the treatment of T2D in adults who are already being treated with dapagliflozin and metformin (Met) as separate tablets and achieving glycemic control, or in combination with insulin or a sulfonylurea.

Indication under review
Post-Notice of Compliance (NOC) Indications (NOC date December 10, 2015) 1. XigDuo (dapagliflozin/metformin hydrochloride 5 mg /850 mg or 5 mg /1,000 mg) is indicated for use as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already being treated with dapagliflozin and metformin as separate tablets and achieving glycemic control. 2. XigDuo (5 mg /850 mg or 5 mg /1,000 mg) is indicated for use in combination with insulin as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already achieving glycemic control with dapagliflozin, metformin, and insulin. **Pre-NOC Indication (NOC date April 12, 2016)** 3. XigDuo (5 mg /850 mg or 5 mg /1,000 mg) is indicated for use in combination with a sulfonylurea as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already achieving glycemic control with dapagliflozin, metformin, and a sulfonylurea.

Listing criteria requested by sponsor
– XigDuo is indicated for use as an adjunct to diet and exercise in adults with type 2 diabetes who are already being treated with dapagliflozin and metformin as separate tablets and achieving glycemic control. – XigDuo is indicated for use in combination with insulin as an adjunct to diet and exercise in adults with type 2 diabetes who are already achieving glycemic control with dapagliflozin, metformin, and insulin. – XigDuo is indicated for use in combination with a sulfonylurea as an adjunct to diet and exercise in adults with type 2 diabetes who are already achieving glycemic control with dapagliflozin, metformin, and a sulfonylurea.

Results and Interpretation

Included Studies

One double-blind, placebo-controlled, multi-centre, randomized, phase 3 study (D1691C00003) that investigated the efficacy and safety of dapagliflozin (DAPA) treatment regimens of 2.5 mg b.i.d. and

5 mg b.i.d. co-administered with metformin (Met) therapy, compared with placebo plus Met, was included in this review. In addition, a pivotal Canadian BE study (D1691C00007) that compared dapagliflozin/Met 5 mg/850 mg FDC tablets with the individual monotherapy tablets was included in this review.

The main limitations in study D1691C00003 is that no statistical comparisons were made between the treatment groups DAPA 10 mg q.d. + Met, and DAPA 5mg + Met b.i.d.; hence, no conclusion regarding the comparative efficacy of these treatments to each other can be made. In addition, dapagliflozin 10 mg once daily (q.d.) failed to reach statistical significance for the proportion of subjects reaching glycated hemoglobin (A1C) below 7% (a key secondary efficacy variable), which calls into question the robustness of the study design and efficacy results, especially that 10 mg q.d. is currently an approved dosage for dapagliflozin.

Efficacy

In trial D1691C00003, it was found that, at 16 weeks, dapagliflozin 5mg twice daily with Met achieved a statistically higher reduction of A1C compared with placebo and Met. Although the difference from placebo was statistically significant, it was < –0.3% with dapagliflozin 10 mg daily, but it was > –0.3% difference between placebo and dapagliflozin 5.0 mg twice daily. The 10 mg daily dose included did not achieve the threshold difference of > –0.3% from placebo. These efficacy conclusions are supported by the statistical analyses that were conducted for dapagliflozin 5 mg twice daily for the short-term study treatment duration of 16 weeks, but the clinical significance is not robustly supported. Furthermore, the dapagliflozin 10 mg daily failed to achieve a difference of > –0.3% from placebo. It is worth noting that a previous placebo-controlled study of dapagliflozin in add-on combination with Met showed a statistically significant placebo-adjusted reduction in A1C by approximately 0.41% and 0.54% with dapagliflozin 5 mg daily and 10 mg daily, respectively;[1] whereas, the study D1691C00003 only showed a difference of 0.35% and 0.29% with dapagliflozin 5 mg twice daily and 10mg daily, respectively. However, previous studies had end points at 24 weeks; whereas, the b.i.d. study (D1690C00003) had end points at 16 weeks. There were no direct comparisons between dapagliflozin 5 mg twice daily and 10 mg daily in study D1691C00003; therefore, comparability between dapagliflozin 5 mg twice daily and dapagliflozin 10 mg daily cannot be inferred.

Harms

The short 16-week D1691C0003 study did not raise any new signals that were not already reported by previous clinical studies reviewed in the Forxiga CADTH Common Drug Review report. The FDC regimens appear to have similar tolerability and safety profiles to the individually co-administered components.

Bioequivalence

In XigDuo, the doses of individual components allow for a range of dosing options often required for patients with type 2 diabetes. Evidence from study D1691C00007 provided by the manufacturer and the Health Canada Reviewer's report indicate that XigDuo FDC tablets meet the recommended standard for BE with individually co-administered dapagliflozin and Met tablets.[2] Where the results from study D1691C00007 that compared dapagliflozin/Met 5 mg/850 mg FDC tablets with the individual monotherapy tablets showed that the geometric mean ratios of the area under the curve from 0 to t of both dapagliflozin and Met are close to unity, and the corresponding 90% confidence interval for the treatment comparisons falls well within the limits of 0.8 and 1.25. The geometric mean ratios of maximum concentration (peak exposure) also fall within the limits of 0.8 and 1.25,

and hence confirm the BE of each active ingredient in the FDC product to that of the individual components administered concomitantly under both fasted and fed conditions. The FDC tablet and individual tablets seems to have similar mean concentration-time profiles under both fasted and fed conditions. This evidence supports the BE of XigDuo with Met and dapagliflozin administered as separate tablets.

Other Considerations

Patient adherence to medications for chronic conditions such as diabetes is often suboptimal. The FDC tablet may improve adherence by simplifying the medication regimen, which may result in better outcomes. Studies that formally assess adherence with XigDuo compared with unfixed combination regimens of Met and dapagliflozin would be useful to determine whether this does, in fact, occur.

Conclusions

In study D1691C00003, the dapagliflozin 5 mg twice daily arm met statistical significance for the primary and secondary efficacy variables. No new safety concerns regarding co-administration of dapagliflozin and Met were raised in study D1691C0003. The safety profile of dapagliflozin co-administered with Met is consistent with the safety profiles of the individual components. The BE of administering the components of this FDC has been demonstrated; however, the comparative efficacy of administering dapagliflozin 5 mg twice daily rather than 10 mg q.d. is uncertain, as no statistical analysis was planned or completed in study D1691C00003 to compare these two treatment arms.

1. PRODUCT INFORMATION

1.1 Health Canada–Approved Indications

Indication(s) to be Reviewed by the CADTH Common Drug Review (CDR)
Post-Notice of Compliance (NOC) Indications (NOC date December 10, 2015)
XigDuo (dapagliflozin/metformin hydrochloride) is indicated for use as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already being treated with dapagliflozin and metformin as separate tablets and achieving glycemic control.
XigDuo is indicated for use in combination with insulin as an adjunct to diet and exercise in adults with type 2 diabetes who are already achieving glycemic control with dapagliflozin, metformin, and insulin.
Pre-NOC Indication (Anticipated NOC date April 4, 2016)[a]
XigDuo is indicated for use in combination with a sulfonylurea as an adjunct to diet and exercise in adults with type 2 diabetes who are already achieving glycemic control with dapagliflozin, metformin, and a sulfonylurea.

[a] The XigDuo submission is being filed on a pre-NOC basis for the potential use of XigDuo in patients who are already treated with dapagliflozin and Met when the use is also in combination with a sulfonylurea (i.e., triple therapy), for which the NOC will not be received until April 4, 2016. Permission was granted by CADTH to file these three indications within a single tailored CDR review on November 16, 2015.

1.2 Requested Listing Criteria

Requested Listing Criteria
The request is for reimbursement aligned with the Health Canada–approved indications (post- and pre-NOC): **Post-NOC:** • XigDuo is indicated for use as an adjunct to diet and exercise in adults with type 2 diabetes who are already being treated with dapagliflozin and metformin as separate tablets and achieving glycemic control. • XigDuo is indicated for use in combination with insulin as an adjunct to diet and exercise in adults with type 2 diabetes who are already achieving glycemic control with dapagliflozin, metformin, and insulin. **Pre-NOC:** • XigDuo is indicated for use in combination with a sulfonylurea as an adjunct to diet and exercise in adults with type 2 diabetes who are already achieving glycemic control with dapagliflozin, metformin, and a sulfonylurea.

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

Adherence to therapy is important for the management of diabetes. The need for multiple daily antidiabetic medications to achieve and sustain adequate glycated hemoglobin (A1C) control often leads to poor adherence and complications. A new fixed-dose combination (FDC) therapy of dapagliflozin and Met would provide an important treatment option for patients with type 2 diabetes by offering glycemic control and a low propensity for hypoglycemia, as well as simplification of the treatment regimen.

1.3.1 Rationale

The central goal of diabetes care is to achieve adequate glycemic control in order to reduce the long-term microvascular and macrovascular complications caused by chronic hyperglycemia. Whereas adherence to therapy is important for the management of chronic diseases such as diabetes, the need for multiple daily antidiabetic medications to achieve and then sustain adequate glycemic control (glycated hemoglobin — A1C) often leads to poor adherence and is associated with increased hospitalization, mortality, and increased health care costs.[1-6] Recent studies indicate that levels of non-adherence in patients with type 2 diabetes are as high as 30%.[7-11]

The simplification and convenience of FDC therapy improves adherence by reducing pill burden, regimen complexity, and costs, while improving treatment satisfaction. [9; 12-15] Clinical evidence from studies of diabetes and other chronic diseases indicates that FDC therapy can result in reductions in the risk of non-adherence of 24% to 26% compared with free-drug combination regimens. [12] Importantly, a meta-analysis comparing glycemic control and medication adherence between FDC and co-administered dual therapy demonstrated that the FDC regimen was associated with improved glycemic control and adherence in type 2 diabetes patients (regimens included Met/sulfonylurea and Met/ thiazolidinedione therapies). [15] The introduction of an FDC provides the opportunity for improved patient adherence, and the attainment of glycemic targets by a larger proportion of patients.

XigDuo is an FDC tablet that is taken twice a day and is available in two strengths containing the following mono-components per tablet: dapagliflozin 5 mg/Met immediate release (IR) 850 mg or dapagliflozin 5 mg/Met IR 1,000 mg. Given the currently approved indications for dapagliflozin in Canada, dapagliflozin will be used commonly as an adjunct to Met (with or without other therapies; i.e., sulfonylurea, insulin). The combination of an drug that inhibits renal glucose reabsorption (dapagliflozin) with an drug that decreases hepatic glucose output (Met) has additive glucose-lowering effects. Concomitant treatment with dapagliflozin and Met provides effective glycemic control through complementary mechanisms of action, with a low risk of hypoglycemia. Importantly, therapy with dapagliflozin and Met offers additional advantages such as beneficial effects on body weight (i.e., weight loss) and systolic blood pressure, which may be important for long-term maintenance of glycemic control and, therefore, may help prevent diabetes complications. Providing an FDC option for dapagliflozin/Met (XigDuo) provides patients with an opportunity to continue with their dapagliflozin and Met regimens, with the additional benefits of an FDC.

1.3.2 Place in therapy

Treatment for glycemic control in type 2 diabetes is usually initiated with lifestyle modifications; however, when control cannot be achieved through changes in diet and exercise, Met is typically recommended as first-line pharmacotherapy based on its effectiveness in lowering blood glucose, its relatively mild side effect profile, long-term safety, low risk of hypoglycemia, and low risk of weight gain. [16] Canadian utilization data indicate that 60% of patients with type 2 diabetes who initiate pharmacotherapy are started on Met. [17] Over time, the progressive nature of diabetes commonly necessitates the use of additional treatments in combination with Met. Data for Canada indicate that 50% of type 2 diabetes patients require at least one second-line therapy. [17; 18] When selecting among second-line agents, Canadian guidelines highlight that type 2 diabetes patients are quite heterogeneous and, as such, both regimens and targets should be individualized. Importantly, following the recent approval of sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors in Canada, the Canadian Diabetes Association (CDA) updated guidelines on the pharmacological management of type 2 diabetes to recommended that SGLT2 inhibitors be considered among other therapies based on patient needs following first-line treatment with Met. [19] CADTH recently provided a positive listing recommendation for dapagliflozin, which includes use in combination with Met. Given Canadian treatment practices of prescribing first-line Met, and the recommendations from both the CDA and CADTH regarding use of dapagliflozin as an add-on to Met, it is likely that a large proportion of Canadians treated with dapagliflozin will also be treated with Met.

As per the Health Canada indications, XigDuo is indicated for patients who are already treated with dapagliflozin and Met and thus XigDuo is not indicated to be used for initiating therapy with dapagliflozin and Met. The clinical dose of the FDC tablet is 5 mg, which provides 10 mg per day, with twice daily dosing, as per recommended dosing. Dapagliflozin 10 mg was selected as the clinical dose

with the best benefit-risk balance in the comprehensive clinical development program. Although the dosing patterns for Met are more variable (ranging from 500 mg to 2,550 mg per day), the daily dose of Met that XigDuo provides (between 1,700 and 2,000 mg per day) captures a large proportion of Met users. Importantly, a consensus statement from the American Diabetes Association and EASD (the European Association of the Study for Diabetes) [20] on the medical management of hyperglycemia stated that the optimal effects of Met are considered to be achieved by doses of 1,000 mg twice daily, and often by 850 mg twice daily. Thus, the Met dosage strengths of the dapagliflozin/Met IR FDC (850 mg and 1,000 mg) should provide an adequate range of dosing options for patients. In addition, the Met doses of 850 mg and 1,000 mg are aligned with the doses currently available in other twice daily FDC oral antidiabetic products reimbursed in Canada.

