XIGDUO XR™

(Dapagliflozin/Metformin HCl)

1 NAME OF THE MEDICINAL PRODUCT

Xigduo XR tablet 5mg/1000mg, and 10 mg/1000mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

XIGDUO XR 5 mg/1000 mg: Each film-coated tablet contains 5 mg dapagliflozin as dapagliflozin propanediol and 1000 mg metformin hydrochloride extended-release.

XIGDUO XR 10 mg/1000 mg: Each film-coated tablet contains 10 mg dapagliflozin as dapagliflozin propanediol and 1000 mg metformin hydrochloride extended-release.

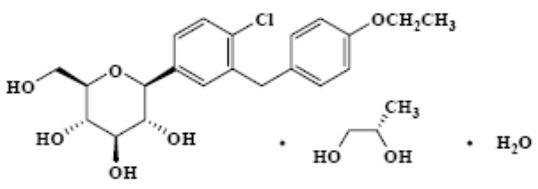
3 PHARMACEUTICAL FORM

- XIGDUO XR (dapagliflozin/metformin HCl extended-release) 5 mg/1000 mg tablets are pink to dark pink, biconvex, oval-shaped, film-coated tablet with "1071" and "5/1000" debossed on one side and plain on the reverse side.
- XIGDUO XR (dapagliflozin/metformin HCl extended-release) 10 mg/1000 mg tablets are yellow to dark yellow, biconvex, oval-shaped, film-coated tablet with "1073" and "10/1000" debossed on one side and plain on the reverse side.

Dapagliflozin

Dapagliflozin propanediol is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl) methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1). The empirical formula is $C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$ and the formula weight is 502.98.

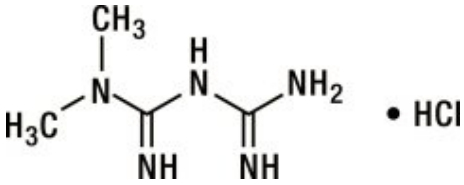
The structural formula is:



Metformin hydrochloride

Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \bullet HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water, slightly soluble in alcohol, and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

The structural formula is:



System components and performance:

XIGDUO XR fixed dose combinations (FDCs) are bi-layer tablets compressed with extended-release metformin as the first layer and immediate-release dapagliflozin as the second layer. The extended-release metformin layer comprises a dual hydrophilic polymer matrix system. Metformin hydrochloride is combined with a drug release controlling polymer to form an “inner” phase, which is then incorporated as discrete particles into an “external” phase of a second polymer. After oral administration, the dapagliflozin layer dissolves immediately. The metformin layer absorbs the fluid from the gastrointestinal (GI) tract, causing the polymers to hydrate and swell. Drug is released slowly from the metformin layer by a process of diffusion through the gel matrix that is essentially independent of pH. The hydrated polymer system is not rigid and is expected to be broken up by normal peristalsis in the GI tract. The biologically inert components of the tablet may occasionally remain intact during GI transit and will be eliminated in the feces as a soft, hydrated mass.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

XIGDUO XR is indicated in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate for:

- The treatment of type 2 diabetes mellitus as an adjunct to diet and exercise.
- The prevention of new or worsening heart failure or cardiovascular death in type 2 diabetes mellitus (see section 5.1).

- The prevention of new or worsening nephropathy (see section 5.1).

XIGDUO XR are not indicated for use in patients with type 1 diabetes.

4.2 Posology and method of administration

4.2.1 Dapagliflozin/Metformin HCl Extended-Release Tablets

XIGDUO XR should be administered once daily with the evening meal.

The recommended dose of dapagliflozin is 10 mg once daily. The recommended starting dose of metformin is 500 mg once daily, which can be titrated to 2000 mg once daily, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.

In patients treated with metformin, the dose of XIGDUO XR should provide metformin at the dose already being taken, or the nearest therapeutically appropriate dose.

If no adequate strength of XIGDUO XR is available, individual mono-components should be used instead of the fixed dose combination.

Patients should be informed that XIGDUO XR tablets must be swallowed whole and never crushed, cut, or chewed. Occasionally, the inactive ingredients of XIGDUO XR will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.

4.2.2 Special populations

Patients with renal impairment

Assess renal function prior to initiation of XIGDUO XR and periodically thereafter (see sections 4.4 and 5.2).

Dosing of XIGDUO XR in patients with renal impairment

eGFR (mL/min/1.73 m2)	Dose
≥45	No dose adjustment is required.
30-44	Maximum daily dose of metformin is 1000 mg, therefore the maximum recommended dose of XIGDUO XR is 10 mg/1000 mg once daily.

	Initiation of metformin treatment is not recommended. If during treatment, eGFR falls to levels persistently below 45 mL/min/1.73 m2, the benefit and risk of continuing therapy should be assessed. The glucose lowering efficacy of dapagliflozin is reduced in patients with eGFR below 45 mL/min/1.73 m2 (see section 4.4).
<30	Due to the metformin component, XIGDUO XR is contraindicated (see section 4.3).

Severe renal impairment

Due to the metformin component, XIGDUO is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) (see section 4.3).

Patients with hepatic Impairment

Since impaired hepatic function has been associated with some cases of lactic acidosis in patients taking metformin, XIGDUO XR should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment (see section 4.4.6).

Pediatric and adolescent patients

Safety and effectiveness of XIGDUO XR in pediatric and adolescent patients have not been established.

Elderly patients

Because metformin is eliminated by the kidney, and because elderly patients are more likely to have decreased renal function, XIGDUO XR should be used with caution as age increases. The renal function recommendations provided for all patients also apply to elderly patients (see section 4.4).

Patients at Risk for Volume Depletion

For patients at risk for volume depletion due to co-existing conditions, a 5 mg starting dose of dapagliflozin may be appropriate (see sections 4.4 and 4.8).

4.3 Contraindications

XIGDUO XR is contraindicated in patient with:

- Severe renal impairment (eGFR < 30 mL/min/1.73 m^2).
- Metabolic acidosis.
- Patients with a history of any serious hypersensitivity reaction to the active substance or to any of the excipients.

4.4 Special warnings and special precautions for use

4.4.1 Lactic Acidosis

Metformin hydrochloride

Lactic acidosis is a rare, but serious, and potentially fatal in the absence of prompt treatment, metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency, dehydration, any acute conditions associated with hypoxia or impacting renal function, (see section 4.4).

Medicinal products that can acutely impair renal function, such as antihypertensives, diuretics and NSAIDs, should be initiated with caution in metformin-treated patients (see also section 4.5).

Patients and/or care-givers should be informed on the risk of lactic acidosis. Lactic acidosis is characterized by symptoms such as acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If lactic acidosis is suspected, treatment with XIGDUO should be discontinued and the patient hospitalized immediately.

4.4.2 Use in patients with renal impairment

Dapagliflozin

The glucose lowering efficacy of dapagliflozin is dependent on renal function, and is reduced in patients with eGFR <45 mL/min/1.73 m2 (see section 4.2.2).

Metformin hydrochloride

Metformin is excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function (see section 4.4.1) -assess renal function prior to initiation of XIGDUO XR and then periodically thereafter:

- at least annually
- at least two to four times a year in patients with renal function where eGFR levels are approaching 45 mL/min/1.73 m^2 and in elderly patients.

Due to the metformin component, it is not recommended to initiate treatment with XIGDUO in patients with eGFR <45 mL/min/1.73 m^2.

The maximum dose of metformin in patients with an eGFR of 30 to less than 45 mL/min/1.73 m^2 is 1000 mg daily.

If during treatment eGFR falls to levels persistently below 45 mL/min/1.73 m2, assess the benefit and risk of continuing therapy and limit the maximum dose of XIGDUO to 10 mg/1000 mg daily (see section 4.2).

XIGDUO is contraindicated in patients with severe renal impairment (eGFR< 30 mL/min/1.73 m^2) (see section 4.3).

4.4.3 Acute conditions associated with hypoxic or impacting renal function

Metformin hydrochloride

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. Acute conditions such as dehydration, severe infections, and hypoperfusion, have potential to alter renal function. In these situations, metformin must be discontinued.

4.4.4 Radiologic studies with intravascular iodinated contrast materials

Metformin hydrochloride

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. XIGDUO XR should

temporarily be discontinued prior to or at the time of the procedure, and not reinstituted until 48 hours afterwards and only after renal function has been re-evaluated and found to be stable.

4.4.5 Surgical procedures

Metformin hydrochloride

Use of XIGDUO XR should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as stable.

4.4.6 Use in patients with hepatic impairment

Metformin hydrochloride

Since impaired hepatic function has been associated with some cases of metformin associated lactic acidosis, XIGDUO XR should be avoided in patients with clinical or laboratory evidence of hepatic disease.

4.4.7 Excessive alcohol intake

Metformin hydrochloride

Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving XIGDUO XR.

4.4.8 Ketoacidosis

Dapagliflozin

There have been reports of ketoacidosis, including diabetic ketoacidosis, in patients with type 1 and type 2 diabetes mellitus taking dapagliflozin and other SGLT2 inhibitors. XIGDUO XR is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with XIGDUO XR who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, discontinuation or temporary interruption of XIGDUO XR should be considered and the patient should be promptly evaluated.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin dose

reduction, reduced caloric intake or increased insulin requirements due to infections, illness or surgery and alcohol abuse. XIGDUO XR should be used with caution in these patients.

4.4.9 Change in clinical status of patients with previously controlled type 2 diabetes

A patient with type 2 diabetes previously well controlled on XIGDUO XR who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, XIGDUO XR must be stopped immediately and other appropriate corrective measures initiated.

4.4.10 Vitamin B12 decrease/deficiency

Metformin hydrochloride

Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

4.4.11 Use in patients at risk for volume depletion

Dapagliflozin

Due to its mechanism of action, dapagliflozin induces osmotic diuresis which may lead to the modest decrease in blood pressure observed in clinical studies (see section 5.1). For patients at risk for volume depletion due to co-existing conditions, a starting dose of dapagliflozin 5 mg once daily may be appropriate as XIGDUO XR or individual component. Temporary interruption of XIGDUO XR should be considered for patients who develop volume depletion.

4.4.12 Use with other medications known to cause hypoglycemia

Dapagliflozin

Insulin and insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with dapagliflozin (see section 5.1).

Metformin

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Interaction with dapagliflozin and metformin

Coadministration of multiple doses of dapagliflozin and metformin did not meaningfully alter the pharmacokinetics of either dapagliflozin or metformin in healthy subjects.

There have been no formal interaction studies for XIGDUO XR. The following statements reflect the information available on the individual active substances.

4.5.2 Drug interactions with dapagliflozin

The metabolism of dapagliflozin is primarily mediated by UGT1A9-dependent glucuronide conjugation. The major metabolite, dapagliflozin 3-O-glucuronide, is not an SGLT2 inhibitor.