1.3.3 Dosing considerations

As per the product monograph, [21] the recommended dose of XigDuo is one tablet twice daily with meals. Patients switching from separate tablets of dapagliflozin (10 mg daily) and Met to XigDuo should receive the same daily dose of dapagliflozin and Met already being taken or the nearest therapeutically appropriate dose of Met. The following dosage strengths of XigDuo are available: 5 mg dapagliflozin/850 mg Met, and 5 mg dapagliflozin/1,000 mg Met. Both dosage strengths are to be administered twice daily (b.i.d.), for a daily total dose of 10 mg dapagliflozin/1,700 mg Met or 10 mg dapagliflozin/2,000 mg Met.

Note that dose titration of individual components is not required prior to switching to XigDuo. The available doses of XigDuo contain commonly prescribed daily doses of the individual components. Given the availability of two doses of XigDuo, there is some ability to titrate the daily dose of Met (i.e., up to 2,000 mg Met per day). If a patient requires an excess of 2,000 mg Met per day, additional XigDuo tablets may not be taken to achieve this dose given that it will result in an increase in the daily dose of dapagliflozin, which will exceed the recommended daily maximum dose of dapagliflozin (10 mg).

2. CLINICAL EVIDENCE

The dapagliflozin/Met FDC program includes biopharmaceutics studies which assessed bioequivalence (BE) and food effects data, and a phase 3 study (D1691C00003) that investigated the efficacy and safety of twice daily dosing. Overall, the results of the dapagliflozin/Met FDC program and the IR FDC biopharmaceutics studies confirm that treatment with dapagliflozin 2.5 mg twice daily and 5 mg twice daily co-administered with Met achieved statistically significant lowering of A1C and support the use of dapagliflozin/Met IR FDC tablets as being equivalent to the administration of the individual monotherapy tablets.

Overview of the Phase 3 Fixed-Dose Combination Clinical Program for XigDuo

The dapagliflozin clinical development program was comprehensive and included 14 phase 3 studies designed to assess the safety and efficacy of dapagliflozin in a wide range of patients with type 2 diabetes. The use of dapagliflozin in combination with Met was assessed in a broad variety of clinical settings. Eleven phase 3 studies supported the safety and tolerability of dapagliflozin in combination with Met, while one phase 3 study of dapagliflozin monotherapy supported the safety and tolerability of q.d. dosing with either the morning or evening meals. As the safety and efficacy profiles of Met extended release (XR) and IR are similar, [22] studies conducted with both Met XR and Met IR provide supportive data for the proposed dapagliflozin/Met IR FDC.

Dapagliflozin has been studied in placebo-controlled and standard-of-care direct comparisons in:

- drug-naive patients at an early stage of disease
- patients who required additional therapy after failure to reach adequate glycemic control with their current regimen of oral antidiabetic drugs
- patients with later-stage disease who failed to reach glycemic goals with insulin therapy
- patients with cardiovascular disease and hypertension with inadequate glycemic control on standard care
- diabetic patients with moderate renal impairment.

Drug-naive patients were included in studies directly comparing dapagliflozin head-to-head with Met and with the initial combination of dapagliflozin plus Met. Head-to-head studies were also conducted comparing dapagliflozin plus Met with the sulfonylurea, glipizide, plus Met.

The efficacy of dapagliflozin in combination with Met is described in detail in the Common Technical Document Module 2.5 Clinical Overview[23] and subsequently summarized below. Overall, in combination with Met, dapagliflozin was associated with significant reductions in A1C. [23] Similarly, in combination with Met, dapagliflozin was associated with significant reductions in fasting plasma glucose (FPG). [23] Dapagliflozin was also associated with significant reductions in body weight when used in combination with Met. [23] Importantly, glycemic efficacy persisted up to 208 weeks, together with sustained weight loss and blood pressure reduction during long-term treatment. For additional details, please see Appendix 3 for an overview and the accompanying clinical summary for an expanded discussion of the clinical studies of dapagliflozin in combination with Met.

The dapagliflozin/Met FDC program included one pivotal phase 3 study (D1691C00003) that investigated the efficacy and safety of dapagliflozin 2.5 mg twice daily, 5 mg twice daily, and 10 mg daily co-administered with Met ≥ 1,500 mg/day, compared with placebo plus Met. The findings from this study support the consistent efficacy of dapagliflozin 5 mg twice daily, along with the benchmark efficacy

observed with dapagliflozin 10 mg daily, both co-administered with Met (Table 1 and Section 2.1.1). Moreover, the BE of XigDuo with the individual components (dapagliflozin + Met) under fed and fasted conditions was demonstrated in the pivotal Canadian BE study (D1691C00007) (Table 1 and Section 2.4).

TABLE 1: PIVOTAL STUDIES

Study Name	Design	Objectives	Population
Canadian Bioequivalence Study D1691C00007 NCT01535677	Open-label, single centre, randomized, 4-period, 4-treatment, 4-way crossover study	Determine the BE of the Met IR FDC tablet of dapagliflozin/Met (5 mg/ 850 mg) relative to single tablets of dapagliflozin (5 mg) and Met (850 mg) Glucophage (marketed in Canada by Sanofi-aventis) administered together in healthy volunteers under fasted and fed conditions: • Dapagliflozin and Met AUC, $AUC_{(0-t)}$, and C_{max} • Dapagliflozin and Met t_{max}, t_{last}, λ_z, and $t_{1/2}$.	Men or women aged ≥ 18 to ≤ 55 years old, healthy adult volunteers.
Placebo-Controlled b.i.d. Study D1691C00003 NCT01217892	Double-blind, placebo-controlled, multi-centre, randomized, parallel assignment study	Examine the dapagliflozin treatment regimens of 2.5 mg b.i.d. and 5 mg b.i.d. co-administered with Met therapy: • Compare the change from baseline in A1C with each b.i.d. dose of dapagliflozin co-administered with Met versus placebo co-administered with Met at 16 weeks. • Examine changes in body weight from baseline to week 16, changes in FPG from baseline to week 1 and week 16, and proportion of subjects with baseline A1C ≥ 7.0% that achieved A1C levels < 7%.	Men or women aged ≥ 18 to ≤ 77 years old with T2DM, treated with stable doses of Met monotherapy ≥ 1,500 mg/day for at least 10 weeks prior to enrolment and showed inadequate glycemic control (A1C ≥ 6.7% and ≤ 10.5% at screening or A1C ≥ 6.5% and ≤ 10.0% 1 week before randomization).

A1C = glycated hemoglobin; AUC = area under the curve (from 0 to t); BE = bioequivalence; b.i.d. = twice a day; C_{max} = maximum concentration (peak exposure); FDC = fixed-dose combination; FPG = fasting plasma glucose; IR = immediate release; Met = metformin; T2DM = type 2 diabetes mellitus.

2.1 Pivotal Clinical Studies

2.1.1 Placebo-controlled b.i.d. study (D1691C00003)

Overall, this study demonstrated that dapagliflozin taken twice daily in combination with Met provides significant reductions in A1C, FPG, and body weight from baseline to week 16 compared with placebo in combination with Met. [25] Moreover, the study demonstrated that the twice daily administration of 5 mg dapagliflozin provides equivalent efficacy to 10 mg dapagliflozin taken q.d., both co-administered with Met.

2.2 Study Characteristics

This pivotal double-blind, placebo-controlled, multi-centre, randomized, parallel assignment phase 3 study investigated the efficacy and safety of dapagliflozin treatment regimens of 2.5 mg twice daily and 5 mg twice daily co-administered with Met therapy, compared with placebo plus Met. The primary end point was change from baseline A1C at week 16. Secondary end points included changes in FPG level and body weight.

TABLE 2: STUDY CHARACTERISTICS OF D1691C00003

Characteristics		Details for *(D1691C00003)*
STUDY DESIGN	**Objective**	Pivotal efficacy and safety
	Blinding	Double-blind
	Study period	2010-2011 to 2011-2008
	Study centres	This international study was conducted at 53 centres in Europe and South Africa.
	Design	Superiority RCT
STUDY POPULATION	**Randomized (N)**	400[a]
	Inclusion criteria	• Men or women aged ≥ 18 to ≤ 77 years old • Diagnosis of T2DM • Patients were treated with stable doses of Met monotherapy ≥ 1,500 mg/day monotherapy for at least 10 weeks prior to enrolment • A1C ≥ 6.7% and ≤ 10.5% at screening or A1C ≥ 6.5% and ≤ 10.0% one week prior to randomization
	Exclusion criteria	• Patients with endocrine and metabolic disorders (e.g., T1DM, diabetic ketoacidosis, symptoms of poorly controlled diabetes, FPG > 15 mmol/L, BMI > 45 kg/m^2, history of bariatric surgery, diabetes insipidus, TSH, and free T4 values outside normal range) • Patients with kidney, hepatic, cardiovascular, hematologic/oncologic, infectious disease/immunologic, musculoskeletal disorders and conditions[b] • Patients who were pregnant or breastfeeding • Patients using antihyperglycemic medications (other than Met) 10 weeks prior to enrolment, or use of insulin within 24 weeks of enrolment
DRUGS	**Intervention**	• Dapagliflozin (2.5 mg) orally, b.i.d. + open-label Met IR (500 mg tablets)[c] orally b.i.d. to 1,500, 2,000, or 2,500 mg/day • Dapagliflozin (5.0 mg) orally, b.i.d. + open-label Met IR (500 mg tablets)[c] orally b.i.d. to 1,500, 2,000, or 2,500 mg/day • Dapagliflozin (10 mg), orally, q.d. + open-label Met IR (500 mg tablets) [c] orally b.i.d. to 1,500, 2,000, or 2,500 mg/day
	Comparator(s)	Placebo orally, b.i.d. + open-label Met IR (500 mg) orally b.i.d. to 1,500, 2,000, or 2,500 mg/day
DURATION	**Run-in**	4 weeks
	Treatment	16 weeks
	Follow-up	4 weeks
OUTCOMES	**Primary end point(s)**	• Adjusted mean change in A1C levels from baseline following 16 weeks of double-blind treatment
	Other end points	• Adjusted per cent change in body weight from baseline at week 16 • Adjusted mean change in FPG from baseline to week 1 • Adjusted mean change in FPG from baseline to week 16 • Proportion of participants who achieved A1C < 7.0% at 16 weeks in subjects with an A1C ≥ 7.0% at baseline

Characteristics		Details for *(D1691C00003)*
NOTES	**Publications**	• Schumm-Draeger et al. (2015) [25] • Clinicaltrials.gov identification code: NCT01217892

A1C = glycated hemoglobin; b.i.d. = twice a daily; BMI = body mass index; FPG = fasting plasma glucose; IR = immediate release; Met = metformin; q.d. =once daily; RCT = randomized controlled trial; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TSH = thyroid-stimulating hormone.

[a] Overall, 400 patients were randomized. The full analysis set included 399 patients. In the dapagliflozin 5 mg b.i.d. group, the full analysis set included one less patient than the safety analysis set (N = 400) because of a lack of post-baseline efficacy values. [24]

[b] Kidney disorders was defined as: creatinine clearance: < 60 mL/minute (calculated by the Cockcroft-Gault formula) or a measured serum creatinine value of 133 µmol/L for male patients and 124 µmol/L for female patients, or urine albumin: creatinine ratio > 1,800 mg/g, or a history of unstable or rapidly progressing kidney disease, or a known condition of familial renal glucosuria. Cardiovascular disorders were defined as: congestive heart failure defined as New York Heart Association Class III or IV, unstable or acute congestive heart failure, or significant cardiovascular history within the past 3 months prior to the screening visit, defined as: myocardial infarction, unstable angina pectoris, transient ischemic attack, unstable or previously undiagnosed arrhythmia, cardiac surgery or revascularization (coronary angioplasty or bypass grafts), or cerebrovascular accident. In addition, patients who have unstable cardiovascular disease at enrolment in the judgment of the investigator are excluded from the study. Or blood pressure (BP): at enrolment (visit 1): systolic BP ≥ 170 mm Hg and/or diastolic BP ≥ 110 mm Hg, and at randomization (visit 4): systolic BP ≥ 160 mm Hg and/or diastolic BP ≥ 100 mm Hg. Musculoskeletal disorders was defined as: creatine kinase (CK) > 3x upper limit of normal, or a history of drug-induced myopathy or drug-induced CK elevation.

[c] Met IR 500 mg was adjusted to 1,500 mg, 2,000 mg, or 2,500 mg according to the pre-specified adjustment table during the 4-week lead-in period and continued during 16-week double-blind treatment period.

a) Intervention and Comparators

Dapagliflozin (2.5 mg and 5 mg) or matching placebo were taken twice daily; dapagliflozin (10 mg) or matching placebo were taken q.d. in the morning. Met (500 mg tablets, for a total q.d. dose of 1,500 mg, 2,000 mg, or 2,500 mg) was taken orally with food — once with breakfast and once with the evening meal — during the study period.

Doses were:

- Dapagliflozin 2.5 mg and 5 mg tablets, administered orally b.i.d. for the 16-week double-blind treatment period
- Dapagliflozin 10 mg tablets, administered orally q.d. in the morning for the 16-week double-blind treatment period
- Placebo administered orally twice daily for the 4-week placebo lead-in period, and the 16-week double-blind treatment period
- Open-label Met IR 500 mg tablets, administered orally b.i.d. at doses of ≥ 1,500 mg/day (adjusted to 1,500 mg, 2,000 mg, or 2,500 mg, according to a pre-specified adjustment table during the 4-week lead-in period and continued for the 16-week double-blind treatment period).