In *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes, and drugs that inhibit or induce these enzymes are not expected to alter the metabolic clearance of dapagliflozin. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

4.5.3 Effect of other drugs on dapagliflozin

In interaction studies conducted in healthy subjects, using mainly single dose design, the pharmacokinetics of dapagliflozin were not altered by metformin (an hOCT-1 and hOCT-2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (an hOAT-3 substrate and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate), voglibose (an α-glucosidase inhibitor), hydrochlorothiazide, bumetanide, valsartan, or simvastatin (a CYP3A4 substrate). Therefore, meaningful interaction of dapagliflozin with other substrates of hOCT-1, hOCT-2, hOAT-3, P-gp, CYP2C8, CYP2C9, CYP3A4, and other α-glucosidase inhibitor would not be expected.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolizing enzymes) or mefenamic acid (an inhibitor of UGT1A9), a 22% decrease and a 51% increase, respectively, in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion in either case.

Coadministration of dapagliflozin and bumetanide did not meaningfully change the pharmacodynamic effect of dapagliflozin to increase urinary glucose excretion in healthy subjects.

4.5.4 Effect of dapagliflozin on other drugs

Concomitant use of dapagliflozin and lithium may lead to a reduction in serum lithium concentrations due to a possible increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

In studies conducted in healthy subjects, using mainly a single dose design, as described below, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, simvastatin, digoxin (a P-gp substrate), or warfarin (S-warfarin is a CYP2C) substrate). Therefore, dapagliflozin is not a clinical meaningful inhibitor of hOCT-1, hOCT-2, hOAT-3, P-gp transporter pathway, and CYP2C8, CYP2C9, CYP2C19 and CYP3A4 mediated metabolism.

Coadministration of dapagliflozin and bumetanide did not meaningfully alter the steady-state pharmacodynamic responses (urinary sodium excretion, urine volume) to bumetanide in healthy subjects.

Dapagliflozin did not affect the anticoagulant activity of warfarin as measured by the prothrombin time (International Normalized Ratio [INR]).

4.5.5 Interactions between metformin hydrochloride and other drugs

Cationic drugs

Cationic drugs (eg. amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of metformin and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Glyburide

In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and maximum concentration (C_{max}) were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide

A single-dose, metformin-furosemide drug-interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal

clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug-interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Use with other drugs

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving metformin, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin, the patient should be observed closely for hypoglycemia.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and, therefore, is less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

4.5.6 Other interactions

The effects of smoking, diet, herbal products, and alcohol use on the pharmacokinetics of dapagliflozin have not been specifically studied.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

4.6 Pregnancy and lactation

4.6.1 Pregnancy

XIGDUO XR must not be used in the second and third trimesters of pregnancy. In the time period corresponding to second and third trimester of pregnancy with respect to human renal maturation, maternal exposure to dapagliflozin in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny (see section 5.3).

In conventional studies of embryo-fetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the first trimester period of non-renal organogenesis in humans. No developmental toxicities were observed in rabbits at any dose tested (1191x the maximum recommended human dose [MRHD]). In rats, dapagliflozin was neither embryolethal nor teratogenic (1441x the MRHD) in the absence of maternal toxicity.

Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

When pregnancy is detected, XIGDUO XR should be discontinued. No adequate and well-controlled studies of XIGDUO XR have been conducted in pregnant women.

4.6.2 Lactation

XIGDUO XR must not be used by a nursing woman.

No studies in lactating animals have been conducted with the combined components of XIGDUO XR. In studies performed with the individual components, both dapagliflozin and metformin are excreted in the milk of lactating rats.

Direct and indirect exposure of dapagliflozin to weanling juvenile rats and during late pregnancy are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny, although the long-term functional consequences of these effects are unknown. These periods of exposure coincide with a critical window of renal maturation in rats. As functional maturation of the kidneys in humans continues in the first 2 years of life, dapagliflozin-associated dilated renal pelvis and tubules noted in juvenile rats could constitute potential risk for human renal maturation during the first 2 years of life. Additionally, the negative effects on body-weight

gain associated with lactational exposure in weanling juvenile rats suggest that dapagliflozin must be avoided during the first 2 years of life (see section 5.3).

It is not known whether dapagliflozin or metformin are secreted in human milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

4.8.1 Clinical trial

Dapagliflozin and Metformin

Data from a prespecified pool of patients from 8 short-term, placebo-controlled studies of dapagliflozin coadministered with metformin immediate- or extended-release was used to evaluate safety data. This pool included several add-on studies (metformin alone and in combination with a DPP4 inhibitor and metformin, or insulin and metformin, 2 initial combination with metformin studies, and 2 studies of patients with cardiovascular disease (CVD) and type 2 diabetes who received their usual treatment (with metformin as background therapy). For studies that included background therapy with and without metformin, only patients who received metformin were included in the 8-study placebo-controlled pool. Across these 8 studies 983 patients were treated once daily with dapagliflozin 10 mg and metformin and 1185 were treated with placebo and metformin. These 8 studies provide a mean duration of exposure of 23 weeks. The mean age of the population was 57 years and 2% were older than 75 years. Fifty-four percent (54%) of the population was male; 88% White, 6% Asian, and 3% Black or African American. At baseline, the population had diabetes for an average of 8 years, mean hemoglobin A1c (HbA1c) was 8.4%, and renal function was normal or mildly impaired in 90% of patients and moderately impaired in 10% of patients.

Dapagliflozin

The safety profile of dapagliflozin in type 2 diabetes mellitus has been evaluated in clinical studies including more than 15000 subjects treated with dapagliflozin. For further information about the clinical studies, see section 5.1. Dapagliflozin has also been studied in patients with heart failure and in patients with chronic kidney disease. No information in these patient populations is available for the dapagliflozin/metformin fixed dose combination.

The incidence of adverse reactions was determined using a pre-specified pool of patients from 13 short-term (mean duration 22 weeks), placebo-controlled studies in type 2 diabetes. Across these 13 studies, 2360 patients were treated once daily with dapagliflozin 10 mg and 2295 were treated with placebo (either as monotherapy or in combination with other antidiabetic therapies).

Additionally, dapagliflozin 5 mg was evaluated in a 12-study, short-term, placebo-controlled pool of patients that included 1145 patients treated with dapagliflozin 5 mg (mean exposure = 22 weeks) and 1393 patients treated with (mean exposure = 21 weeks), either as monotherapy or in combination with other antidiabetic therapies.

In the dedicated cardiovascular (CV) outcomes study in patients with type 2 diabetes mellitus (DECLARE), 8574 patients received dapagliflozin 10 mg and 8569 received placebo for a median exposure time of 48 months. In total, there were 30623 patient-years of exposure to dapagliflozin.

Adverse reactions

The adverse reactions in patients treated with dapagliflozin 10 mg with and without metformin in clinical trials in type 2 diabetes mellitus and postmarketing are shown in Table 1.

Table 1 Adverse Drug Reactions by Frequency and System Organ Class (SOC)

System Organ Class	Common	Rare	Unknown
Infections and Infestations	Genital infection[a,b] Urinary tract infection[a,c]		
Metabolism and Nutrition Disorders		Diabetic ketoacidosis[f]	
Skin and subcutaneous tissue disorders			Rash[g,h]

System Organ Class	Common	Rare	Unknown
Musculoskeletal and Connective Tissue Disorders	Back pain[d]		
Renal Urinary Disorders	Pollakiuria[a] and polyuria[a,e]		

[a] Identified from 8 placebo-controlled studies, including 2 initial combination with metformin, 2 add-on to metformin, 1 add-on to insulin, 1 add-on to sitagliptin, and 2 studies with combination add-on therapy.

[b] Multiple adverse events terms, including vulvovaginal infections and candidiasis, balanoposthitis, balanitis candida, penile abscess, penile infection, vulval abscess and vaginitis bacterial.

[c] Multiple adverse events terms, including genitourinary tract infection, cystitis, pyelonephritis, trigonitis, urethritis and prostatitis.

[d] Additional events identified from 13 placebo-controlled studies with dapagliflozin 10 mg in type 2 diabetes mellitus including 3 monotherapy, 1 initial combination with metformin, 2 add-on to metformin, 2 add-on to insulin, 1 add-on to pioglitazone, 1 add-on to sitagliptin, 1 add-on to glimepiride, and 2 studies with combination add-on therapy.

[e] Represents multiple adverse events terms, including polyuria, urine output increased.

[f] Identified from the cardiovascular outcomes study in patients with type 2 diabetes. Frequency is based on annual rate.

[g] Identified during postmarketed use of dapagliflozin. Because these reactions are reported voluntarily from a population of an uncertain size, it is not always possible to reliably estimate their frequency.

[h] Rash includes the following preferred terms, listed in order of frequency in clinical trials: Rash, Rash generalized, Rash pruritic, Rash macular, Rash maculo-papular, Rash pustular, Rash vesicular, Rash erythematous. In active- and placebo-controlled clinical trials (Dapagliflozin, N=5936, All control, N=3403), the frequency of Rash was similar for Dapagliflozin (1.4%) and All control (1.4%), respectively, corresponding to the frequency 'Common'.

4.8.2 Clinical trial data and post-marketing data – metformin hydrochloride

Table 2 presents adverse reactions by system organ class and by frequency category. Frequency categories are based on information available from the metformin Summary of Product Characteristics available in the EU.

Table 2 The Frequency of Metformin Adverse Reactions Identified from Clinical Trial and Postmarketing Data

System Organ Class	Very common	Common	Very rare
Metabolism and Nutrition Disorders		Vitamin B_{12} deficiency	Lactic acidosis
Nervous System Disorders		Taste disturbance	
Gastrointestinal Disorders	Gastrointestinal symptoms[a]		
Hepatobiliary Disorders			Liver function disorders, hepatitis
Skin and Subcutaneous Tissue Disorders			Urticaria, erythema, pruritus

a Gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain, and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

4.8.3 Description of selected adverse reactions

Genital infections

Events of genital infections were reported in 5.5% and 0.6% of patients who received dapagliflozin 10 mg and placebo, respectively, in the 13-study, short-term, placebo-controlled pool. The events of genital infections reported in patients treated with dapagliflozin 10 mg were all mild to moderate. Most events of genital infection responded to an initial course of standard treatment and rarely resulted in discontinuation from the study (0.2% dapagliflozin 10 mg vs 0% in placebo). Infections were reported more frequently in females (8.4% dapagliflozin 10 mg vs 1.2% placebo) than in males (3.4% dapagliflozin 10 mg vs 0.2% placebo). The most frequently reported genital infections were vulvovaginal mycotic infections in females, and balanitis in males.

In the DECLARE study, the number of patients with serious adverse events (SAE) of genital infections were few and balanced: 2 (<0.1%) patients in each of the dapagliflozin and placebo groups.