Concomitant medications such as non-antidiabetic medications (e.g., antihypertensive, diuretic, and lipid-lowering drugs) were permitted; however, changes in dosing were avoided unless medically indicated. The total daily dose of the following medications had to be reported: Met, insulin, diuretics, antihypertensive agents, and 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors (statins). Other medications considered necessary for the patient's safety and well-being were permitted at the discretion of the investigator. After having completed or discontinued the study, subjects had to receive usual care antidiabetic treatment according to the investigator's judgment and according to local medical practice. [25]

b) Outcomes (As Described in the Clinical Study Report [24; 26])

The outcomes subsequently described below are as reported in the Clinical Study Report for study D1691C00003.

Primary end point: A1C was the clinical and regulatory parameter of choice for monitoring glycemic control because of the well-established correlation between A1C and diabetic microvascular complications.[27] The primary efficacy objective of this study was to compare the change from baseline in A1C achieved with dapagliflozin 2.5 mg twice daily and 5 mg twice daily co-administered with Met versus placebo co-administered with Met following 16 weeks of double-blind treatment.[24; 25; 27]

Secondary end points: Key secondary end points included the per cent change from baseline in body weight, change from baseline in FPG achieved at weeks 1 and 16, and the proportion of patients with A1C levels ≥ 7% at baseline and A1C levels < 7% following 16 weeks of double-blind treatment.[24; 25] The testing of key secondary variables was performed in the following order: per cent change in body weight from baseline to week 16, change in FPG from baseline to week 1, change in FPG from baseline to week 16, and proportion of subjects with A1C < 7.0% in subjects with A1C ≥ 7% at baseline.[27] Additional secondary end points included the change from baseline in seated systolic and diastolic blood pressure. Secondary objectives and assessments were identical for the benchmark treatment group with dapagliflozin 10 mg q.d.[25]

The safety and tolerability evaluations of dapagliflozin co-administered with Met included analyses of adverse events (AEs), such as hypoglycemic events, laboratory values, vital signs (electrocardiogram, blood pressure), calculated creatinine clearance (CL_{Cr}), estimated glomerular filtration rate (eGFR), and physical examination findings.[24; 25]

For the evaluation of hypoglycemic events, this study used the definitions provided in the Committee for Proprietary Medicinal Products guidance on clinical investigation of medicinal products in the treatment of diabetes, as described here:

- major hypoglycemic events, defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour, with a capillary or plasma glucose value of < 54mg/dL (< 3.0 mmol/L), and prompt recovery after glucose or glucagon administration
- minor hypoglycemic event, defined as either a symptomatic episode with a capillary or plasma glucose measurement of < 63mg/dL (< 3.5 mmol/L) regardless of the need for external assistance, or an asymptomatic capillary or plasma glucose measurement below 63 mg/dL (3.5 mmol/L) that does not qualify as a major episode
- events suggestive of hypoglycemia, defined as a symptomatic event without a confirmatory blood glucose measurement.

c) Statistical Analyses (As Described in the Clinical Study Report, Section 5.7.1.1[24])

A statistical analysis plan outlining all planned analyses was prepared before the unblinding of the data.[24]

All efficacy analyses were based on the full analysis set. Randomized patients receiving at least one dose of double-blind study medication, with baseline values and at least one post-baseline value for an efficacy variable, were included in the full analysis set. At week 16, missing values were to be replaced by last observation carried forward (LOCF). The primary efficacy variable of change from baseline in A1C also had to be analyzed using the per-protocol analysis set if more than 10% of the subjects in any regimen were found to significantly violate the terms and conditions of the protocol. The study had a power of 90% to detect a 0.5% difference in mean change from baseline in A1C using a two-sample *t*-test at a 0.025 two-sided significance level.

3. RESULTS

3.1 Baseline Characteristics

Baseline demographic characteristics of patients enrolled in the pivotal D1691C00003 phase 3 study are presented in Table 3.

TABLE 3: BASELINE DEMOGRAPHIC CHARACTERISTICS OF PATIENTS ENROLLED IN D1691C00003 PHASE 3 STUDY

Variable (Unit) Statistic/Category	PLA + Met	DAPA 2.5 mg b.i.d. + Met	DAPA 5 mg b.i.d. + Met	DAPA 10 mg q.d. + Met	Total
	N = 101	N = 100	N = 99	N = 99	N = 399
Age (years)					
Mean (SD)	58.5 (9.40)	58.3 (9.01)	55.3 (9.34)	58.5 (9.78)	57.7 (9.45)
Min, Max	34, 76	34, 77	31, 75	31, 76	31, 77
Age categorization (%)					
< 65	77 (76.2)	77 (77.0)	85 (85.9)	70 (70.7)	309 (77.4)
≥ 65 and < 75	23 (22.8)	21 (21.0)	13 (13.1)	27 (27.3)	84 (21.1)
≥ 75	1 (1.0)	2 (2.0)	1 (1.0)	2 (2.0)	6 (1.5)
Gender (%)					
Male	47 (46.5)	37 (37.0)	46 (46.5)	49 (49.5)	179 (44.9)
Race					
White	82 (81.2)	79 (79.0)	84 (84.8)	81 (81.8)	326 (81.7)
Black/African American	5 (5.0)	10 (10.0)	5 (5.1)	6 (6.1)	26 (6.5)
Asian	10 (9.9)	8 (8.0)	7 (7.1)	3 (3.0)	28 (7.0)
Other	4 (4.0)	3 (3.0)	3 (3.0)	9 (9.1)	19 (4.8)
BMI categorization (%)					
< 25 kg/m^2	7 (6.9)	2 (2.0)	5 (5.1)	6 (6.1)	20 (5.0)
≥ 25 kg/m^2	94 (93.1)	98 (98.0)	94 (94.9)	93 (93.9)	379 (95.0)
≥ 27 kg/m^2	87 (86.1)	91 (91.0)	88 (88.9)	85 (85.9)	351 (88.0)
≥ 30 kg/m^2	62 (61.4)	70 (70.0)	70 (70.7)	67 (67.7)	269 (67.4)
Prior history of CVD (%)					
Yes	81 (80.2)	86 (86.0)	84 (84.8)	86 (86.9)	337 (84.5)
Hypertension only	43 (42.6)	50 (50.0)	48 (48.5)	45 (45.5)	186 (46.6)
At least one other than hypertension	38 (37.6)	36 (36.0)	36 (36.4)	41 (41.4)	151 (37.8)
No	20 (19.8)	14 (14.0)	15 (15.2)	13 (13.1)	62 (15.5)
CHF					
Yes	4 (4.0)	4 (4.0)	4 (4.0)	5 (5.1)	17 (4.3)
NYHA Class I	3 (3.0)	1 (1.0)	1 (1.0)	2 (2.0)	7 (1.8)
NYHA Class II	1 (1.0)	3 (3.0)	3 (3.0)	3 (3.0)	10 (2.5)
No	97 (96.0)	96 (96.0)	95 (96.0)	94 (94.9)	382 (95.7)
Duration of Type 2 Diabetes (Years)					
Mean (SD)	5.53 (4.23)	4.80 (3.87)	5.12 (4.20)	5.45 (4.05)	5.23 (4.08)
Min, Max	0.2, 25.0	0.3, 19.2	0.5, 24.7	0.2, 18.6	0.2, 25.0
A1C (%)					
Mean (SD)	7.94 (0.85)	7.77 (0.75)	7.78 (0.76)	7.71 (0.71)	7.80 (0.77)

Variable (Unit) Statistic/Category	PLA + Met	DAPA 2.5 mg b.i.d. + Met	DAPA 5 mg b.i.d. + Met	DAPA 10 mg q.d. + Met	Total
	N = 101	N = 100	N = 99	N = 99	N = 399
Min, Max	6.4, 10.0	6.6, 10.1	6.5, 11.2	6.3, 9.6	6.3, 11.2
FPG (mmol/L)					
Mean (SD)	8.76 (1.99)	8.51 (1.85)	8.62 (1.77)	8.62 (2.01)	

A1C = glycated hemoglobin; b.i.d. = twice daily; BMI = body mass index; CHF = congestive heart failure; CVD = cardiovascular disease; DAPA = dapagliflozin; FPG = fasting plasma glucose; Met = Met; Min, Max = minimum, maximum; NYHA = New York Heart Association; PLA = placebo; q.d. = once daily; SD = standard deviation.
Note: Percentages reported are based on the total number of subjects in each treatment group; race subgroup of "Other" includes Native Hawaiian or other Pacific Islander, American Indian/Alaska Native, or other. All values are taken from Tables 10, 11, and 13 of D1691C00003 Clinical Study Report.[24] FPG values taken from published report of trial given reporting in SI units (mmol/L) (mg/dL values are reported in the Clinical Study Report).[25]

In general, the treatment groups were balanced in demographic and baseline characteristics (Table 3). The mean age was 58 years old. The proportions of men and women were similar in all groups, with approximately 45% men and 55% women. Around two-thirds of the subjects were obese (BMI ≥ 30 kg/m^2), and approximately 38% of the subjects had at least one history of cardiovascular disease other than hypertension. A total of 4.3% of subjects had congestive heart failure defined as New York Heart Association Class I and II.[24; 28]

Overall, treatment groups were also balanced in diabetes-related baseline characteristics. Mean duration of type 2 diabetes was 5.23 years, and 12.0% of the subjects had a duration of more than 10 years. At baseline, mean A1C was 7.80%, and mean FPG was approximately 8.63 mmol/L. The mean background dose of Met at enrolment and at randomization was around 1,900 mg/day in both treatment groups.[24; 28]

3.1.1 Patient Disposition

In total, 520 subjects were enrolled and 428 subjects entered the lead-in period (Table 4). The most common reasons for not entering the lead-in period were incorrect enrolment and withdrawal of consent. Overall, 400 subjects were randomized. More than 90% of randomized subjects completed the 16-week double-blind treatment period, with few discontinuations (n = 30). Three subjects were withdrawn from the study due to AEs.

TABLE 4: SUMMARY OF PATIENT DISPOSITION FOR D1691C00003

Disposition	D1691C00003				
	PLA + Met	DAPA 2.5 mg b.i.d. + Met	DAPA 5 mg b.i.d. + Met	DAPA 10 mg q.d. + Met	Total
Enrolled, N					528
Randomized, N	101	100	100	99	400
Discontinued from treatment period, N (%)	8 (7.9)	7 (7.0)	6 (6.0)	9 (9.1)	30 (7.5)
***WDAEs,* N (%)**	0	1 (1.0)	1 (1.0)	1 (1.0)	3 (0.8)
Incorrect enrolment	0	0	1 (1.0)	1 (1.0)	2 (0.5)
Subject no longer meets study criteria, N (%)	8 (7.9)	5 (5.0)	2 (2.0)	4 (4.0)	19 (4.8)
Subject withdrew consent, N (%)	0	0	2 (2.0)	1 (1.0)	3 (0.8)

Disposition	D1691C00003				
	PLA + Met	DAPA 2.5 mg b.i.d. + Met	DAPA 5 mg b.i.d. + Met	DAPA 10 mg q.d. + Met	Total
Poor/non-compliance	0	0	0	1 (1.0)	3 (0.8)
Other	0	1 (1.0)	0	1 (1.0)	2 (0.5)
Subjects completing study, N (%)	93 (92.1)	93 (93.0)	94 (94.0)	90 (90.9)	370 (92.5)
Reasons for not completing study, N (%)					
WDAEs, N (%)	0	1 (1.0)	1 (1.0)	1 (1.0)	3 (0.8)
Incorrect enrolment	0	0	1 (1.0)	1 (1.0)	2 (0.5)
Subject no longer meets study criteria, N (%)[a]	8 (7.9)	5 (5.0)	2 (2.0)	4 (4.0)	19 (4.8)
Subject withdrew consent, N (%)	0	0	2 (2.0)	1 (1.0)	3 (0.8)
Poor/non-compliance	0	0	0	1 (1.0)	1 (0.3)
Other	0	1 (1.0)	0	1 (1.0)	2 (0.5)
Full analysis set, N	101	100	99	99	399
Per-protocol, N	101	98	95	96	390
Safety, N	101	100	100	99	400

b.i.d. = twice a day; DAPA = dapagliflozin; PLA = placebo; Met = metformin; q.d. = once daily; WDAEs = withdrawal due to adverse events.

Note: percentages reported are based on the total number of subjects in each treatment group; All values are taken from Table 7 and 8 of D1691C00003 Clinical Study Report.[24]

[a] The most common reason for discontinuation was that the patient no longer met the study criteria; however, the manufacturer did not define or explain in the Clinical Study Report what this meant. The Health Canada clinical reviewer report[2] indicated that a total of 19 subjects were discontinued due to the reason that the patient no longer met the study criteria. Seven of the 19 subjects discontinued because of a lack of glycemic control (5 placebo; 1 dapagliflozin 2.5 mg; 1 dapagliflozin 10 mg). Twelve of the 19 subjects discontinued because of decreased creatinine clearance (3 placebo; 4 dapagliflozin 2.5 mg; 2 dapagliflozin 5 mg; 3 dapagliflozin 10 mg). The subjects who were discontinued because of decreased creatinine clearance were not the same subjects who were discontinued because of a lack of glycemic control.