Urinary tract infections

Events of urinary tract infections (UTI) were reported in 4.7% and 3.5% of patients who received dapagliflozin 10 mg and placebo, respectively, in the 13-study, short-term, placebo-controlled pool. Most events of urinary tract infections reported in patients treated with dapagliflozin 10 mg were mild to moderate. Most patients responded to an initial course of standard treatment, and urinary tract infections rarely caused discontinuation from the study (0.2% dapagliflozin 10 mg vs 0.1% placebo). Infections were more frequently reported in females (8.5% dapagliflozin 10 mg vs 6.7% placebo) than in males (1.8% dapagliflozin 10 mg vs 1.3% placebo).

In the DECLARE study there were fewer patients with SAEs of UTI in the dapagliflozin group compared with the placebo group: 79 (0.9%) and 109 (1.3%), respectively.

Diabetic ketoacidosis (DKA)

In the DECLARE study with a median exposure time of 48 months, events of DKA were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population (see section 4.4).

4.9 Overdose

Dapagliflozin

Orally administered dapagliflozin has been shown to be safe and well-tolerated in healthy subjects at single doses up to 500 mg (50 times the MRHD). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension, or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycemia for patients treated with dapagliflozin was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the MRHD) of dapagliflozin were administered for 2 weeks in healthy subjects and type 2 diabetes patients, the incidence of hypoglycemia for subjects administered dapagliflozin was slightly higher than placebo and was not dose related. Rates of adverse events including dehydration or hypotension for patients treated with dapagliflozin were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

Metformin hydrochloride

High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in a hospital. The most effective method to remove lactate and metformin is hemodialysis. Events of hypoglycemia have been reported with overdoses of metformin, although a causal association has not been established.

5 PHARMACOLOGICAL PROPERTIES

Mechanism of Action

XIGDUO XR combines two antihyperglycemic agents with complementary mechanisms of action to improve both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) in patients with type 2 diabetes: dapagliflozin, an SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.

Dapagliflozin

Dapagliflozin is a highly potent, selective, and reversible inhibitor of sodium glucose co-transporter 2 (SGLT2) that improves glycemic control in patients with type 2 diabetes mellitus and provides cardio-renal benefits.

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and preserve renal function. Other effects include an increase in hematocrit and reduction in body weight.

The cardio-renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect. In addition to the osmotic diuretic and related hemodynamic actions of SGLT2 inhibition, potential secondary effects on myocardial metabolism, ion channels, fibrosis,

adipokines and uric acid may be mechanisms underlying the cardio-renal beneficial effects of dapagliflozin.

Dapagliflozin improves both fasting and postprandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval, and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal blood glucose and/or low GFR, dapagliflozin has a low propensity to cause hypoglycemia, as the amount of glucose filtrated is small and can be reabsorbed by SGLT1 and unblocked SGLT2 transporters. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycemia.
Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta-cell function (HOMA-2) has been observed in clinical studies with dapagliflozin.

The majority of weight reduction is body-fat loss, including visceral fat rather than lean tissue or fluid loss as demonstrated by dual energy x-ray absorptiometry (DXA) and magnetic resonance imaging.

SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is greater than 1400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

Metformin hydrochloride

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see section 5.8) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.1 Pharmacodynamics properties

5.1.1 General

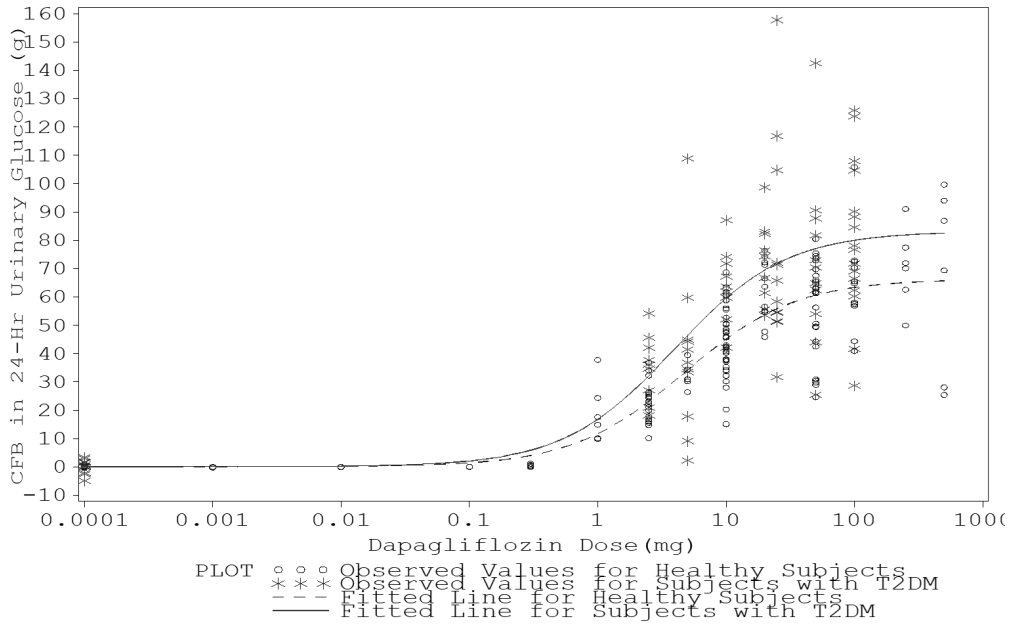
Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin (figure 1). Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in patients with type 2 diabetes mellitus for 12 weeks. This glucose elimination rate approached the maximum glucose excretion observed at 20 mg/day of dapagliflozin. Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume. Urinary volume increases in patients with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from 0.33 mg/dL to 0.87 mg/dL.

Figure 1: Scatter Plot and Fitted Line of Change from Baseline in 24-hr Urinary Glucose Amount *vs.* Dapagliflozin Dose in Healthy Subjects and Subjects with T2DM (Semi-Log Plot)



Cardiac Electrophysiology

Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15 times the recommended dose) in a study of healthy subjects. In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50 times the recommended dose) dapagliflozin in healthy subjects.

5.1.2 Clinical Trial Information

Clinical efficacy

Glycemic efficacy

The coadministration of dapagliflozin and metformin XR has been studied in treatment-naive patients inadequately controlled on diet and exercise alone. The coadministration of dapagliflozin and metformin IR or XR has been studied in patients with type 2 diabetes inadequately controlled on metformin, metformin plus a sulfonylurea, DPP4 inhibitors (with or without metformin), or insulin (with or without other oral antidiabetic therapy) and compared with a sulfonylurea in combination with metformin in patients with inadequate glycemic control on metformin alone.

Treatment with dapagliflozin plus metformin at all doses produced clinically relevant and statistically significant improvements in mean change from baseline at Week 24 in HbA1c and fasting plasma glucose compared to control. The coadministration of dapagliflozin and metformin IR tablets in concomitant initiation therapy with saxagliptin has been studied in type 2 diabetes patients inadequately controlled on metformin, which produced clinically relevant and

statistically significant improvements in mean change from baseline at Week 24in HbA1c, compared to control.

These clinically relevant glycemic effects were sustained in long-term extensions up to 208 weeks. HbA1c reductions were seen across subgroups including gender, age, race, duration of disease, and baseline body mass index (BMI).

Additionally, at Week 24, clinically relevant and statistically significant reductions in mean changes from baseline in body weight were seen with dapagliflozin and metformin combination treatments compared to control. Body-weight reductions were sustained in long-term extensions up to 208 weeks.

In a dedicated clinical study, decrease in weight was mainly attributable to a reduction in body-fat mass as measured by DXA. Dapagliflozin twice-daily treatment added to metformin was shown to be effective and safe in type 2 diabetic patients.

Additionally, dapagliflozin 10 mg or placebo were studied in type 2 diabetes patients with cardiovascular disease (approximately 37% of patients across 2 studies received dapagliflozin 10 mg or placebo plus metformin alone [with or without insulin]) and type 2 diabetes patients with hypertension (approximately 90% of patients across 2 studies received dapagliflozin 10 mg or placebo plus metformin).

In two studies of dapagliflozin 10 mg in type 2 diabetes patients with cardiovascular disease, statistically significant improvements in HbA1c and significant reductions in body weight and seated systolic blood pressure were seen at Week 24 in patients treated with dapagliflozin 10 mg compared to those treated with placebo, and were sustained through Week 104.

In two studies of dapagliflozin 10 mg in type 2 diabetes patients with hypertension, statistically significant reductions in mean seated systolic blood pressure were also seen in patients treated with dapagliflozin 10 mg combined with other OADs and antihypertensive treatments (an angiotensin-converting enzyme inhibitor [ACEi] or angiotensin receptor blocker [ARB] in one study and an ACE or ARB plus one additional antihypertensive treatment in another study) compared to those treated with placebo at Week 12.

Initial combination therapy with dapagliflozin Metformin

A total of 1236 treatment-naive patients with inadequately controlled type 2 diabetes (HbA1c ≥7.5% and <12%) participated in two active-controlled studies of 24-weeks duration to evaluate the efficacy and safety of initial therapy with dapagliflozin 5 mg or 10 mg in combination with metformin extended-release formulation (XR).

In one study, 638 patients were randomized to one of three treatment arms following a 1-week lead-in period: dapagliflozin 10 mg plus metformin XR (up to 2000 mg per day), dapagliflozin 10 mg plus placebo, or metformin XR (up to 2000 mg per day) plus placebo. Metformin dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg.

The combination treatment of dapagliflozin 10 mg plus metformin provided significant improvements in HbA1c and FPG, compared with either of the monotherapy treatments and significant reductions in body weight compared with metformin alone (Table 3, Figures 2 and 3). Dapagliflozin 10 mg as monotherapy also provided significant improvements in FPG and significant reduction in body weight compared with metformin alone and was non-inferior to metformin monotherapy in lowering HbA1c. The proportion of patients who were rescued or discontinued for lack of glycemic control during the 24-week double-blind treatment period (adjusted for baseline HbA1c) was higher for treatment with metformin plus placebo (13.5%) than for dapagliflozin 10 mg plus placebo and dapagliflozin 10 mg plus metformin (7.8% and 1.4%).