3.1.2 Efficacy (As Reported in Clinical Study Report, Section 7.1.1 & Section 7.1.2[24])

a) Primary efficacy end point

Compared with placebo, dapagliflozin was superior in reducing A1C from baseline to week 16 (LOCF). A reduction in A1C at week 16 (LOCF) compared with baseline was observed in all treatment arms (Table 5). The adjusted mean change from baseline in A1C at week 16 (LOCF) showed statistically significant reductions of –0.65% (95% CI, –0.77 to –0.53) in the dapagliflozin 5 mg b.i.d.treatment group and –0.52% (95% CI, –0.63 to –0.40) in the dapagliflozin 2.5 mg b.i.d. treatment group.[27] Treatment with dapagliflozin 10 mg daily resulted in an adjusted mean change from baseline in A1C of –0.59% (95% CI, –0.70 to –0.47), which was consistent with results achieved in the dapagliflozin 5 mg b.i.d. treatment group. The placebo treatment group showed an adjusted mean change from baseline in A1C of –0.30% (95% CI, –0.42 to –0.18).[27]

TABLE 5: PRIMARY END POINT AT WEEK 16

	Placebo + Met N = 101	Dapa 2.5 mg b.i.d. + Met N = 100	Dapa 5 mg b.i.d. + Met N = 99	Dapa 10 mg q.d. + Met N = 99
A1C (%)				
Baseline (mean)	7.94	7.78	7.79	7.71
Change from baseline	–0.30	–0.52 (–0.63 to	–0.65 (–0.77 to	–0.59 –0.70 to

	Placebo + Met N = 101	Dapa 2.5 mg b.i.d. + Met N = 100	Dapa 5 mg b.i.d. + Met N = 99	Dapa 10 mg q.d. + Met N = 99
(adjusted mean) (95% CI)	(–0.42 to –0.18)	–0.40)	–0.53)	–0.47)
Difference from Placebo + Met (95% CI)		–0.22 (–0.38 to –0.05) *P* = 0.0106	–0.35 (–0.52 to –0.18) *P* < 0.0001	–0.29 (–0.45 to –0.12) *P* = 0.0007

Source: Table 16 of D1691C00003 Clinical Study Report.[24]
A1C = glycated hemoglobin; b.i.d. = twice a day; Dapa = dapagliflozin; CI = confidence interval; Met = metformin; q.d. = once daily.

Dapagliflozin 5 mg b.i.d. provided greater placebo-corrected mean reductions in A1C (–0.35%) compared with dapagliflozin 2.5 mg b.i.d. (–0.22%). The placebo-corrected mean reductions in A1C were statistically significant for both dapagliflozin 2.5 mg b.i.d. and 5 mg b.i.d. treatment groups. The placebo-corrected mean reduction in A1C was –0.29% (95% CI, –0.45 to –0.12) for the dapagliflozin 10 mg daily group, which was consistent with results achieved in the dapagliflozin 5 mg b.i.d. treatment group (–0.35%; 95% CI, –0.52 to –0.18).[27] In the dapagliflozin group, the course of A1C reduction was faster from baseline to week 8 than from week 8 to week 16, and faster during both of these periods compared with the A1C reduction in the placebo group. In the placebo group, A1C reduction followed a slow linear pattern across the complete 16-week period.

b) Secondary efficacy end points

There was a mean reduction in body weight in all treatment groups from baseline to week 16 (LOCF), with the largest reduction seen in the dapagliflozin groups (Table 6). The placebo-adjusted mean per cent change from baseline to week 16 (LOCF) was –1.82%, –2.18%, and –1.73 % in the dapagliflozin 2.5 mg b.i.d., 5 mg b.i.d., and 10 mg daily groups, respectively.[24; 27] The respective *P* value for the difference between treatment groups was *P* < 0.0001 in all dapagliflozin groups. The per cent decrease in total body weight occurred relatively faster during the first week and decreased steadily in the dapagliflozin treatment groups over time to week 16 (D1691C00003 Clinical Study Report[24]).

TABLE 6: SECONDARY END POINTS AT WEEK 16

	Placebo + Met N = 101	Dapa 2.5 mg b.i.d. + Met N = 100	Dapa 5 mg b.i.d. + Met N = 99	Dapa 10 mg q.d. + Met N = 99
Body weight (kg)				
Baseline (mean)	88.82	92.49	93.62	90.58
Mean per cent change from baseline (adjusted mean) (95% CI)	–1.04 (–1.65 to –0.43)	–2.84 (–3.45 to –2.23)	–3.20 (–3.82 to –2.59)	–2.76 (–3.36 to –2.15)
Difference from Placebo + Met (95% CI)		–1.82 (–2.53 to –1.10) *P* < 0.0001	–2.18 (-2.89 to –1.46) *P* < 0.0001	–1.73 (–2.44 to –1.01) *P* < 0.0001
FPG (mmol/L)				
Baseline (mean)	8.76	8.51	8.62	8.62
Mean change from baseline (adjusted mean) (95% CI)	–0.58 (–0.87 to –0.28)	–1.15 (–1.45 to –0.85)	–1.42 (–1.73 to –1.12)	–1.13 (–1.43 to –0.84)
Difference from Placebo + Met (95% CI)		–0.58 (-0.92 to –0.23) *P* = 0.0010	–0.85 (–1.19 to –0.51) *P* < 0.001	–0.56 (–0.90 to –0.22) *P* = 0.0015

	Placebo + Met N = 101	Dapa 2.5 mg b.i.d. + Met N = 100	Dapa 5 mg b.i.d. + Met N = 99	Dapa 10 mg q.d. + Met N = 99
Subjects with A1C < 7.0% at week 16				
X/N#	17/87	32/89	37/90	22/81
Per cent adjusted (95% CI)	21.4% (13.2 to 29.6)	33.6% (24.6 to 42.5)	38.2% (29.1 to 47.3)	28.1% (19.0 to 37.1)
Difference vs. Placebo + Met (95% CI)		12.2% (0.2 to 24.1) *P* = 0.0455	16.8% (4.8 to 28.9) *P* = 0.0062	6.7% (–5.3 to 18.7) *P* = 0.2755

Source: Table 16 of D1691C00003 Clinical Study Report[24] FPG values taken from published report of trial given reporting in SI units (mmol/L) (mg/dL values are reported in the Clinical Study Report).[25]
A1C = glycated hemoglobin; b.i.d. = twice a day; CI = confidence interval; Dapa = dapagliflozin; FPG = fasting plasma glucose; Met = metformin; q.d. = once daily; vs. = versus.

Dapagliflozin showed an effect in the lowering of mean FPG in all dapagliflozin treatment groups from baseline to week 16 (LOCF) (Table 6). The placebo-adjusted reduction from baseline was 0.58 (*P* = 0.001), 0.85 (*P* < 0.0001), and 0.56 mmol/L (*P* = 0.0015) in the dapagliflozin 2.5 mg b.i.d., 5 mg b.i.d., and 10 mg daily groups, respectively. In the dapagliflozin groups, most of the decrease in FPG was already observed at week 1, and then continued in a slower fashion. In the placebo group, FPG showed a small increase at week 1, followed by a relatively constant decrease in FPG until week 16.

The proportion of subjects with A1C below 7% at week 16 (LOCF) who had an A1C ≥ 7% at baseline was larger in the dapagliflozin treatment groups (33.6%, 38.2%, and 28.1% in the dapagliflozin 2.5 mg b.i.d., 5 mg b.i.d., and 10 mg daily groups) than in the placebo group (21.4%) (Table 6). The difference was statistically significant in the dapagliflozin 2.5 mg b.i.d. (*P* = 0.0455) and 5 mg b.i.d. group (*P* = 0.0062). The placebo-adjusted proportions were 12.2%, 16.8%, and 6.7% in the dapagliflozin 2.5 mg b.i.d., 5 mg b.i.d., and 10 mg daily groups, respectively. The exploratory *P* value for the difference between the dapagliflozin 10 mg daily group and placebo was > 0.05.[24]

3.2 Critical Appraisal of Pivotal Clinical Studies

3.2.1 Internal Validity

Randomization was stratified according to baseline A1C, and adequate measures appear to have been taken to maintain allocation concealment, although no procedures to confirm this were described. Blinding was achieved through the use of a placebo matched in appearance to the study drug. There are adverse effects associated with sodium-dependent glucose co-transporter inhibitors that could potentially lead to unblinding, most notably urogenital infections, as these are events that are relatively common and readily detectable by the patient.

A Bonferroni procedure for multiple tests of significance was used to control the overall type 1 error rate for the two treatment group comparisons (dapagliflozin 2.5 mg b.i.d. and 5 mg b.i.d.) versus placebo for the primary efficacy variable. Further testing of treatment group(s) versus placebo for key secondary variables was performed using a hierarchical, fixed-sequence testing procedure such that testing proceeded only if the primary efficacy variable was found to be significant. The manufacturer appears to have adhered to their stated hierarchical testing procedure.

Missing data were generally imputed by use of LOCF in the primary analyses. This is an appropriate but conservative method for imputation that may impact findings. The percentages of patients who dropped out were balanced between treatment arms, ranging from 6.0% in the dapagliflozin 5 mg twice-daily arm to 9.1% in dapagliflozin 10 mg daily arm. Sensitivity analyses were generally carried out in order to support these primary analyses and this thus mitigates any concern with using this method.

No statistical comparisons were made between the treatment groups dapagliflozin 10 mg daily and dapagliflozin 5 mg b.i.d., hence no conclusion regarding the comparative efficacy of these treatments to each other can be made.

The study inclusion and exclusion criteria appear appropriate, as well as the dosages chosen for this study. The length of the study meets the minimum duration (three months) required for establishing efficacy; however, the study duration was not sufficient for a thorough safety analysis. On the other hand, 10 mg daily is currently an approved dosage for dapagliflozin. The fact that in study D1691C00003 dapagliflozin 10 mg daily failed to reach statistical significance for the proportion of subjects reaching A1C below 7% (a key secondary efficacy variable) calls into question the robustness of the study design and efficacy results.

The distribution of patients based on baseline A1C stratification was not balanced between treatment groups. For instance, the dapagliflozin (DAPA) 10 mg daily group had more than twice (17.2%) as many patients with A1C < 7.0% than the DAPA 5 mg b.i.d. group, while the placebo group had more than twice (18.8%) as many patients with A1C ≥ 9.0% than any other treatment group. In addition, the placebo group had 68.3% of patients with baseline A1C ≥ 7.0% and < 9.0%, while 83%, 84.8%, and 76.8% of patients with baseline A1C ≥ 7.0% and < 9.0% in the treatment groups DAPA 2.5 mg b.i.d., DAPA 5 mg b.i.d., and DAPA 10 mg daily, respectively. Baseline A1C levels have an effect on treatment efficacy and/or effect size. The manufacturer incorporated baseline A1C levels into the analysis of covariance model, but the baseline effect is only stratified by < 7.0% or ≥ 7.0% at baseline.

3.2.2 External Validity

This pivotal study (D1691C00003) is the only phase III study conducted to evaluate the effect of dapagliflozin administered b.i.d. (5 mg) as an add-on to metformin IR to support the FDC of dapagliflozin and Met (5 mg/850 mg and 5 mg/1,000 mg). The maximum dose of Met as per the dosing regimen for the FDC is 2,000 mg/day. As 7% to 13% of study subjects had a Met dose higher than 2,000 mg/daily — the maximum recommended dose for the FDC at enrolment and at randomization — this might affect the generalizability of results in the clinical practise for use of the FDC tablet.

The included studies were not designed to assess key clinical outcomes such as morbidity and mortality, and this is reflected in the relatively small size and short follow-up in these studies. Type 2 diabetes mellitus is a chronic condition with multiple serious sequelae that take years, perhaps decades, to develop; therefore, it is unlikely that a registration trial would be designed to address these key outcomes. A1C is a widely used surrogate marker for glycemic control, and was thus the primary outcome of all but one of the included studies. However, although improvement in A1C has been linked to improvement in these clinical outcomes, the exact nature of the changes in A1C that are needed to achieve clinical benefit have not been fully elucidated.

The included study had a majority of patients identified as "White" (more than 80% of the population in most studies), with Asians and Blacks being the next most common ethnic groups. The included clinical study had no Canadian sites, and this may be a generalizability issue for overall Canadians, especially for patients of Aboriginal descent given how common type 2 diabetes is among Aboriginal Canadians. There may be differences in the standard of care between Canada (particularly for the beneficiaries of public drug plans) and the European countries where the study was conducted.

Patients with recent cardiovascular events (examples include myocardial infarction and transient ischemic attack) or unstable cardiovascular disease were excluded from the study. Although it is understood that investigators want to have a stable population for the study, this may be a generalizability issue, as many of these types of patients would be candidates for add-on oral antidiabetic therapy such as dapagliflozin.

3.3 Summary of Safety

3.3.1 Safety evaluation plan

The safety and tolerability of dapagliflozin/Met IR FDC treatment in patients with type 2 diabetes mellitus is supported by the D1691C00003 trial.

Data for safety evaluations were collected on AEs, clinical laboratory tests, and vital signs (including electrocardiograms). Safety analyses were performed using all available data regardless of rescue during the treatment period specified. Additional analyses of hypoglycemia were performed excluding data after rescue and in a Dapa + Met Alone Pool, in which subjects treated with rescue medications and/or other background antihyperglycemic drugs were excluded.

Specific laboratory parameters were identified for more extensive monitoring, including: serum creatinine, serum sodium, serum CK, serum liver enzymes and total bilirubin, and plasma glucose. AEs of special interest for the dapagliflozin program included: hypoglycemia, genital infection, urinary tract infection including pyelonephritis (kidney infection), volume depletion, renal impairment or failure, fractures, polyuria, and hepatic events. In addition, cardiovascular events and malignancies were analyzed.

3.3.2 Safety populations evaluated

Dapagliflozin administered 2.5 mg or 5 mg b.i.d. was well-tolerated with a safety profile similar to that of dapagliflozin administered daily. Across all treatment groups, AEs and AEs leading to discontinuation from the study drug were similar (Table 7).[28] Serious adverse events (SAEs) were rare and slightly more frequent in groups receiving dapagliflozin (1.0% to 4.0%) compared to placebo (0.0%).[28] None of the SAEs were reported as related to the study medication, and no serious adverse event led to discontinuation. Additionally, no deaths were reported across all treatment groups.[28] Hypoglycemic events were rare and reported by 1.0% to 2.0% of dapagliflozin patients; whereas, no hypoglycemic events were reported in the placebo group.[28] No major episodes of hypoglycemia were reported across treatment groups, and no patient discontinued study treatment because of a hypoglycemic event.[28]

Events of genital infection were uncommon, and were reported as 0.0%, 5.0%, and 3.0% in the dapagliflozin 2.5 mg and 5 mg b.i.d., and dapagliflozin 10 mg daily groups, respectively, versus 1.0% in the placebo group (Table 7).[28] Similarly, urinary infection events were uncommon, occurring in 2.0%, 4.0%, and 2.0% in the dapagliflozin 2.5 mg and 5 mg b.i.d., and dapagliflozin 10 mg daily groups, respectively, compared with 1.0% for placebo.[28] No kidney infections were reported across all treatment groups. AEs of renal impairment were reported in similar proportions across all treatment groups; however, overall, there was no relevant change in renal function with dapagliflozin therapy.[28]

TABLE 7: SUMMARY OF PATIENTS WITH ADVERSE EVENTS IN STUDY D1691C00003 SAFETY ANALYSIS SET

	Placebo + Met N = 101	Dapa 2.5 mg b.i.d. + Met N = 100	Dapa 5 mg b.i.d. + Met N = 100	Dapa 10 mg q.d. + Met N = 99
At least one AE	37 (36.6)	40 (40.0)	33 (33.0)	46 (46.5)
At least one event of hypoglycemia	0	1 (1.0)	0	2 (2.0)
Death	0	0	0	0
At least one SAE	0	4 (4.0)	1 (1.0)	2 (2.0)
AE leading to discontinuation[a]	3 (3.0)	5 (5.0)	3 (3.0)	4 (4.0)
SAE leading to discontinuation[a]	0	0	0	0
Hypoglycemia leading to discontinuation[a]	0	0	0	0
At least one AE of genital infection	1 (1.0)	0	5 (5.0)	3 (3.0)
At least one AE of urinary tract infection	1 (1.0)	2 (2.0)	4 (4.0)	2 (2.0)

AE = adverse event; b.i.d. = twice daily; Dapa = dapagliflozin; Met = metformin; q.d. = once daily; SAE = serious adverse event.
[a] Discontinuation of study medication.

A small, dose-related, mean increase in hematocrit was reported in treatment groups receiving dapagliflozin IR; whereas, hematocrit did not change in the placebo group.[28] In two subjects receiving dapagliflozin, a marked laboratory abnormality of hematocrit > 55% was reported but was not associated with any thromboembolic event.[28] Slight mean increases in serum magnesium and decreases with serum uric acid level were reported with dapagliflozin treatment, and were reversible during follow-up.[28] Additionally, there were no reported signs of hepatic impairment in dapagliflozin-treated patients. A slight mean decrease in systolic blood pressure was reported in dapagliflozin treatment groups, while no meaningful change in diastolic blood pressure was reported.

3.4 Bioequivalence

In order to bridge the results of the phase 3 clinical studies, which utilized the individual dapagliflozin and Met monotherapy tablets, three biopharmaceutics studies were conducted (D1691C00007, D1691C00002, D1691C00005). The pivotal Canadian BE study (D1691C00007) compared dapagliflozin/Met 5 mg/850 mg FDC tablets to the individual monotherapy tablets, including a Canada-specific Met reference product, namely Glucophage marketed in Canada by Sanofi-Aventis, under both fasted and fed conditions.[23]

Overall, the data presented in this section illustrate the BE of XigDuo, with the individual components (dapagliflozin + Met) under fed and fasted conditions. Dapagliflozin has uncomplicated pharmacokinetic characteristics.[30] Met has non-linear pharmacokinetics (a less than proportional increase in exposure, with the increase in dose due to saturable absorption).[31] The pharmacokinetic properties XigDuo are similar to those of the individual components.

3.4.1 Canadian Bioequivalence Study (D1691C00007)

Key pharmacokinetic parameters and statistical comparisons of these parameters are presented in Table 8 for dapagliflozin and Met, based on the Canadian BE study (D1691C00007).[29]

The Canadian BE study (D1691C00007) was an open-label, randomized, four-period, four-treatment, four-way crossover study conducted to determine the BE of the Met immediate-release (IR), FDC tablet of dapagliflozin/Met (5 mg/850 mg) (XigDuo) relative to single tablets of dapagliflozin (5 mg) and Met (850 mg; Glucophage marketed in Canada by Sanofi-Aventis) administered together in healthy volunteers under fasted and fed conditions.

The Canadian BE study confirmed BE between the 5 mg/850 mg FDC XigDuo tablet and its respective individual monotherapy tablets after single-dose administration in the fasted and fed states. In the fasted state, the XigDuo formulation (5 mg/850 mg) was BE to the 5 mg dapagliflozin and 850 mg Met tablets with respect to total exposure, area under the curve (AUC) from 0 to t ($AUC_{[0-t]}$), and maximum concentration (peak exposure) (C_{max}) for both dapagliflozin and Met (90% CIs on the geometric least squares mean ratios were all within 80.00 to 125.00%) (Table 8).[29]

Food appeared to decrease dapagliflozin and Met C_{max} but not AUC in both the XigDuo and reference formulations. In the fed state, the XigDuo formulation (5 mg/850 mg) was BE to the 5 mg dapagliflozin and 850 mg Met tablets with respect to AUC, $AUC_{(0-t)}$, and C_{max} for both dapagliflozin and Met based on the Canadian BE requirements (Table 8).

Dapagliflozin and Met t_{max}, t_{last}, λ_z, and $t_{1/2}$ were comparable between the 5 mg dapagliflozin and 850 mg Glucophage tablets, and the dapagliflozin/Met (5 mg/850 mg) IR FDC tablet (XigDuo), following administration in the fasted state (Table 8).[29] Dapagliflozin and Met median t_{max} occurred at one and three hours post-dose, respectively, in both formulations. Median t_{last} was comparable between the two formulations for dapagliflozin at 54 hours post-dose but was shorter in the FDC tablet (XigDuo) at 60 hours compared with 66 hours in the reference tablets for Met.

Similarly, dapagliflozin and Met t_{max}, λ_z, and $t_{1/2}$ were comparable between the 5 mg dapagliflozin and 850 mg Glucophage tablets and the dapagliflozin/Met (5 mg/850 mg) IR FDC (XigDuo) tablet following administration in the fed state (Table 8).[29] Dapagliflozin and Met median t_{max} occurred at three and four hours post-dose, respectively, in both formulations. Median t_{last} was comparable between the two formulations for dapagliflozin at 60 hours post-dose but was longer in the FDC tablet at 72 hours compared with 60 hours in the reference tablets for Met.

Overall, for patients taking dapagliflozin and Met as separate tablets, XigDuo provides an effective maintenance treatment option with long-term efficacy benefits, as well as a reduced pill burden, increased convenience, and potentially improved adherence.

TABLE 8: BIOEQUIVALENCE PROFILE FOR COMBINATION PRODUCT[A]

Parameter	Treatment		N	Geometric Mean	Geometric Coefficient of Variation (%)	Geometric LS Mean	95% CI	Pairwise Comparison		
								Pair	Ratio (%)	90% CI (%)
Dapagliflozin										
AUC (ng*h/mL)	A	Free dose (fasted)	38	220	27.0	219.7	202.0 to 238.9	B/A	104.94	102.44 to 107.50
	B	FDC (fasted)	36	231	26.3	230.5	212.0 to 250.7	D/C	101.11	98.68 to 103.60
	C	Free dose (fed)	37	236	26.0	238.0	218.9 to 258.8	D/B	104.39	101.88 to 106.95
	D	FDC (fed)	36	243	27.4	240.6	221.3 to 261.7	C/A	108.34	105.77 to 110.98
$AUC_{(0-t)}$ (ng*h/mL)	A	Free dose (fasted)	38	214	26.6	213.6	196.7 to 232.1	B/A	104.85	102.31 to 107.44
	B	FDC (fasted)	36	224	26.0	224.0	206.2 to 243.4	D/C	100.93	98.47 to 103.45
	C	Free dose (fed)	37	230	25.6	231.2	212.8 to 251.2	D/B	104.19	101.65 to 106.79
	D	FDC (fed)	36	235	27.2	233.4	214.8 to 253.5	C/A	108.23	105.62 to 110.90
C_{max} (ng/mL)	A	Free dose (fasted)	38	58.6	30.4	58.81	53.28 to 64.91	B/A	101.45	92.14 to 111.69
	B	FDC (fasted)	36	59.7	29.1	59.66	53.92 to 66.01	D/C	116.36	105.62 to 128.20
	C	Free dose (fed)	37	31.9	34.7	31.83	28.81 to 35.18	D/B	62.09	56.34 to 68.43
	D	FDC (fed)	36	37.0	31.1	37.04	33.49 to 40.98	C/A	54.13	49.20 to 59.57
T_{max} (h) (Median [Min, Max])	A	Free dose (fasted)	38	Median (Min, Max): 1.00 (0.50, 2.00)						
	B	FDC (fasted)	36	Median (Min, Max): 1.00 (0.50, 2.00)						
	C	Free dose (fed)	37	Median (Min, Max): 3.00 (0.50, 8.02)						
	D	FDC (fed)	36	Median (Min, Max): 3.00 (1.50, 8.07)						
Met										
AUC (ng*h/mL)	A	Free dose (fasted)	37	9400	26.5	9,499	8,726 to 10,340	B/A	99.05	93.36 to 105.08
	B	FDC (fasted)	35	9370	29.6	9,409	8,632 to 10,260	D/C	101.84	95.67 to 108.42
	C	Free dose (fed)	33	8860	22.9	8,997	8,245 to 9,817	D/B	97.38	91.62 to 103.50
	D	FDC (fed)	34	9140	24.3	9,162	8,404 to 9,989	C/A	94.71	89.11 to 100.66
$AUC_{(0-t)}$ (ng*h/mL)	A	Free dose (fasted)	38	9430	27.0	9,460	8,691 to 10,300	B/A	98.99	93.48 to 104.82
	B	FDC (fasted)	36	9430	30.3	9,364	8,593 to 10,200	D/C	101.38	95.70 to 107.40
	C	Free dose (fed)	37	9010	24.4	8,945	8,214 to 9,742	D/B	96.85	91.42 to 102.60
	D	FDC (fed)	36	9130	24.2	9,069	8,323 to 9,881	C/A	94.56	89.32 to 100.11

Parameter	Treatment		N	Geometric Mean	Geometric Coefficient of Variation (%)	Geometric LS Mean	95% CI	Pairwise Comparison		
								Pair	Ratio (%)	90% CI (%)
C_{max} (ng/mL)	A	Free dose (fasted)	38	1480	27.4	1,493	1,380 to 1,615	B/A	101.51	95.24 to 108.18
	B	FDC (fasted)	36	1510	30.4	1,515	1,399 to 1,641	D/C	101.63	95.31 to 108.37
	C	Free dose (fed)	37	1140	17.7	1,131	1,045 to 1,224	D/B	75.87	71.15 to 80.91
	D	FDC (fed)	36	1150	20.9	1,150	1,062 to 1,245	C/A	75.78	71.13 to 80.74
T_{max} (h) (Median [Min, Max])	A	Free dose (fasted)	38	Median (Min, Max): 3.00 (1.00, 5.01)						
	B	FDC (fasted)	36	Median (Min, Max): 3.00 (1.50, 5.05)						
	C	Free dose (fed)	37	Median (Min, Max): 4.00 (1.00, 6.02)						
	D	FDC (fed)	36	Median (Min, Max): 4.00 (1.50, 5.02)						

AUC = area under curve; $AUC_{(0-t)}$ = area under curve from 0 to t; CI = confidence interval; C_{max} = maximum concentration; FDC = fixed-dose combination; h = hour; LS = least squares; Min = minimum; Max = maximum; Met = metformin; mL = millilitres; ng = nanogram; T_{max} = time at which the maximum concentration is observed.
[a]In accordance with current Health Canada bioequivalence standards and data requirements.
Note: All values were taken from Table S2 and S3 of D1691C00007 Clinical Study Report.[29]

4. PHARMACOECONOMIC EVALUATION

4.1 Manufacturer-Submitted Cost Information

A cost comparison of XigDuo (dapagliflozin/Met) and the individual components (dapagliflozin + Met) is provided in Table 9. Unit drug costing reflects the average drug prices across public plans and excludes markups and dispensing fees. The daily cost of XigDuo [redacted] previously submitted to CADTH as part of the Forxiga Standard CDR Submission filed on a Post-NOC Basis (April 2015) and on a New Indication Submission filed on a pre-NOC basis (September 2015). The price of XigDuo is a confidential price submitted by the manufacturer.