Table 3: Results at Week 24 (LOCF*) in an Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR

Efficacy Parameter	**Dapagliflozin 10 mg + Metformin XR N=211†**	**Dapagliflozin 10 mg N=219†**	**Metformin XR N=208†**
HbA1c (%)			
Baseline (mean)	9.10	9.03	9.03
Change from baseline (adjusted mean‡)	−1.98	−1.45	−1.44
Difference from dapagliflozin (adjusted mean‡)	−0.53§ (−0.74, −0.32)		

Efficacy Parameter	Dapagliflozin 10 mg + Metformin XR	Dapagliflozin 10 mg	Metformin XR
(95% CI)			
Difference from metformin (adjusted mean‡) (95% CI)	−0.54§ (−0.75, −0.33)	−0.01¶ (−0.22, 0.20)	
Percent of patients achieving HbA1c <7% adjusted for baseline	46.6%#	31.7%	35.2%
Change from baseline in HbA1c in patients with baseline HbA1c ≥9% (adjusted mean‡)	−2.59#	−2.14	−2.05
FPG (mg/dL)			
Baseline (mean)	189.6	197.5	189.9
Change from baseline (adjusted mean‡)	−60.4	−46.4	−34.8
Difference from dapagliflozin (adjusted mean‡) (95% CI)	−13.9§ (−20.9, −7.0)		
Difference from metformin (adjusted mean‡) (95% CI)	−25.5§ (−32.6, −18.5)	−11.6¶ (−18.6, −4.6)	
Body Weight (kg)			
Baseline (mean)	88.56	88.53	87.24
Change from baseline (adjusted mean‡)	−3.33	−2.73	−1.36
Difference from metformin (adjusted mean‡) (95% CI)	−1.97§ (−2.64, −1.30)	−1.37§ (−2.03, −0.71)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

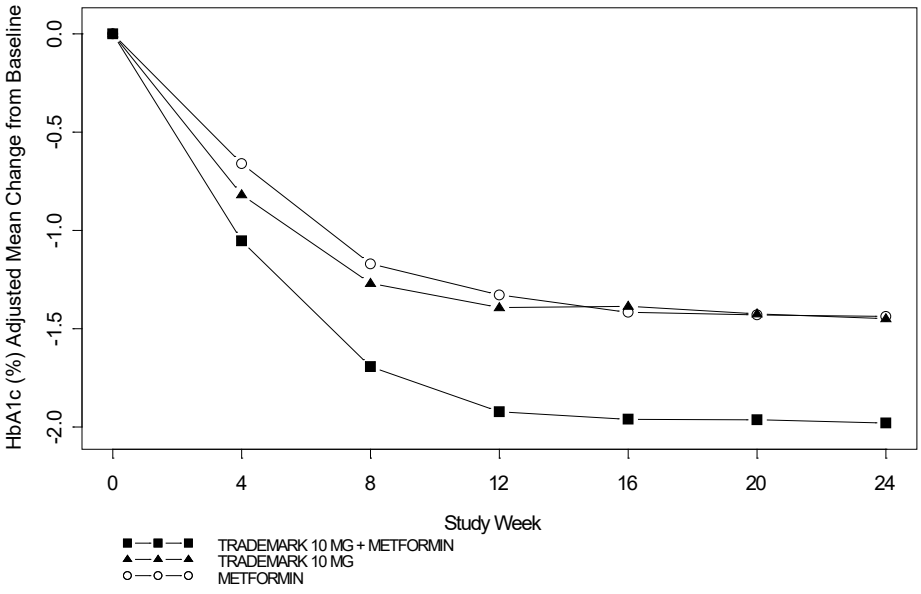
‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001.

¶ Non-inferior versus metformin.

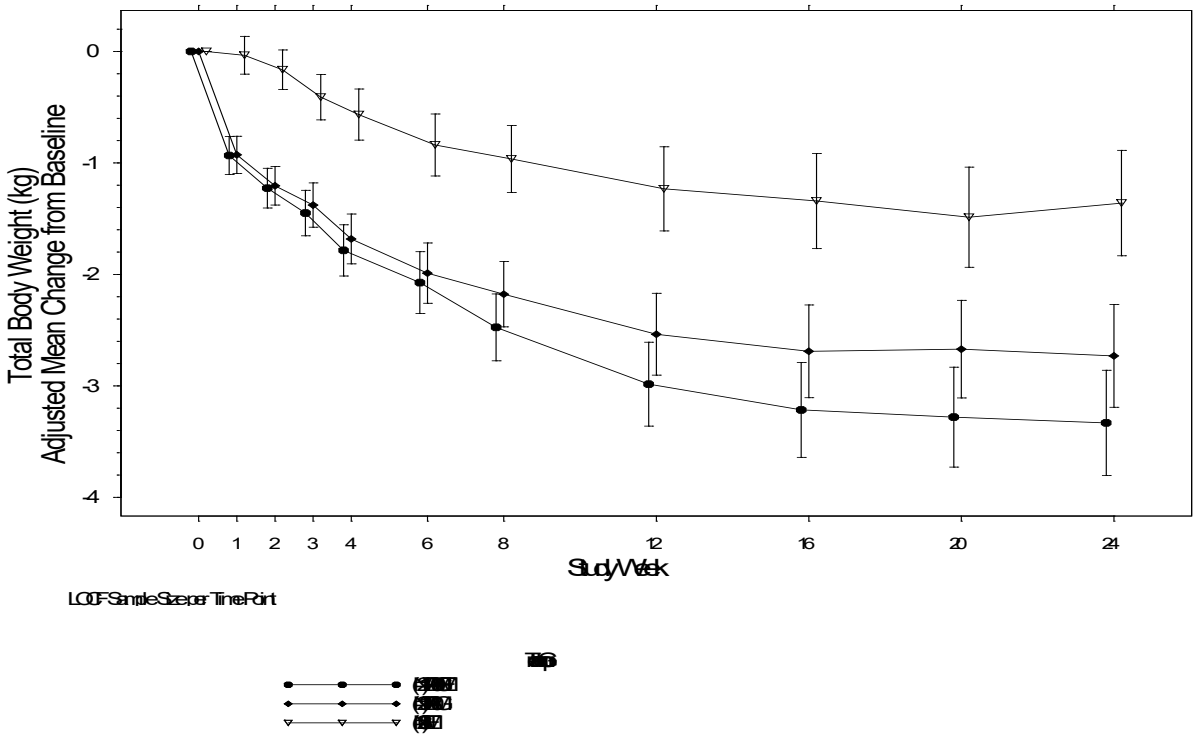
p-value <0.05.

Figure 2: **Adjusted Mean Change from Baseline Over Time (LOCF[a]) in HbA1c (%) in a 24-Week Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR**



Values in the plot represent adjusted mean and 95% confidence intervals (for week 24 only) based on the ANCOVA model using LOCF (Last observation (prior to rescue for rescued subjects) carried forward) data

Figure 3: **Adjusted Mean Change from Baseline Over Time (LOCF[a]) in Total Body Weight (kg) in a 24-Week Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR**



[a] LOCF: last observation (prior to rescue for rescued patients) carried forward

Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Another 24-week study evaluating dapagliflozin 5 mg plus metformin XR showed clinically relevant and statistically significant improvements in glycemic parameters *versus* dapagliflozin 5 mg monotherapy and metformin XR monotherapy.

Addition of Dapagliflozin to Metformin

A total of 546 patients with type 2 diabetes with inadequate glycemic control (HbA1c ≥7% and ≤10%) participated in a 24-week placebo-controlled study with a 78-week controlled, blinded extension period to evaluate dapagliflozin in combination with metformin. Patients on metformin at a dose of at least 1500 mg per day were randomized after completing a 2-week single-blind placebo lead-in period. Following the lead-in period, eligible patients were randomized to dapagliflozin 2.5 mg, 5 mg, or 10 mg, or placebo in addition to their current dose of metformin.

As add-on treatment to metformin, dapagliflozin 10 mg provided significant improvements in HbA1c, and FPG, and significant reduction in body weight compared with placebo at Week 24 (Table 4). At Week 102, adjusted mean change from baseline in HbA1c (Figure 4), FPG, and body weight was −0.78%, −24.5 mg/dL, and −2.81 kg , respectively, for patients treated with dapagliflozin 10 mg plus metformin and 0.02%, −10.4 mg/dL, and −0.67 kg for patients treated with placebo plus metformin based on the longitudinal repeated measures analysis excluding data after rescue. The proportion of patients who were rescued or discontinued for lack of glycemic control during the 24-week double-blind treatment period (adjusted for baseline HbA1c) was higher in the placebo plus metformin group (15.0%) than in the dapagliflozin 10 mg plus metformin group (4.4%). By week 102 (adjusted for baseline HbA1c), more patients treated with placebo plus metformin (60.1%) required rescue therapy than patients treated with dapagliflozin 10 mg plus metformin (44.0%).

Table 4: Results of a 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin

Efficacy Parameter	**Dapagliflozin 10 mg + Metformin N=135†**	**Placebo + Metformin N=137†**
HbA1c (%)		
Baseline mean	7.92	8.11

Efficacy Parameter	Dapagliflozin 10 mg + Metformin N=135†	Placebo + Metformin N=137†
Change from baseline (adjusted mean‡)	−0.84	−0.30
Difference from placebo (adjusted mean‡) (95% CI)	−0.54§ (−0.74, −0.34)	
Percent of patients achieving HbA1c <7% adjusted for baseline	40.6%¶	25.9%
Change from baseline in HbA1c in patients with baseline HbA1c ≥9% (adjusted mean‡)	−1.32¶ (N= 18)	−0.53 (N= 22)
FPG (mg/dL)		
Baseline mean	156.0	165.6
Change from baseline at week 24 (adjusted mean‡)	−23.5	−6.0
Difference from placebo (adjusted mean‡) (95% CI)	−17.5§ (−25.0, −10.0)	
Change from baseline at week 1 (adjusted mean‡)	−16.5§ (N=115)	1.2 (N=126)
Body Weight (kg)		
Baseline mean	86.28	87.74
Change from baseline (adjusted mean‡)	−2.86	−0.89
Difference from placebo (adjusted mean‡) (95% CI)	−1.97§ (−2.63, −1.31)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

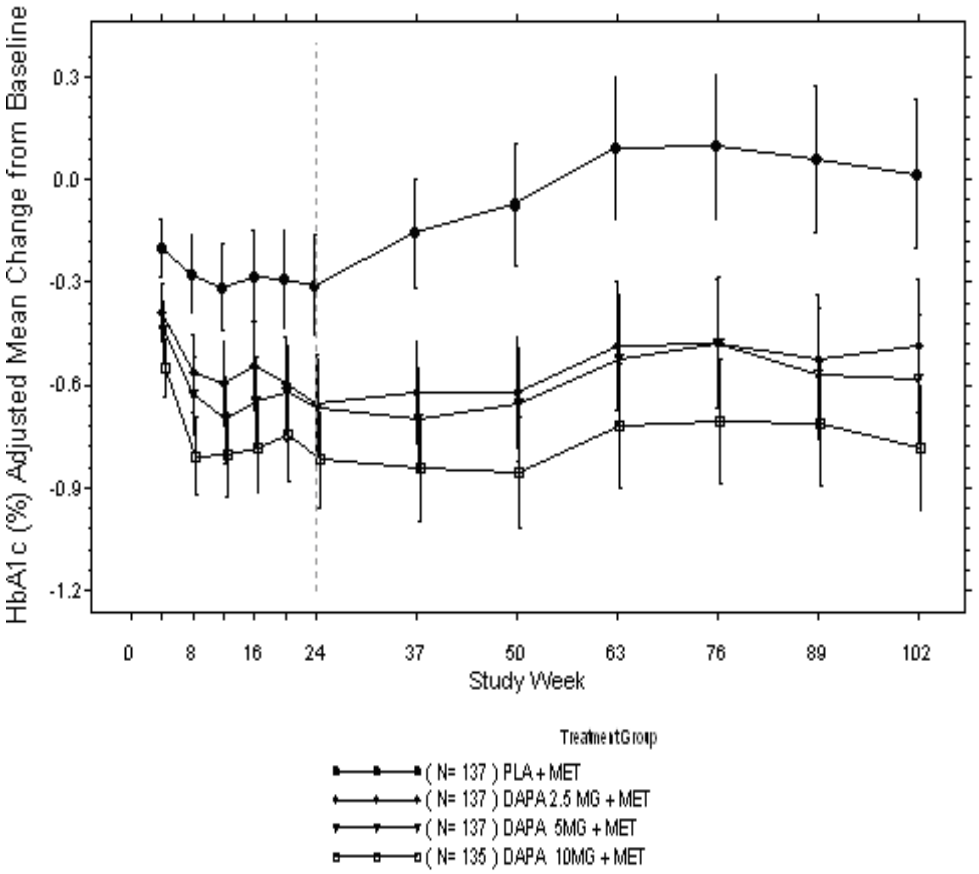
‡ Least squares mean adjusted for baseline value.