TABLE 9: COST COMPARISON OF NEW COMBINATION PRODUCT AND INDIVIDUAL COMPONENTS

Drug/Comparator	Strength	Dosage Form	Price[a] ($)	Recommended Daily Use	Daily Drug Cost[b] ($)
Combination product dapagliflozin/Met (XigDuo)	**5 mg/850 mg** **5 mg/1,000 mg**	Tablet Tablet	[redacted]	**b.i.d.** **b.i.d.**	[redacted]
Individual component A (Forxiga)	5 mg 10 mg	Tablet Tablet	[redacted]	q.d. q.d.	[redacted]
Individual component B (Met)	850 mg 500 mg	Tablet Tablet	$0.0610 $0.0444	b.i.d. q.i.d.	$0.1220 daily B $0.1776 daily B
Total (dapagliflozin + Met)	**10 mg q.d. + 850 mg b.i.d.** **10 mg q.d. + 500 mg q.i.d.**				[redacted]

b.i.d. = twice daily; Met = metformin; q.d. = once daily; q.i.d. = four times daily.
[a] The price for XigDuo is the manufacturer confidential price; prices for Forxiga reflect the manufacturer-submitted confidential price; prices for Met reflect the public formulary list prices across provinces; Met 850 mg is not a benefit covered by the Ontario Drug Benefit Program; therefore, the unit cost for this treatment reflects the average price among public plans (i.e., British Columbia, Alberta, Saskatchewan, Newfoundland and Labrador Prescription Drug Program, Nova Scotia).
[b] Daily cost excludes markups and dispensing fees.
Patent expiration for dapagliflozin is 2020-10-02 and 2023-05-15.
Met is available as a multisource generic pharmaceutical product across Canada.

Compared to the individual component combination of dapagliflozin and Met, calculations of drug costs indicate that XigDuo is cost-saving for all dosing regimens. The daily cost savings range from [redacted] to [redacted] per patient (Table 10). Monthly cost savings range from [redacted] to [redacted] per patient, and annual cost savings range from [redacted] to [redacted] per patient (Table 10).

TABLE 10: COST COMPARISON OF NEW COMBINATION PRODUCT AND INDIVIDUAL COMPONENTS

Drug/Comparator	Strength	Unit Cost[a] ($)	Daily Drug Cost[b] ($)	Monthly Drug Cost ($)	Annual Drug Cost ($)
Combination product dapagliflozin/Met (XigDuo)	**5 mg/850 mg** **5 mg/1,000 mg**	[redacted]	[redacted]	[redacted]	[redacted]
Individual component A (Forxiga)	5 mg q.d. 10 mg q.d.	[redacted]	[redacted]	[redacted]	[redacted]
Individual component B	850 mg b.i.d.	$0.0610	$0.1220	$3.7108	$44.5300

Drug/Comparator	Strength	Unit Cost[a] ($)	Daily Drug Cost[b] ($)	Monthly Drug Cost ($)	Annual Drug Cost ($)
(Met)	500 mg q.d.	$0.0444	$0.1776	$5.4020	$64.8240
Total (dapagliflozin +Met)	**10 mg q.d. + 850 mg b.i.d. 10 mg q.d. + 500 mg q.i.d.**		[redacted]	[redacted]	[redacted]
[redacted]					
Cost Difference (XigDuo —dapagliflozin + Met)	**5 mg/850 mg 5 mg/1,000 mg**		[redacted]	[redacted]	[redacted]

b.i.d.=twice daily; Met = metformin; q.d.=once daily; q.i.d.=four times daily.
[a]Price for XigDuo is the manufacturer confidential price; prices for Forxiga reflect the manufacturer-submitted confidential price; prices for Met reflect the public formulary list prices across provinces; Met 850 mg is not a benefit covered by the Ontario Drug Benefit Program; therefore, the unit cost for this treatment reflects the average price among public plans (i.e., British Columbia, Alberta, Saskatchewan, Newfoundland and Labrador Prescription Drug Program, Nova Scotia).
[b]Daily cost excludes markups and dispensing fees.

In the base-case analysis provided in Table 9 and described earlier, additional costs to provincial drug plans such as markups and dispensing fees were excluded. Given that these fees are a relevant cost consideration for provincial drug plans, a sensitivity analysis which considered these costs is provided in Table 11. Compared to the individual component combination of dapagliflozin and Met when considering markups and dispensing fees, calculations indicate that XigDuo provides additional cost savings (Table 11). The daily cost savings range from [redacted] to [redacted] per patient, monthly cost savings range from [redacted] to [redacted] per patient, and annual cost savings range from [redacted] to [redacted] per patient.

TABLE 11: COST COMPARISON OF NEW COMBINATION PRODUCT AND INDIVIDUAL COMPONENTS INCLUDING 10% MARKUP AND $7.00 PHARMACY FEE (PER 90-DAY SUPPLY)

Drug/Comparator	Strength	Price[a] ($)	Recommended Daily Use	Daily Drug Cost[b] ($)
Combination product dapagliflozin/Met (XigDuo)	**5 mg/850 mg 5 mg/1,000 mg**	[redacted]	**b.i.d. b.i.d.**	[redacted]
Individual component A (Forxiga)	5 mg 10 mg	[redacted]	q.d. q.d.	[redacted]
Individual component B (Met)	850 mg 500 mg	$0.0610 $0.0444	b.i.d. q.i.d.	$0.2120 daily B $0.2731 daily B
Total (dapagliflozin +Met)	**5 mg q.d. + 850 mg b.i.d. 5 mg q.d. + 500 mg q.i.d.**			[redacted]

b.i.d. = twice daily; Met = metformin; q.d. = once daily; q.i.d. = four times daily.
[a] Price for XigDuo is the manufacturer confidential price; prices for Forxiga reflect the manufacturer-submitted confidential price; prices for Met reflect the public formulary list prices across provinces; Met 850 mg is not a benefit covered by the Ontario Drug Benefit Program; therefore, the unit cost for this treatment reflects the average price among public plans (i.e., British Columbia, Alberta, Saskatchewan, Newfoundland and Labrador Prescription Drug Program, Nova Scotia).
[b] Daily cost includes 10% markup and a $7.00 pharmacy fee per 90-day supply according to the methodology employed by CADTH.[32]
Note: Patent expiration for dapagliflozin is 2020-10-02 and 2023-05-15 (Section 3.2). Met is available as a multisource generic across Canada.

In addition to providing cost savings, patients benefit from a reduced pill burden (Table 12). Patients taking the 1,700 mg Met per day regimen will reduce their pill burden by one tablet per day and 365 tablets per year when switching to a XigDuo regimen. Patients taking the 2,000 mg Met per day regimen (with 500 mg tablets) will reduce their pill burden by three tablets per day and 1,095 tablets per year when switching to a XigDuo regimen.

TABLE 12: PILL BURDEN COMPARISON OF XIGDUO AND INDIVIDUAL COMPONENTS

Drug/Comparator	Strength	Tablets Per Day	Tablets Per Month[a]	Tablets Per Year
Combination product dapagliflozin/Met (XigDuo)	**5 mg/850 mg**	2	60	730
	5 mg/1,000 mg	2	60	730
Individual component A (dapagliflozin)	5 mg q.d.	1	30	365
	10 mg q.d.	1	30	365
Individual component B (Met)	850 mg b.i.d.	2	60	730
	500 mg q.i.d.	4	120	1,460
Total (dapagliflozin + Met)	**10 mg q.d. + 850 mg b.i.d.**	**3**	**90**	**1,095**
	10 mg q.d. + 500 mg q.i.d.	**5**	**150**	**1,825**
Tablet Difference with XigDuo vs. Individual Components (Dapagliflozin + Met)				
Tablet Difference (XigDuo — dapagliflozin + Met)	**5 mg/850 mg**	**–1**	**–30**	**–365**
	5 mg/1,000 mg	**–3**	**–90**	**–1,095**

b.i.d. = twice daily; Met = metformin; q.d. = once daily; q.i.d. = four times daily; vs. = versus.
[a] Tablets per month assumes 30 days per month; tablets per year assumes 365 days per year.

4.2 Cost Comparison Table

The cost comparison table that follows (Table 13) contains the costs of XigDuo, as well as the available DPP-4-inhibitor/Met combination products currently available within Canada. XigDuo is the first SGLT2/Met combination product in Canada. The unit cost and daily drug cost of XigDuo is below the average cost for all other DPP-4 inhibitor/Met combination products listed within Canada.

TABLE 13: COST COMPARISON TABLE

Drug/Comparator	Strength	Dosage Form	Price[a] ($)	Recommended Daily Use	Average Daily Drug Cost ($)
Dapagliflozin/Met (XigDuo)	**5 mg/850 mg 5 mg/1,000 mg**	**Tablet**	[redacted]	**b.i.d. b.i.d.**	[redacted]
Alogliptin/Met (Kazano)	12.5 mg/500 mg 12.5 mg/850 mg 12.5 mg/1,000 mg	Tablet	$1.3700 $1.3700 $1.3700	b.i.d. b.i.d. b.i.d.	$2.7400 $2.7400 $2.7400
Linagliptin/Met (Jentadueto)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/ 1,000 mg	Tablet	$1.3337 $1.3337 $1.3337	b.i.d. b.i.d. b.i.d.	$2.6674 $2.6674 $2.6674
Saxagliptin/Met (Komboglyze)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/ 1,000 mg	Tablet	$1.2700 $1.2700 $1.2700	b.i.d. b.i.d. b.i.d.	$2.5400 $2.5400 $2.5400
Sitagliptin/Met (Janumet)	50 mg/500 mg 50 mg/850 mg 50 mg/1,000 mg	Tablet	$1.6159 $1.6159 $1.6159	b.i.d. b.i.d. b.i.d.	$3.2318 $3.2318 $3.2318

b.i.d. = twice daily; Met = metformin.
[a] Price for XigDuo is the manufacturer list price; prices for comparators reflect the public formulary list price obtained from the Ontario Drug Benefits Formulary/Comparative Drug Index (Accessed October 2015); [33] price for Kazano is based on the submitted price in the CADTH review of Kazano[34] given that it was not listed in any province (excluding Quebec) at the time of preparation of this table. The price of Kazano in Quebec is $1.1450 per tablet.

4.3 Manufacturer-Submitted Information Regarding Current Patent Status

The required information in this section includes the patent expiry dates for dapagliflozin and Met, which follow. Please note that Met is available as a multisource generic drug within Canada.

TABLE 14: CURRENT PATENT STATUS OF STUDY DRUGS IN CANADA

Medicinal Ingredient	Brand Name	Strength	DIN	Patent	Patent Expiry
Dapagliflozin/Met	XigDuo	5 mg/850 mg	02449935	2388818 2486539	2020-10-02 2023-05-15
Dapagliflozin/Met	XigDuo	5mg/1,000 mg	02449945	2388818 2486539	2020-10-02 2023-05-15
Dapagliflozin	Forxiga	5 mg	02435462	2388818 2486539	2020-10-02 2023-05-15
Dapagliflozin	Forxiga	10 mg	02435470	2388818 2486539	2020-10-02 2023-05-15
Met	Glumetza	500 mg	02268493	2290624 2412671	2018-06-05 2021-02-26
Met	Glumetza	1,000 mg	02300451	2476496	2023-02-21

DIN = drug identification number; Met = metformin.

Patent expiry is reported as posted on the Health Canada Patent Register available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/patregbrev/index-eng.php (accessed November 12, 2015).
Note: The Glumetza patent is for a Met XR formulation, which is not listed in the formularies of CDR-participating plans. IR Met formulations are no longer under patent.

4.4 Critical Appraisal of Cost Information

The manufacturer's confidentially submitted price of [redacted] per dapagliflozin/Met FDC tablet [redacted], meaning that plans would save [redacted] one pharmacy dispensing fee per claim when patients achieving glycemic control with dapagliflozin and Met as separate dosage forms are switched to the FDC formulation.

Limitations

- The manufacturer did not consider the average daily cost of canagliflozin plus Met or empagliflozin plus Met in their analyses. However, as the publicly available list or wholesale prices for both canagliflozin and empagliflozin are higher than [redacted] per day before Met is taken into account, dapagliflozin plus Met FDC would be the least expensive method of treating patients requiring an sodium-dependent glucose co-transporter inhibitor and Met therapy.
- Patients achieving glycemic control with Met and dapagliflozin 5 mg q.d. (with or without a sulfonylurea or insulin) will not be able to switch to the FDC formulation without either increasing their doses of dapagliflozin or having a separate prescription of Met alone for the second dose of the day. The former option may lead to increased side effects or intolerance; whereas, the latter reduces the convenience and eliminates the pharmacy fee savings associated with an FDC product, although a small amount of cost savings because of reduced individual Met use would remain ($0.04 to $0.09 per patient per day). According to nationwide IMS Brogan PharmaStat data from private drug plans, the 5 mg strength of dapagliflozin accounted for approximately 35% of dapagliflozin units, claims, costs, prescription-days, and patients across the last three-quarters of 2015. Whereas, some of these claims were likely for patients who were subsequently switched to the higher 10 mg once daily (q.d.) dose; there is likely a significant proportion of dapagliflozin patients whose dosing needs will not be met by the currently available FDC doses.

Issues for Consideration:

- The lower pill burden associated with FDC products may increase adherence, which may improve glycemic control for some patients.
- An FDC of canagliflozin plus Met was recently submitted to CDR as a pre-NOC submission,[3] and an FDC of empagliflozin plus Met is also expected to enter the Canadian market in the near future.[4] The submitted prices for these products may alter the relative attractiveness of the dapagliflozin/Met FDC.
- The actual costs paid by public plans for comparators to the dapagliflozin/Met FDC may be lower than publicly available list prices, which could impact the relative attractiveness of the FDC.

5. DISCUSSION

The following clinical studies are included in this review to support the efficacy and safety of XigDuo in the treatment of patients with type 2 diabetes. A phase 3 study, D1691C00003, is an FDC-specific study designed to evaluate the effect of dapagliflozin administered b.i.d. as add-on to Met IR after 16 weeks of treatment. The second was a pivotal Canadian BE study (D1691C00007) that compared dapagliflozin/Met 5 mg/850 mg FDC tablets to the individual monotherapy tablets, including a Canada-specific Met reference product (i.e., Glucophage marketed in Canada by Sanofi-Aventis) under both fasted and fed conditions. No clinical studies have been conducted with XigDuo FDC tablets. BE studies were used to support the co-administration of dapagliflozin and Met using a b.i.d. dosing regimen.

In trial D1691C00003, it was found that, at 16 weeks, dapagliflozin 5 mg b.i.d. with Met achieved a statistically higher reduction of A1C compared with placebo and Met. Although the difference from placebo was statistically significant, it was less than –0.3% with dapagliflozin 10 mg q.d., but it was greater than –0.3% difference between placebo and dapagliflozin 5 mg b.i.d. The 10 mg q.d. dose included did not achieve the recommended threshold difference by the Food and Drug Administration of greater than –0.3% from placebo. [5] These efficacy conclusions are supported by the statistical analyses that were conducted for dapagliflozin 5 mg b.i.d. for the short-term study treatment duration of 16 weeks. It is worth noting that a previous placebo-controlled study of dapagliflozin in add-on combination with Met showed a statistically significant placebo-adjusted reduction in A1C by approximately 0.41% and 0.54% with dapagliflozin 5 mg q.d. and 10 mg q.d., respectively;[1] whereas, the study D1691C00003 only showed a difference of 0.35% and 0.29% with dapagliflozin 5 mg b.i.d. and 10 mg q.d., respectively. However, previous studies had end points at 24 weeks; whereas, the b.i.d. study (D1690C00003) had end points at 16 weeks.

The dapagliflozin 5 mg b.i.d. arm met statistical significance for the primary and secondary efficacy variable. The effect of 10 mg dapagliflozin was consistent in all key secondary efficacy variables except for the proportion of subjects with A1C below 7% at week 16 (LOCF), even though baseline A1C levels were incorporated into the analysis of covariance model and should adjust for baseline imbalances in patient selection.

In study D1691C00003, the dapagliflozin 10 mg q.d. group is currently an approved dosage for dapagliflozin; however, this treatment arm (dapagliflozin 10 mg q.d.) failed to reach statistical significance for the proportion of subjects reaching A1C below 7% (a key secondary efficacy variable) and calls into question the robustness of the study design and efficacy results.

There were no direct comparisons between dapagliflozin 5 mg b.i.d. and 10 mg daily in study D1691C00003; therefore, comparability between dapagliflozin 5 mg b.i.d. and dapagliflozin 10 mg q.d. cannot be inferred. This is the most critical analysis required for assessing the comparability of this FDC, as the dosing of the available dapagliflozin product is q.d., and this product requires b.i.d. dosing.

The maximum dose of Met as per the dosing regimen for the XigDuo FDC is 2,000 mg/day, which is less than the maximum dose of Met at 2,550 mg/day[6] and less than that used in the reviewed trial. The maximum dose of Met was not capped for the D1691C00003 study. The minimum dose of Met was 1,500 mg and the maximum dose was 2,500 mg at randomization and during treatment; whereas, the maximum dose was 3,000 mg at enrolment. It was reported that 7% to 13% of study subjects had a Met dose higher than 2,000 mg/q.d. at enrolment and at randomization, which affects the applicability of

this trial to the approved dosing regimen of this FDC. In addition, the clinical expert who was involved in this review was concerned that the indication is only for DAPA 5 mg b.i.d., and that some patients in clinical practice may not require a 10 mg daily dose, limiting the utility of this FDC in clinical practice.

The short 16-week D1691C0003 study did not raise any new safety signals that were not already reported by previous clinical studies reviewed in the Forxiga CDR review.[7] The two hypoglycemic events reported in the dapagliflozin 10 mg q.d. group were categorized as "major." No events were recorded in the placebo group or the dapagliflozin 5 mg q.d. group. The observations on urinary tract infections in the D1691C0003 study were similar to previous trials with dapagliflozin, where urinary tract infections were more frequently reported in females than males. Dapagliflozin 5 mg b.i.d. had the highest frequency compared with all other treatment groups .

Although the number of patients being discontinued from the D1691C0003 study due to renal impairment/failure was similar between the dapagliflozin groups and placebo, the observations of decreases in renal creatinine clearance and eGFR in the D1691C0003 study were similar to previous trials with dapagliflozin, in which decreases in renal creatinine clearance and eGFR were more frequently reported in patients treated with dapagliflozin than placebo.

The results of the pivotal Canadian BE study (D1691C00007) compared dapagliflozin/Met 5 mg/850 mg FDC tablets with the individual monotherapy tablets show that the geometric mean ratios of $AUC_{(0-t)}$ of both dapagliflozin and Met are close to unity, and the corresponding 90% confidence interval for the treatment comparisons fall well within the limits of 0.8 and 1.25. The geometric mean ratios of C_{max} also fall within the limits of 0.8 and 1.25, and hence confirm the BE of each active ingredient in the FDC product to that of the individual components administered concomitantly under both fasted and fed conditions. The FDC tablet and individual tables seem to have similar mean concentration-time profiles under both fasted and fed conditions.

Conclusion

In study D1691C00003, the dapagliflozin 5 mg b.i.d. arm met statistical significance for the primary and secondary efficacy variables. No new safety concerns regarding co-administration of dapagliflozin and Met were raised in study D1691C0003. The safety profile of dapagliflozin co-administered with Met is consistent with the safety profiles of the individual components. The BE of administering the components of this FDC has been demonstrated; however, the comparative efficacy of administering dapagliflozin 5 mg b.i.d. rather than 10 mg q.d. is uncertain, as no statistical analysis was planned or completed in study D1691C00003 to compare these two treatment arms.

At a daily cost of [redacted] per day, the use of dapagliflozin/Met FDC for patients achieving glycemic control with dapagliflozin plus Met (with or without insulin or a sulfonylurea) would likely save public drug plans between [redacted] and [redacted] per patient per day, or [redacted] to [redacted] per patient per year, based on publicly available list prices, not including markups or pharmacy fees.

APPENDIX 1: DRUG PLAN LISTING STATUS FOR INDIVIDUAL COMPONENTS

For each indication that is approved by Health Canada for the new combination products (or likely to be approved, in the case of a submission filed on a pre-NOC basis), please provide the publicly available listing status and criteria for the individual components of the combination product, as well as other relevant comparators. CADTH may update the information provided by the manufacturer with new information provided by the CDR-participating drug plans, as required.

Step 1: Use a separate table for each indication being reviewed by CDR.

Step 2: Add the non-proprietary names for each individual component to the "Components" column; use a separate row for each component of the new combination product.

Step 3: Use the following abbreviations to complete the table:

Abbreviation	Description
EX	Exception item for which coverage is determined on a case-by-case basis
FB	Full benefit
NB	Not a 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	Alta	Sask	Man	Ont	NB	NS	PEI	Nfld	YK	NT	NIHB	DND	VAC
dapagliflozin[a]	**UR**	**UR**	**UR**	**UR**	**UR**	**UR**	**UR**	**UR**	**UR**	**UR**	**UR**	**UR**	**UR**	**UR**
Met	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**	**FB**

Alta = Alberta, BC = British Columbia, DND = Department of National Defence; FB = full benefit; Man = Manitoba; Met = metformin; NIHB = Non-Insured Health Benefits Program; Nfld = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; Ont = Ontario; PEI = Prince Edward Island; Sask = Saskatchewan; UR = under review; VAC =Veterans Affairs Canada; YK = Yukon.

[a]Although dapagliflozin is not yet reimbursed, dapagliflozin received a positive recommendation from CDR on November 20, 2015 and will be seeking listing with CDR-participating drug plans.

Step 4: For all restricted benefit entries, please state the criteria used by each drug plan. Use a separate table for each indication and add or delete rows, as necessary.

TABLE 16: RESTRICTED BENEFITS CRITERIA FOR (NAME OF COMPONENT) FOR THE TREATMENT OF (STATE THE INDICATION)

Drug Plan	Criteria for Restricted Benefits
Add name	State the exact criteria
Add name	State the exact criteria
Add name	State the exact criteria

APPENDIX 2: SUMMARY OF PATIENT INPUT

This section was summarized by CDR staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input
One patient group provided feedback.

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

2. Condition-Related Information
The submission is based on information obtained through two surveys distributed through social media and email. The first survey (October 2015) gathered information regarding the impact of diabetes from 212 Canadians with type 2 diabetes and 61 caregivers. The second survey (April 2015) gathered information from Canadians with type 2 diabetes (n = 349) and their caregivers (n = 75) about current drug therapies and experience with dapagliflozin, and aspects of diabetes they would like medications to address.

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

Diabetes requires considerable self-management, including healthy eating, regular physical activity, healthy body weight, taking diabetes medications as prescribed, monitoring blood glucose, and stress management. Poor glucose control can result in acute crises and serious long-term complications. For the majority of survey respondents, diabetes has negatively impacted all aspects of their lives and has limited q.d. activities. Diabetes management is a “constant struggle” involving meal planning, testing blood glucose, and taking medications. It is also challenging to manage co-existing conditions or diabetes-related complications. The most commonly reported complications were hypoglycemia (56%), high blood pressure (55%), high cholesterol (47%), foot problems (43%), eye problems (39%), and nerve damage (38%).

The patients and their caregivers who responded to the surveys indicated that diabetes had a psychological and emotional impact on their lives because of the necessary changes in diet and lifestyle, managing medications, stress and anxiety about hypoglycemia, strain on relationships, and financial burden. One respondent said: “It is difficult to lead a normal life when you always need to be

taking meds or checking your [blood sugar] levels and reading labels on all your food while your [blood sugar] levels change with or without food intake. The impact of diabetes on all your other organs is another huge problem and when you treat one, you harm another. Most difficult disease to manage."

3. Current Therapy-Related Information

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

Among the 397 patients and caregivers who responded to the April 2015 survey, the majority (63%) indicated that they were "satisfied" or "very satisfied" with their current therapies; whereas, 18% indicated dissatisfaction. Respondents indicated that current therapies resulted in "better" or "much better" blood glucose and A1C levels. However, a significant number of respondents reported challenges in avoiding low blood sugar ("the same," "worse," or "much worse" for 38%), weight gain ("the same," "worse," or "much worse" for 52%), gastrointestinal effects ("the same," "worse," or "much worse" for 57%); 59% and 55% indicating "same," "worse," or "much worse" for dehydration and urinary tract/yeast infection, respectively. In addition to controlling blood sugar levels without hypoglycemia, the aspects of diabetes that patients report were most important for medications to address included avoiding weight gain, reducing high blood pressure, and avoiding fluid retention, gastrointestinal effects and urinary tract infections.

4. Expectations About the Drug Being Reviewed

A total of 92 respondents indicated using dapagliflozin at the time of the survey, and six had had to stop for reasons other than the completion of clinical trials. A total of 51 of the 92 respondents with experience taking dapagliflozin were also taking Met and/or other medications. Patients and caregivers who had experience with dapagliflozin highlighted its effectiveness in lowering blood sugar and blood pressure compared with other medications. In the words of respondents: "His blood sugar is below 10, he hasn't been below 10 in years; the other day, it was 6.3 — that's amazing;" "readings are best I have ever had;" "bloods sugars the best they have been since diagnosis a year ago." Many who have only been on the medication for a short period of time noticed instant improvement: "I have only taken it for four days and I already feel the effects, which are positive!!" "I've only been on Forxiga for a month, but it seems to be doing the job where the other was not quite working." Many respondents noted less dependency on other drugs such as insulin as a result of dapagliflozin, one person was able to get off one of three blood pressure medications, and another reduced insulin intake by 75%. The reduction of medications is viewed as a substantial improvement to quality of life. The use of dapagliflozin to manage diabetes also led to improved energy levels and mental health, as described by several patients. In their own words: "I have lost a surprising amount of weight in a short time. This helps me remain optimistic about my health improving significantly in the long run;" "My weight has dropped and I feel great! This weight loss has helped put me in a very positive frame of mind and has helped me get off my anti-depression drugs also;" "For me, it is the best thing ever with my combination of meds. It is working for me. First time my body has been happy; I cannot tell you how good my body feels;" " Very positive impact on my self-confidence and feeling of 'being in control' with my diabetes."

Respondents generally did not describe serious side effects; some who did experience side effects such as frequent urination, dehydration, and increased appetite described them as “manageable.” Others, however, did not experience the same benefits and found the side effects challenging — two respondents had to discontinue the medication because of “face… swollen and broke out in a rash” and “concerns about bladder cancer.” In the words of respondents: “First week experienced vaginal yeast infection, severe constipation, and a small weight loss. Subsequently no side effects, no weight loss, and no significant change in blood sugar levels.” “I've used Forxiga for 2 months and I am now feeling the effects, mineable constipation, and I am adjusting my insulin greatly. I now use about half the insulin and I still have lows during the day. My physical activity has increased, but unfortunately the weight loss has not happened yet, still hoping.” “Did lower blood sugar levels but did not reduce weight. Caused repetitive yeast infections and urinary tract infections, as well as unpredictable bouts of bowel incontinence. I have never felt so ill in my life.”

Several surveyed respondents found taking multiple medications challenging and expressed the wish of reducing the number of pills: “I hope one day to be able to take only one or two medications to control my diabetes rather than the three injectables and two tablet medications I take now;” “Would like to be on fewer drugs;” “Combine to only one pill and make it easier for aging patients;” “I hope that it would be a one tablet or injection instead of multiple medications to treat type 2 diabetes;” “A combination pill would be useful.” The availability of XigDuo as a FDC of Met with dapagliflozin for people with type 2 diabetes stabilized on Met, dapagliflozin (with or without a sulfonylurea or insulin) 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 doctors and patients working together to achieve optimal treatment with the lowest effective dose.