§ p-value <0.00001 vs placebo + metformin.

¶ p-value <0.05 vs placebo + metformin.

Figure 4: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 102-Week Placebo-Controlled Study of Dapagliflozin in Combination with

Metformin (Longitudinal Repeated Measures Analysis, Excluding Data after Rescue)



Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

Dapagliflozin twice-daily add-on to Metformin

A total of 399 patients with type 2 diabetes and inadequate glycemic control on metformin alone were randomized in this 16-week, placebo-controlled study to evaluate dapagliflozin 2.5 mg twice daily and 5 mg twice daily as add-on therapy to metformin. Recruitment was stratified by HbA1c <7.0% (approximately 15% of patients) and HbA1c ≥7.0% (approximately 85% of patients) at randomization. Patients on metformin at a dose of at least 1500 mg per day were randomized following a 4-week single-blind, placebo lead-in period to dapagliflozin 5 mg, dapagliflozin 2.5 mg or placebo twice daily. An additional double-blind arm of the study included patients received 10 mg dapagliflozin once daily co-administered with metformin as a 'positive control,' a measure of assay sensitivity. Efficacy and safety in this dapagliflozin once-daily treatment arm was compared only to placebo co-administered with metformin.

As add-on treatment to metformin, dapagliflozin 5 mg twice daily provided significant improvements in HbA1c, and FPG, and significant reduction in body weight compared with placebo

twice daily at Week 16 and was consistent with glycemic and body-weight changes seen with dapagliflozin 10 mg once-daily treatment (see Table 5). Dapagliflozin 2.5 mg plus metformin twice-daily treatment also significantly improved HbA1c (−0.52%) compared to placebo plus metformin twice-daily treatment (−0.30%) at Week 16 ($p< 0.05$).

Table 5: Results of a 16-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin Twice Daily in Add-On Combination with Metformin

Efficacy Parameter	**Dapagliflozin 5 mg BID + Metformin N=99†**	**Placebo BID + Metformin N=101†**
HbA1c (%)		
Baseline mean	7.79	7.94
Change from baseline (adjusted mean‡)	−0.65	−0.30
Difference from placebo (adjusted mean‡) (95% CI)	−0.35§ (−0.52, −0.18)	
Percent of patients with HbA1c >7.0% at baseline achieving HbA1c <7% adjusted for baseline at Week 16	38.2¶ (N=90)	21.4 (N=87)
FPG (mg/dL)		
Baseline mean	155.3	157.8
Change from baseline at week 16 (adjusted mean‡)	−25.6	−10.4
Difference from placebo (adjusted mean‡) (95% CI)	−15.3§ (−21.4, −9.1)	
Change from baseline at week 1 (adjusted mean‡)	−14.7	2.0
Body Weight (kg)		
Baseline mean	93.62	88.82
Change from baseline (adjusted mean‡)	−2.74	−0.86
Difference from placebo (adjusted mean‡) (95% CI)	−1.88# (−2.52, −1.24)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 vs placebo + metformin.

¶ p-value <0.05 vs placebo + metformin.

Percent change in body weight was analyzed as a key secondary endpoint (p-value <0.0001), absolute body-weight change in kg was analyzed with a nominal p-value (p-value <0.001).

The proportion of patients who were discontinued for lack of glycemic control during the 16-week double-blind treatment period (adjusted for baseline HbA1c) was higher in the placebo twice daily plus metformin group (5.0%) than in the dapagliflozin 2.5 mg twice daily plus metformin group (1%). No patients in the dapagliflozin 5 mg twice daily plus metformin group discontinued due to inadequate glycemic control.

Active glipizide-controlled study add-on to metformin

A total of 816 patients with type 2 diabetes with inadequate glycemic control (HbA1c >6.5% and ≤10%) were randomized in a 52-week, glipizide-controlled non-inferiority study with a 156-week extension period to evaluate dapagliflozin as add-on therapy to metformin. Patients on metformin at a dose of at least 1500 mg per day were randomized following a 2-week placebo lead-in period to glipizide or dapagliflozin (5 mg or 2.5 mg, respectively) and were up-titrated over 18 weeks to optimal glycemic effect (FPG <110 mg/dL, <6.1 mmol/L) or to the highest dose level (up to glipizide 20 mg and dapagliflozin 10 mg) as tolerated by patients. Thereafter, doses were kept constant, except for down-titration to prevent hypoglycemia. Rescue for lack of glycemic control was not available in this study through Week 104, but was available between Weeks 105 and 208.

At the end of the titration period, 87% of patients treated with dapagliflozin had been titrated to the maximum study dose (10 mg), versus 73% treated with glipizide (20 mg). Dapagliflozin led to a similar mean reduction in HbA1c from baseline to Week 52, compared with glipizide, thus demonstrating non-inferiority (Table 6). Dapagliflozin treatment led to a significant mean reduction in body weight from baseline to week 52 compared with a mean increase in body weight in the glipizide group.

At Week 104 and 208, adjusted mean change from baseline in HbA1c were −0.32% and -0.10%, and body weight were −3.70 kg and −3.95 kg, respectively, for patients treated with dapagliflozin ; adjusted mean changes from baseline in HbA1c were−0.14% and 0.20%, respectively, and changes in body weight were 1.36 kg and 1.12 kg, respectively, for patients treated with glipizide based on the longitudinal repeated measures analysis (Figures 6 and 7). The percent of patients achieving

weight loss of ≥5% (adjusted) at Weeks 104 and 208 were 23.8% and 51.0%, respectively, for patients treated with dapagliflozin and 2.8% and 9.9%, respectively, for patients treated with glipizide.

By Weeks 52, 104, and 208, the proportion of patients who discontinued for lack of glycemic control (adjusted for baseline HbA1c) was higher for glipizide plus metformin (3.6%, 21.6% and 44.9%, respectively) than for dapagliflozin plus metformin (0.2%,14.5%, and 39.4%, respectively). At 52, 104 and 208 weeks, respectively, a significantly lower proportion of patients treated with dapagliflozin (3.5%, 4.3% and 5.0%) experienced at least one event of hypoglycemia, compared to glipizide (40.8%, 47.0% and 50.0%).

Table 6: Results at Week 52 (LOCF*) in an Active-Controlled Study Comparing Dapagliflozin to Glipizide as Add-on to Metformin

Efficacy Parameter	**Dapagliflozin + Metformin N=400†**	**Glipizide + Metformin N=401†**
HbA1c (%)		
Baseline (mean)	7.69	7.74
Change from baseline (adjusted mean‡)	−0.52	−0.52
Difference from Glipizide+Metformin (adjusted mean‡)	0.00§	
(95% CI)	(−0.11, 0.11)	
Body Weight (kg)		
Baseline (mean)	88.44	87.60
Change from baseline (adjusted mean‡)	−3.22	1.44
Difference from Glipizide+Metformin (adjusted mean‡)	−4.65¶	
(95% CI)	(−5.14, −4.17)	
Percent of patients achieving weight loss ≥5% (adjusted) (95%CI)	33.3%¶ (28.7, 37.9)	2.5% (1.0, 4.0)

* LOCF: last observation carried forward.

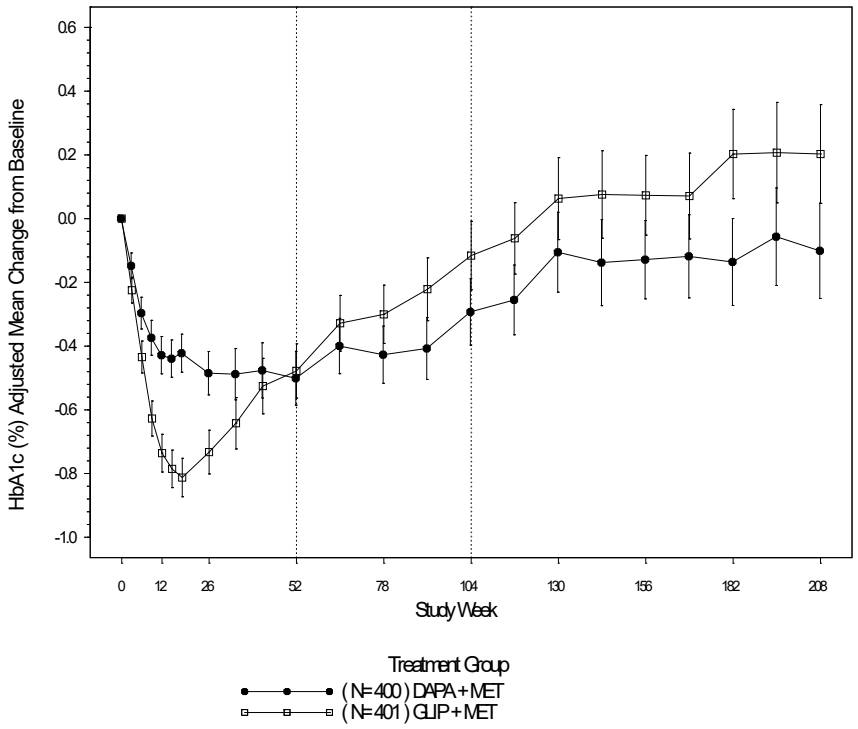
† Randomized and treated patients with baseline and at least 1 post baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ Non-inferior to glipizide + metformin.

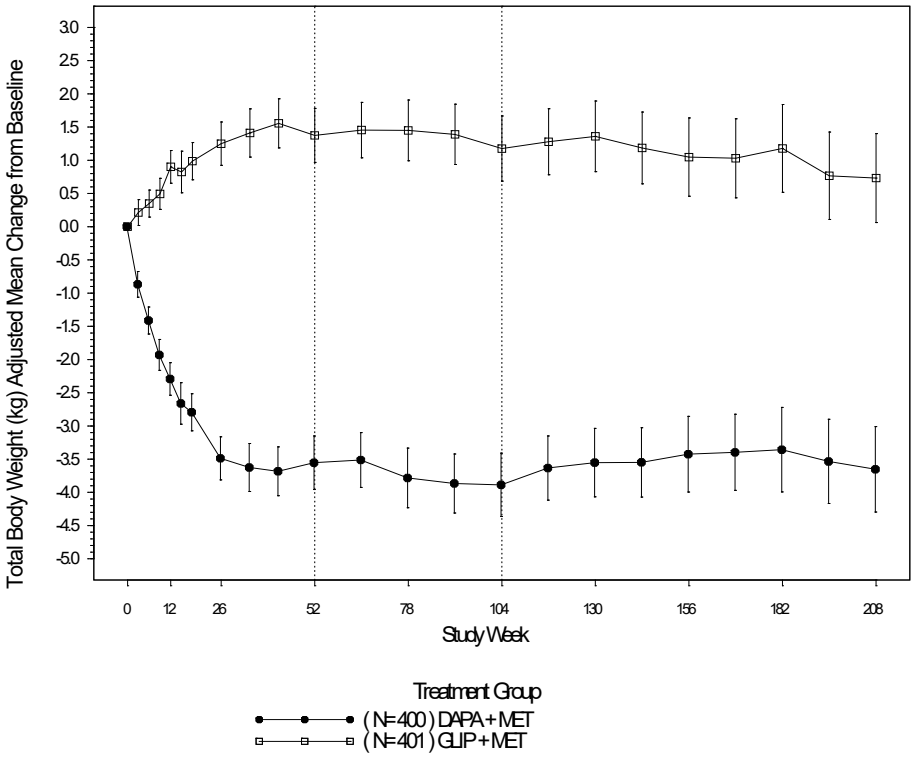
¶ p-value <0.0001.

Figure 5: **Adjusted Mean Change from Baseline Over Time in HbA1c (%)in a 208-Week Active-Controlled Study Comparing Dapagliflozin to Glipizide as Add-on to Metformin (Longitudinal Repeated Measures Analysis)**



Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

Figure 6: Adjusted Mean Change from Baseline Over Time in Body Weight (kg) in a 208-Week Active-Controlled Study Comparing Dapagliflozin to Glipizide as Add-on to Metformin (Longitudinal Repeated Measures Analysis)



Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

Add-on combination therapy of dapagliflozin to metformin and a sulfonylurea

A total of 218 patients with type 2 diabetes and inadequate glycemic control (HbA1c ≥7% and ≤10.5%) participated in a 24-week, placebo-controlled study with a 28-week extension period to evaluate dapagliflozin in combination with metformin and a sulfonylurea. Patients on a stable dose of metformin (immediate- or extended-release formulations) ≥1500 mg/day plus maximum tolerated dose, which must be at least half maximum dose, of a sulfonylurea for at least 8 weeks prior to enrollment were randomized after an 8-week placebo lead-in period todapagliflozin 10 mg or placebo. Dose-titration of dapagliflozin or metformin was not permitted during the 24-week treatment period. Down-titration of sulfonylurea was permitted to prevent hypoglycemia, but no up-titration was permitted.

As add-on treatment to combined metformin and a sulfonylurea, treatment with dapagliflozin 10 mg provided significant improvements in HbA1c and FPG and significant reductions in body weight compared with placebo at Week 24 (Table 7). Significant reduction in seated systolic

blood pressure at Week 8 was also observed in patients treated with dapagliflozin 10 mg compared to placebo. The effects in HbA1cC, FPG and body weight observed at Week 24 were sustained at Week 52.

At Week 24, no patients treated with dapagliflozin 10 mg combined with metformin and a sulfonylurea and 10 patients (9.3%) treated with placebo combined with metformin and a sulfonylurea were rescued or discontinued for lack of glycemic control (adjusted for baseline HbA1c). By Week 52 (adjusted for baseline HbA1c) more patients on placebo combined with metformin and a sulfonylurea (42.7%) were rescued for lack of glycemic control than patients on XIGDUO (10.1%). No patient was discontinued from study medication due to inadequate glycemic control.

Table 7: Results of a 24-Week Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin and Sulfonylurea

Efficacy Parameters	**Dapagliflozin 10 mg +Metformin +SU**	**Placebo +Metformin +SU**
	N=108†	**N=108†**
HbA1c (%)‡‡		
Baseline mean	8.08	8.24
Change from baseline (adjusted mean‡)	−0.86	−0.17
Difference from placebo (adjusted mean‡) (95% CI)	−0.69§ (−0.89, −0.49)	
Percent of patients achieving HbA1c <7% adjusted for baseline	31.8%§	11.1%
FPG (mg/dL)*		
Baseline mean	167.4	180.3
Change from baseline at Week 24 (adjusted mean‡)	−34.2	−0.8

Table 7: Results of a 24-Week Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin and Sulfonylurea

Efficacy Parameters	Dapagliflozin 10 mg +Metformin +SU	Placebo +Metformin +SU
Difference from placebo (adjusted mean‡) (95% CI)	−33.5§ (−43.1, −23.8)	
Body Weight (kg)*		
Baseline mean	88.57	90.07
Change from baseline (adjusted mean‡)	−2.65	−0.58
Difference from placebo (adjusted mean‡) (95% CI)	−2.07§ (−2.79, −1.35)	
Seated Systolic Blood Pressure at Week 8 (mmHg)*		
Baseline mean	134.7	136.3
Change from baseline at Week 8 (adjusted mean‡)	−4.0	−0.3
Difference from placebo (adjusted mean‡) (95% CI)	−3.8** (−7.1, −0.5)	

† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡‡ LRM: longitudinal repeated measures analysis.

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 *versus* placebo.

** p-value <0.05 *versus* placebo.

Add-on of dapagliflozin to sitagliptin alone or in combination with metformin

A total of 452 patients with type 2 diabetes who were drug naive, or who were treated at entry with metformin or a DPP4 inhibitor alone or in combination, and had inadequate glycemic control (HbA1c ≥7.0% and ≤10.0% at randomization), were randomized in a 24-week, placebo-controlled study with a 24-week extension period to evaluate dapagliflozin in combination with sitagliptin (a DPP4 inhibitor) with or without metformin.

Eligible patients were stratified based on the presence or absence of background metformin (≥1500 mg/day) and within each stratum were randomized to either dapagliflozin 10 mg plus sitagliptin 100 mg once daily or placebo plus sitaglipitin 100 mg once daily. Two-hundred-twenty-six (226) patients were analyzed in the sitagliptin with metformin stratum, 113 patients received dapagliflozin 10 mg plus sitagliptin and metformin, and 113 patients received placebo plus sitagliptin and metformin. Dose titration of dapagliflozin, sitagliptin or metformin was not permitted during the study.

For patients who received sitagliptin and metformin, dapagliflozin 10 mg provided significant improvements in HbA1c, HbA1c in patients with baseline HbA1c ≥8%, and FPG, and significant reduction in body weight, compared with the placebo group at Week 24 (Table 8).

At Week 48, adjusted mean change from baseline in HbA1c, HbA1c in patients with HbA1c ≥8% at baseline (unadjusted), FPG, PPG, and body weight were −0.44%, −1.05 %, −23.7 mg/dL, −47.2 mg/dL, and −2.53 kg, respectively, for patients treated with dapagliflozin 10 mg plus sitagliptin with metformin, and 0.15%, −0.54 %, 6.3 mg/dL, −18.6 mg/dL, and −0.45 kg for patients treated with placebo plus sitagliptin with metformin based on the longitudinal repeated measures analysis excluding data after rescue.

Table 8: Results of a 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Sitagliptin (Strata with Metformin)

Efficacy Parameter	Dapagliflozin 10 mg + Sitagliptin + Metformin	Placebo + Sitagliptin + Metformin
	N=113[†]	N=113[†]
HbA1c (%)		
Baseline (mean)	7.80	7.87
Change from baseline (adjusted mean[‡])	−0.43	−0.02
Difference from placebo (adjusted mean[‡]) (95% CI)	−0.40[§] (−0.58, −0.23)	
Change from baseline in HbA1c in patients with baseline HbA1c ≥8% (adjusted mean[‡])	−0.79[§] (N=39)	0.0 (N=43)
FPG (mg/dL)		
Baseline (mean)	165.9	164.7
Change from baseline at Week 24 (adjusted mean[‡])	-26.2	3.0
Difference from placebo (adjusted mean[‡]) (95% CI)	−29.2[§] (−38.0, −20.4)	
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[§] (−2.61, −1.13)	
Seated SBP at Week 8 in patients with baseline seated SBP ≥130 mmHg (mmHg)		
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, 4.32)	
2-hour PPG[¶](mg/dL)		
Baseline (mean)	230.2	221.0
Change from baseline (adjusted mean[‡])	−48.9	−7.2
Difference from placebo (adjusted mean[‡]) (95% CI)	−41.6 (−55.4, −27.8)	

Patients with HbA1c decrease ≥0.7% (adjusted %)	28.0	16.0

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 versus placebo.

¶ 2-hour PPG level as a response to a 75-gram oral glucose tolerance test (OGTT).

Add-on combination therapy of dapagliflozin with insulin

A total of 808 patients with type 2 diabetes who had inadequate glycemic control (HbA1c ≥7.5% and ≤10.5%) were randomized in a 24-week, placebo-controlled study with an 80-week extension period to evaluate dapagliflozin as add-on therapy to insulin. Patients on a stable insulin regimen, with a mean dose of at least 30 IU of injectable insulin per day, for a period of at least 8 weeks prior and on a maximum of two OADs including metformin were randomized after completing a 2-week enrollment period to receive dapagliflozin 2.5 mg, 5 mg, or 10 mg, or placebo in addition to their current dose of insulin and other OADs, if applicable. Patients were stratified according to the presence or absence of background OADs. Up- or down-titration of insulin was only permitted during the treatment phase in patients who failed to meet specific glycemic goals. Dose modifications of blinded study medication or OADs were not allowed during the treatment phase, with the exception of decreasing OADs where there were concerns over hypoglycemia after cessation of insulin therapy.