APPENDIX 3: SUMMARY OF EFFICACY PARAMETERS FROM PHASE 3 STUDIES OF DAPAGLIFLOZIN IN COMBINATION WITH METFORMIN

TABLE 17: SUMMARY OF KEY EFFICACY PARAMETERS FROM PHASE 3 STUDIES OF DAPAGLIFLOZIN IN COMBINATION WITH MET, WITH A1C AS THE PRIMARY END POINT

Efficacy Parameter	Study MB102034 (Initial combination with Met XR, 24 Weeks)			Study MB102021 (Initial combination with Met XR, 24 Weeks)			Study MB102014 (Add-On to Met IR Compared With Placebo, 24 Weeks)		
	Dapa 10 mg + Met XR (N = 211)	Dapa 10 mg (N = 219)	Met XR (N = 208)	Dapa 5 mg + Met XR (N = 194)	Dapa 5 mg (N = 203)	Met XR (N = 201)	Dapa 10 mg + Met IR (N = 135)	Dapa 5 mg + Met IR (N = 137)	Placebo + Met IR (N = 137)
A1C (%)									
Baseline (mean) 9.1		9.0	9.0	9.2	9.1	9.1	7.9	8.2	8.1
Change from Baseline (adjusted mean) –2.0		–1.5	–1.4	–2.1	–1.2	–1.4	–0.8	–0.7	–0.3
		--	--	–0.9[a] (–1.1 to –0.6)	--	--	--	--	--
Difference from Dapa (adjusted mean) –0.5[a] (95% CI) (–0.7 to –0.3)		0.0[b] (–0.2, 0.2)	--	–0.7[a] (–0.9 to –0.5)	--		–0.5[a] (–0.7 to –0.3)	–0.4[a] (–0.6 to –0.2)	
Difference from Met mono/placebo (adjusted mean)–0.5[a] (95% CI) (–0.8 to –0.3)									
FPG (mg/dL)[a]									
Baseline (mean) 189.6		197.5	189.9	193.4	190.8	196.7	156.0	169.2	165.6
Change from Baseline (adjusted mean)		–46.4	–34.8	–61.0	–42.0	–33.6	–23.5	–21.5	–6.0
			--	–19.1[a] (–26.7 to –11.4)	--	--	--	--	--
Difference from Dapa (adjusted mean) Difference from Met mono/placebo (adjusted –25.5[a] mean[‡]) (95% CI) (–32.6 to –18.5)		–11.6[c] (–18.6 to –4.6)	--	–27.5[a] (–35.1 to –19.8)	--		–17.5[a] (–25.0 to –10.0)	–15.5[a] (–22.9 to –8.1)	

Efficacy Parameter	Study MB102034 (Initial combination with Met XR, 24 Weeks)			Study MB102021 (Initial combination with Met XR, 24 Weeks)			Study MB102014 (Add-On to Met IR Compared With Placebo, 24 Weeks)		
	Dapa 10 mg + Met XR (N = 211)	Dapa 10 mg (N = 219)	Met XR (N = 208)	Dapa 5 mg + Met XR (N = 194)	Dapa 5 mg (N = 203)	Met XR (N = 201)	Dapa 10 mg + Met IR (N = 135)	Dapa 5 mg + Met IR (N = 137)	Placebo + Met IR (N = 137)
Body Weight (kg)									
Baseline (mean)		88.5	87.2	84.2	86.2	85.8	86.3	84.7	87.7
Change from Baseline (adjusted mean)		–2.7	–1.4	–2.7	–2.6	–1.3	–2.9	–3.0	–0.9
Difference from Met mono/placebo (adjusted mean) –1.3)		–1.4[a] (–2.0 to –0.7)	--	–1.4[a] (–2.0 to –0.7)	--	--	–2.0[a] (–2.6 to –1.3)	–2.2[a] (–2.8 to –1.5)	--

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; FPG = fasting plasma glucose; IR = immediate release; Met = metformin; XR = extended release.
Note: N represents all randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period. Adjusted means are least squares mean adjusted for baseline value. For D1690C00012, the primary end point was to evaluate the effect of dapagliflozin 10 mg q.d. in combination with Met compared with placebo in combination with Met on total body weight, so no data from this study is presented in this table.
[a] For FPG presented in SI units, see CTD Module 2.7.3, Table 21 and Table 26.[27] [a] *P* value < 0.0001.
[b] Non-inferior versus Met.
[c] *P* value < 0.05.

Efficacy Parameter	Study D1690C00004 (Add-On to Met IR Compared With Glipizide, 52 Weeks)		Study D1690C00006 (24 Weeks)		
	Dapa + Met (N = 400)	Glipizide + Met (N = 401)	Dapa 10 mg + Insulin + ≤ 2 OADs (N = 194)	Dapa 5 mg+ Insulin + ≤ 2 OADs (N = 211)	Placebo+ Insulin + ≤ 2 OADs (N = 193)
A1C (%)					
Baseline (mean)	7.7	7.7	8.6	8.6	8.5
Change from Baseline (adjusted mean)	–0.5	0.5	–0.9	–0.8	–0.3
Difference from comp/placebo (adjusted mean‡) (95% CI) (–0.1 to 0.1)	0.0[a]	--	–0.6[b] (–0.7 to –0.4)	–0.5[b] (–0.7 to –0.4)	--
FPG (mg/dL [mmol/L])					
Baseline (mean)	162.3 (9.0 mmol/L)	164.3 (9.1)	173.7 (9.6)	185.1 (10.3)	170.0 (9.4)
Change from Baseline (adjusted mean) (–1.2 mmol/L)	–22.4	–18.8 (–1.0)	–21.7 (–1.2)	–18.8 (–1.0)	3.3 (–0.2)
Difference from comp/placebo (adjusted mean) (95% CI) (–0.2 [–0.4 to 0.0] mmol/L)	–3.6 (–8.0 to 0.9)	--	–25.0[b] (–34.3 to –15.8) (–1.4 [–1.9 to –0.9])	–22.1 (–31.2 to –13.1) (–1.2 [–1.7 to –0.7])	--
Body Weight (kg)					
Baseline (mean)	88.4	87.6	94.6	93.2	94.2
Change from Baseline (adjusted mean)	–3.2	1.4	–1.7	–1.0	0.0
Difference from comp/placebo (adjusted mean) (95% CI) (–5.1 to –4.2)	–4.7[b]	--	–1.7[b] (–2.2 to –1.2)	–1.0[b] (–1.5 to	--

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; FPG = fasting plasma glucose; IR = immediate release; Met = metformin; OAD = oral antidiabetes drugs.
Note: N represents randomized and treated patients with baseline and at least one post-baseline efficacy measurement. Adjusted means are least squares mean adjusted for baseline value.

[a] Non-inferior versus glipizide + Met.

[b] *P* value < 0.0001.

Efficacy Parameter	Study D1690C00018 Add-On to Usual Care Compared With Placebo, 24 Weeks)		Study D1690C00019 (Add-On to Usual Care Compared With Placebo, 24 Weeks)	
	Dapa 10 mg + Usual Treatment (N = 455)	Placebo + Usual Treatment (N = 459)	Dapa 10 mg + Usual Treatment (N = 480)	Placebo + Usual Treatment (N = 482)
A1C (%)				
Baseline (mean)	8.2	8.1	8.0	8.1
Change from Baseline (adjusted mean)	–0.4	0.1	–0.3	0.1
Difference from comp/placebo (adjusted mean) (95% CI)	–0.5 [a] (–0.6 to –0.4)	--	–0.4 [a] (–0.5 to –0.3)	--
Body Weight (kg)				
Baseline (mean)	92.6	93.6	94.5	93.2
Change from Baseline (adjusted mean)	–2.6	–0.3	–2.5	–0.6
Difference from placebo (adjusted mean) (95% CI)	–2.3 [a] (–2.6 to –1.9)	--	–1.9 [a] (–2.3 to –1.5)	--
Seated SBP (mm Hg)				
Baseline (mean)	133	133	135	135
Change from Baseline (adjusted mean)	–3.0	–1.0	–2.7	0.3
Difference from placebo (adjusted per cent) (95% CI)	–2.0 [b] (–3.6 to –0.3)	--	–3.0 [b] (–4.6 to –1.5)	--
Change from baseline seated SBP (mm Hg) patients with baseline SBP ≥ 130 mm Hg (adjusted mean)	-- at week 8 in	--	–5.3 [b]	–1.9

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; SBP = systolic blood pressure.
Note: N represents randomized and treated patients with baseline and at least one post-baseline efficacy measurement. Adjusted means are least squares mean adjusted for baseline value. [a] *P* value < 0.0001.
[b] *P* value < 0.05.

Efficacy Parameter	Study D1690C00010 — Stratum 2 (Add-On to Sitagliptin Plus Met IR Compared With Placebo, 24 Weeks)	
	Dapa 10 mg + Sitagliptin + Met (N = 113)	**Placebo + Sitagliptin + Met (N = 113)**
A1C (%)		
Baseline (mean)	7.80	7.87
Change from Baseline (adjusted mean)	–0.43	–.02
Difference from placebo (adjusted mean) (95% CI)	–0.40[a] (–0.58 to –0.23)	
FPG (mg/dL [mmol/L])		
Baseline (mean)	165.9 (9.2 mmol/L)	164.7 (9.1 mmol/L)
Change from Baseline (adjusted mean)	–26.2 (–1.5 mmol/L)	3.0 (0.2 mmol/L)
Diff from placebo (adjusted mean) (95% CI)	–29.2 [a] (–38.0 to –20.4) (–1.6 [–2.1 to –1.1] mmol/L)	--
Body Weight (kg)		
Baseline (mean)	93.95	94.17
Change from Baseline (adjusted mean)	–2.35	–0.47
Difference from placebo (adjusted mean) (95% CI)	–1.87 [a] (–2.61 to –1.13)	
Seated SBP at week 8 in patients with baseline seated SBP ≥ 130 mm Hg (mm Hg)	**N = 58**	**N = 66**
Baseline (mean)	141.9	140.3
Change from Baseline (adjusted mean)	–5.3	–5.5
Difference from placebo (adjusted mean) (95% CI)	0.2 (–3.85 to 4.32)	--
2-hour PPG (mg/dL [mmol/L])		
Baseline (mean)	230.2 (12.8 mmol/L)	221.0 (12.3 mmol/L)
Change from Baseline (adjusted mean)	–48.9 (–2.7 mmol/L)	–7.2 (–0.4 mmol/L)
Difference from placebo (adjusted mean) (95% CI)	–41.6 (–55.4 to –27.8) (–2.3 [–3.1 to –1.5] mmol/L)	--

A1C = glycated hemoglobin; CI = confidence interval; Dapa = dapagliflozin; FPG = fasting plasma glucose; IR = immediate release; Met = metformin; PPG = postprandial glucose; SBP = systolic blood pressure.
Note: Data displayed for D1690C00010 are only for those patients treated with Met (Stratum 2). N represents randomized and treated patients with baseline and at least one post-baseline efficacy measurement. Adjusted means are least squares mean adjusted for baseline value. 2-hour PPG level as a response to a 75-gram oral glucose tolerance test.
[a] *P* value < 0.0001.

Efficacy Parameter	**MB102073 (Subjects With Inadequately Controlled Hypertension and T2DM on an ACEi or ARB and OADs, 12 Weeks)**		**MB102077 (Subjects With Inadequately Controlled Hypertension and T2DM on an ACEi or ARB and Additional Antihypertensive Drug, and OADs, 12 Weeks)**	
	Dapagliflozin 10 mg N = 302[a]	**Placebo N = 311[a]**	**Dapagliflozin 10 mg N = 225[a]**	**Placebo N = 224[a]**
Seated Systolic Blood Pressure (mm Hg) (LRM)				
Baseline (mean)	149.8	149.5	151.0	151.3
Change from baseline (adjusted mean)[b]	−10.4	−7.3	−11.9	−7.6
Difference from placebo (adjusted mean)[b] (95% CI)	−3.1[c] (−4. to −1.2)		−4.3[c] (−6.5 to −2.0)	
A1C (%) (LRM)				
Baseline (mean)	8.1	8.0	8.1	8.0
Change from baseline (adjusted mean)[b]	−0.6	−0.1	−0.6	0.0
Difference from placebo (adjusted mean)[b] (95% CI)	−0.5[d] (−0.6 to −0.3)		−0.6[d] (−0.8 to −0.5)	
24-hour Mean Ambulatory Systolic Blood Pressure (mm Hg) (LOCF)				
Baseline (mean)	145.9	146.6	146.5	149.2
Change from baseline (adjusted mean)[b]	−9.6	*−6.7*	*−11.3*	−6.9
Difference from placebo (adjusted mean)[b] (95% CI)	−2.9[c] (–4.9 to -0.9)		−4.5[c] (−7.1 to −1.8)	
Seated Diastolic Blood Pressure (mm Hg) (LRM)				
Baseline (mean)	91.1	90.8	91.2	91.4
Change from baseline (adjusted mean)[b]	−5.8	−4.8	−6.3	−5.3
Difference from placebo(adjusted mean)[b] (95% CI)	−1.0 (−2.2 to 0.1)		−1.0 (−2.3 to 0.4)	

A1C = glycated hemoglobin; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CI = confidence interval; FPG = fasting plasma glucose; IR = immediate release; LOCF = last observation carried forward; LRM = longitudinal repeated measures analysis; Met = metformin; OADs = oral antidiabetic drugs; T2DM = type 2 diabetes mellitus. Note: MB102073 and MB102077 results are for week 12 in two placebo-controlled studies of dapagliflozin in combination with oral antidiabetic drugs and/or insulin and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers with or without an additional antihypertensive treatment.

[a] Randomized and treated patients with baseline and at least one post-baseline efficacy measurement.

[b] Least squares mean adjusted for baseline value.

[c] *P* value < 0.05.

[d] *P* value < 0.0001.

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