In this study, 50% of patients were on 1 or 2 OADs in addition to insulin; of these, 80% were on metformin alone and 14% were on metformin plus another OAD. At Week 24, dapagliflozin 10 mg dose provided significant improvement in HbA1c, FPG, and mean insulin dose, and significant reduction in body weight compared with placebo in combination with insulin, with or without up to 2 OADs (Table 9); the effect of dapagliflozin on HbA1c was similar in patients on insulin alone and patients on insulin plus OADs. At Week 48, adjusted mean change from baseline in HbA1c, FPG, and body weight was −0.93%, −21.5 mg/dL, and −1.79 kg, respectively, for patients treated with dapagliflozin 10 mg plus insulin and −0.43%, −4.4 mg/dL, and −0.18 kg, respectively, for patients treated with placebo plus insulin based on the longitudinal repeated measures analysis excluding data after rescue. At Week 104, adjusted mean change from baseline in HbA1c, FPG, and body weight was −0.71%, −18.2 mg/dL, and −1.97 kg, respectively, for patients treated with dapagliflozin 10 mg plus insulin, and −0.06%, −11.2 mg/dL, and 0.91 kg, respectively, for patients

treated with placebo plus insulin based on the longitudinal repeated measures analysis excluding data after rescue (see Figure 7).

At week 24, a significantly higher proportion of patients on dapagliflozin 10 mg reduced their insulin dose by at least 10% compared to placebo. The proportion of patients who required up-titration of their insulin dose or discontinued due to lack of glycemic control (adjusted for baseline HbA1c) was higher for placebo plus insulin (29.2%) than for dapagliflozin 10 mg plus insulin (9.7%). At Weeks 48 and 104, the insulin dose remained stable compared to baseline in patients treated with dapagliflozin 10 mg at an average dose of 76 IU/day, but continued to increase (mean increase 10.5 IU/day and 18.3 IU/day, respectively, from baseline) in placebo-treated patients. By Weeks 48 and 104 (adjusted for baseline HbA1c), more patients treated with placebo (42.8% and 50.4%, respectively) required up-titration with insulin to maintain glycemic levels or discontinued due to lack of glycemic control than patients treated with dapagliflozin 10 mg (15.3% and 25.5%, respectively).

In a separate analysis of patients on insulin plus metformin IR alone, similar improvements to those seen in the total study population were seen in patients treated with dapagliflozin plus insulin with metformin in HbA1c, body weight, and mean insulin dose compared with placebo plus insulin with metformin at Week 24 (Table 9).

Table 9: Results of 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Combination with Insulin with or without up to 2 Oral Antidiabetic Therapies

Efficacy Parameter	**Dapagliflozin 10 mg**	**Placebo**
Intent-to-Treat Population	N=194[†‡]	N=193[†‡]
HbA1c (%)		
Baseline (mean)	8.58	8.46
Change from baseline (adjusted mean[§])	−0.90	−0.30
Difference from placebo (adjusted mean[§]) (95% CI)	−0.60[¶] (−0.74, −0.45)	
Patients who received insulin + metformin alone**	N=83	N=77
HbA1c (%)		
Baseline (mean)	8.52	8.43

Efficacy Parameter	Dapagliflozin 10 mg	Placebo
Change from baseline (adjusted mean[§])	−0.93	−0.31
Difference from placebo (adjusted mean[§]) (95% CI)	−0.61 (−0.83, −0.40)	
Intent-to-Treat Population	N=194[†‡]	N=193[†‡]
Mean Daily Insulin Dose (IU)[††]		
Baseline (mean)	77.96	73.96
Change from baseline (adjusted mean[§])	−1.16	5.08
Difference from placebo (95% CI)	−6.23[¶] (−8.84, −3.63)	
Percent of patients with mean daily insulin dose reduction of at least 10% adjusted for baseline	19.7%[#]	11.0%
Patients who received insulin + metformin alone**	N=83	N=77
Mean Daily Insulin Dose (IU)[††]		
Baseline (mean)	79.75	82.14
Change from baseline (adjusted mean[§])	−1.70	3.46
Difference from placebo (95% CI)	−5.15 (−9.06, −1.25)	
Percent of patients with mean daily insulin dose reduction of at least 10% adjusted for baseline	19.0%	13.1%
Intent-to-Treat Population	N=194[†‡]	N=193[†‡]
FPG (mg/dL)		
Baseline (mean)	173.7	170.0
Change from baseline (adjusted mean[§])	−21.7	3.3
Difference from placebo (adjusted mean[§]) (95% CI)	−25.0[¶] (−34.3, −15.8)	
Patients who received insulin + metformin alone**	N=83	N=77
FPG (mg/dL)		
Baseline (mean)	173.8	166.3
Change from baseline (adjusted mean[§])	−25.7	11.4
Difference from placebo (adjusted mean[§])	−37.1	

Efficacy Parameter	Dapagliflozin 10 mg	Placebo
(95% CI)	(−50.4, −23.8)	
Intent-to-Treat Population	N=194[†‡]	N=193[†‡]
Body Weight (kg)		
Baseline (mean)	94.63	94.21
Change from baseline (adjusted mean§)	−1.67	0.02
Difference from placebo (adjusted mean§) (95% CI)	−1.68[¶] (−2.19, −1.18)	
Patients who received insulin + metformin alone**	N=83	N=77
Body weight (kg)		
Baseline (mean)	95.68	98.69
Change from baseline (adjusted mean[§])	−1.77	−0.06
Difference from placebo (adjusted mean[§]) (95% CI)	−1.71 (−2.47, −0.95)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ 50% of patients were on insulin monotherapy at baseline.

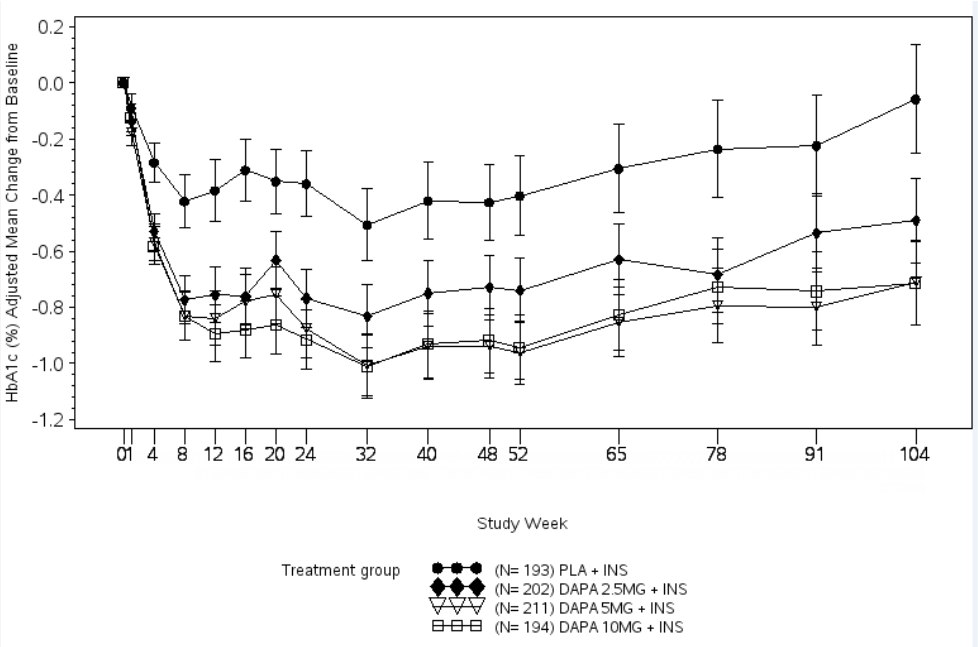
§ Least squares mean adjusted for baseline value.

** Post hoc analysis.

¶ p-value <0.0001 *versus* placebo.

p-value <0.05 *versus* placebo.

Figure 7: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 104-Week Placebo-controlled Study of Dapagliflozin in Combination with Insulin with or without up to 2 Oral Anti-diabetic Therapies Excluding Data After Insulin Up-titration



Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Concomitant initiation of saxagliptin and dapagliflozin in patients inadequately controlled on metformin

A total of 534 adult patients with type 2 diabetes mellitus and inadequate glycemic control on metformin alone (HbA1c ≥8% and ≤12%) participated in this 24-week randomized, double blind, active comparator-controlled superiority trial to compare the combination of saxagliptin and dapagliflozin added concurrently to metformin, *versus* saxagliptin (DPP4 inhibitor) or dapagliflozin added to metformin. Patients were randomized to one of three double-blind treatment groups to receive saxagliptin 5 mg and dapagliflozin 10 mg added to metformin XR, saxagliptin 5 mg and placebo added to metformin XR, or dapagliflozin 10 mg and placebo added to metformin XR.

The saxagliptin and dapagliflozin combination group achieved significantly greater reductions in HbA1c *versus* either saxagliptin group or dapagliflozin group at 24 weeks. Forty-one percent (41%) of patients in the saxagliptin and dapagliflozin combination group achieved HbA1c levels of less than 7% compared to 18% patients in the saxagliptin group and 22% patients in the dapagliflozin group.

Table 10: HbA1c at Week 24 (LRM*) in Active-Controlled Study Comparing the Combination of Saxagliptin and Dapagliflozin Added Concurrently to Metformin with Saxagliptin or Dapagliflozin Added Concurrently to Metformin

Efficacy Parameter	Saxagliptin 5 mg + Dapagliflozin 10 mg + Metformin XR N=179[†]	Saxagliptin 5 mg + Metformin XR N=176[†]	Dapagliflozin 10 mg + Metformin XR N=179[†]
HbA1c (%) at week 24 (LRM)*			
Baseline (mean)	8.93	9.03	8.87
Change from baseline (adjusted mean[‡]) (95% CI) for adjusted mean change from baseline	−1.47 (−1.62, −1.31)	−0.88 (−1.03, −0.72)	−1.20 (−1.43, −1.04)
Difference from saxagliptin + metformin (adjusted mean[‡]) (95% CI)	−0.59[§] (−0.81, −0.37)	-	-
Difference from dapagliflozin + metformin (adjusted mean[‡]) (95% CI)	−0.27[¶] (−0.48, −0.05)	-	-

* LRM = Longitudinal repeated measures (using values prior to rescue).

† Randomized and treated patients with baseline and at least 1 postbaseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001.

¶ p-value =0.0166.

The adjusted mean change in body weight at 24 weeks was −2.05 kg (95% CI [-2.52, -1.58]) in the saxagliptin and dapagliflozin plus metformin group and −2.39 kg (95% CI [-2.87, -1.91]) in the dapagliflozin plus metformin group. The adjusted mean change for body weight in the saxagliptin plus metformin group had no change 0.00 kg (95% CI [-0.48, 0.49]).

Add-on therapy with dapagliflozin in patients inadequately controlled on saxagliptin plus metformin

A 24-week randomized, double-blind, placebo-controlled study compared the sequential addition of 10 mg dapagliflozin to 5 mg saxagliptin and metformin to the addition of placebo to 5 mg saxagliptin (DPP4 inhibitor) and metformin in patients with type 2 diabetes mellitus and inadequate glycemic control (HbA1c ≥7% and ≤10.5%). Three hundred and twenty (320) subjects were randomized equally into either the dapagliflozin added to saxagliptin plus metformin treatment group or placebo plus saxagliptin plus metformin treatment group.

The group with dapagliflozin sequentially added to saxagliptin and metformin achieved statistically significant (p-value <0.0001) greater reductions in HbA1c *versus* the group with placebo sequentially added to saxagliptin plus metformin group at 24 weeks (see Table 11).

Table 11: Results of a 24-Week (LRM*) Placebo-Controlled Study of Dapagliflozin in Add-on Combination with Saxagliptin and Metformin

Efficacy Parameter	**Dapagliflozin 10 mg + Saxagliptin 5 mg + Metformin (N=160)†**	**Placebo + Saxagliptin 5 mg + Metformin (N=160)†**
HbA1c (%) at Week 24*		
Baseline (mean)	8.24	8.16
Change from baseline (adjusted mean‡) (95% CI)	−0.82 (−0.96, 0.69)	−0.10 (−0.24, 0.04)
Comparison of dapagliflozin added to saxa + met *vs.* placebo + saxa + met: Adjusted mean* (95% CI)	−0.72 (−0.91, −0.53) §	
FPG (mg/dL)		

Baseline (mean)	178.5	176.6
Change from baseline (adjusted mean‡) (95% CI)	−32.7 (−38.3, −27.2)	−5.3 (−11.1, 0.6)
Comparison of dapagliflozin added to saxa + met *vs.* placebo + saxa + met: Adjusted mean* (95% CI)	−27.5 (−35.4, −19.6) §	
2-hour PPG¶ (mg/dL)		
Baseline (mean)	239.8	241.3
Change from baseline (adjusted mean‡) (95% CI)	−73.5 (−81.5, −65.5)	−38.0 (−46.1, −29.9)
Comparison of dapagliflozin added to saxa + met *vs.* placebo + saxa + met: Adjusted mean ¶ (95% CI)	−35.5§ (−46.3, −24.7)	

* LRM = Longitudinal repeated measures (*using values prior to rescue*).

† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

¶ LOCF: last observation (prior to rescue for rescued patients) carried forward.

§ p-value <0.0001 *versus* placebo.

saxa= saxagliptin; met=metformin

The proportion of patients achieving HbA1c <7.0% at Week 24 was higher in the saxagliptin plus dapagliflozin plus metformin group 38.0% (95% CI [30.9, 45.1]) compared to the placebo plus saxagliptin plus metformin group 12.4% (95% [7.0, 17.9]).

The adjusted changes from baseline at Week 24 in body weight were −1.91 kg (95% CI [−2.34, −1.48]), in the dapagliflozin plus saxagliptin plus metformin group and -0.41 kg (95% CI [−0.86, 0.04]), in the placebo plus saxagliptin plus metformin group.

The effects in HbA1c, FPG and body weight observed at Week 24 were sustained at Week 52. Adjusted mean change from baseline in HbA1c, FPG, and body weight were −0.74% (95% CI [−0.90, −0.57]), -26.8 mg/dL (95% CI [-34.2, -19.4]) and −2.13 kg (95% CI[-2.70, -1.56]), respectively, for patients treated with dapagliflozin 10 mg plus saxagliptin with metformin, and 0.07% (95% CI [−0.13, 0.27]), 10.2 mg/dL (95% CI[1.6, 18.8]) and −0.37 kg (95% CI[-1.01, 0.26]) for patients treated with placebo plus saxagliptin with metformin based on the longitudinal repeated measures analysis excluding data after rescue.

Cardiovascular and renal outcomes

Dapagliflozin Effect on Cardiovascular Events (DECLARE) was an international, multicenter, randomized, double-blind, placebo-controlled clinical study conducted to determine the effect of dapagliflozin compared with placebo on CV and renal outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either at least two additional CV risk factors (age ≥55 years in men or ≥60 years in women and one or more of dyslipidemia, hypertension or current tobacco use) without having had a CV event at baseline (primary prevention) or established CV disease (secondary prevention). DECLARE was designed to ensure inclusion of a broad population.

Of 17160 randomized patients, 6974 (40.6%) had established CV disease and 10186 (59.4%) did not have established CV disease. 8582 patients were randomized to dapagliflozin 10 mg and 8578 to placebo, and were followed for a median of 4.2 years.

The mean age of the study population was 63.9 years, 37.4% were female, 79.6% were White, 3.5% Black or African-American and 13.4% Asian. In total, 22.4% had had diabetes for ≤5 years, mean duration of diabetes was 11.9 years. Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m^2.

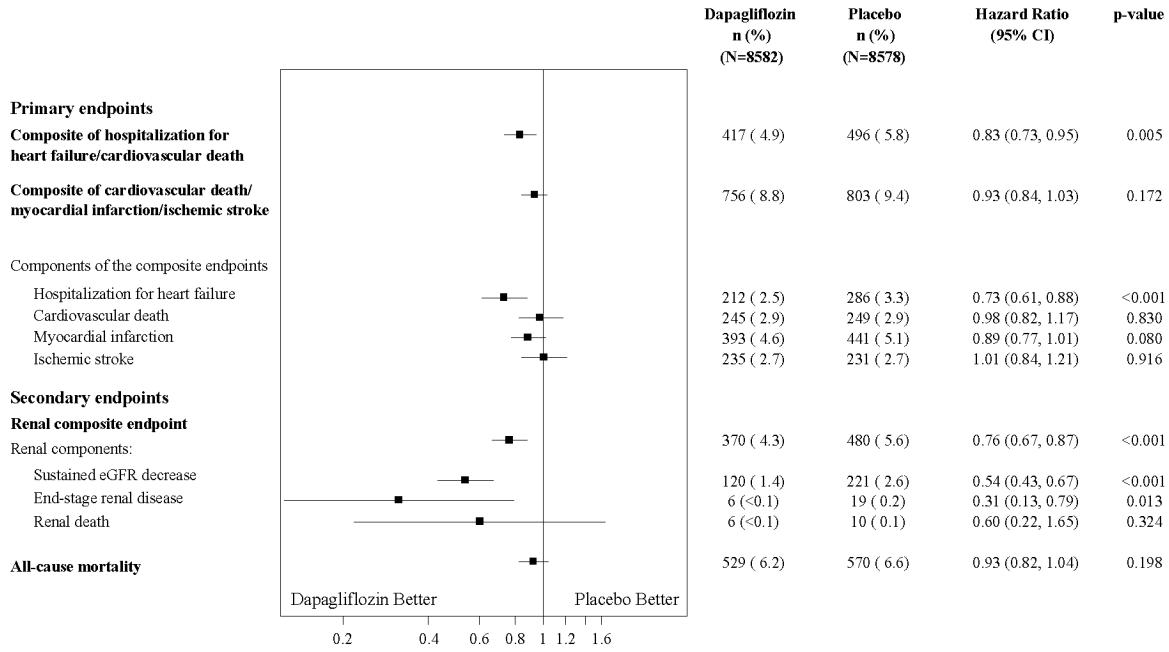
At baseline, 10.0% of patients had a history of heart failure. Mean eGFR was 85.2 mL/min/1.73 m^2, 7.4% of patients had eGFR <60mL/min/1.73 m^2 and 30.3% of patients had micro- or macroalbuminuria (urine albumin to creatinine ration [UACR] ≥30 to ≤300 mg/g or >300 mg/g, respectively).

Most patients (98.1%) used one or more diabetic medications at baseline, 82.0% of the patients were being treated with metformin, 40.9% with insulin, 42.7% with a sulfonylurea, 16.8% with a DPP4 inhibitor, and 4.4% with a GLP-1 agonist.

Approximately 81.3% of patients were treated with ACEi or ARB, 75.0% with statins, 61.1% with antiplatelet therapy, 55.5% with acetylsalicylic acid, 52.6% with beta-blockers, 34.9% with calcium channel blockers, 22.0% with thiazide diuretics and 10.5% with loop diuretics.

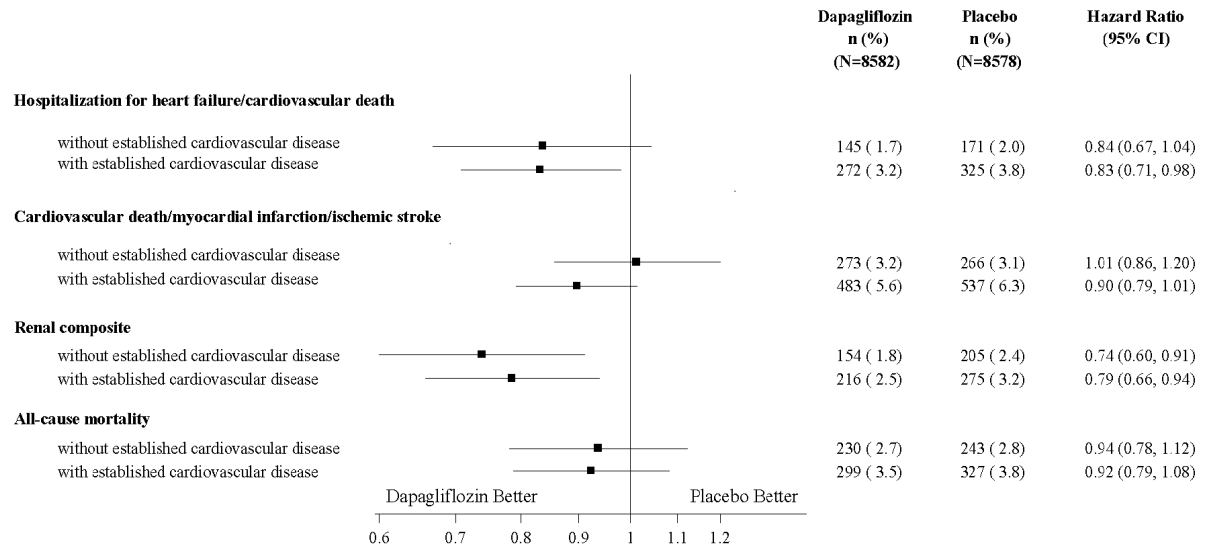
Results on primary and secondary endpoints are displayed in Figures 8 and 9.

Figure 8 Treatment effects for the primary composite endpoints and their components and the secondary endpoints and components



p-values are two-sided p-values for primary endpoints and nominal p-values for secondary endpoints and single components. Time to first event was analyzed in a Cox proportional hazards model. The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint. Renal composite endpoint is defined as sustained confirmed ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 and/or ESRD (dialysis ≥90 days or kidney transplantation, sustained confirmed eGFR <15 mL/min/1.73m^2) and/or renal or CV death. CI=confidence interval.

Figure 9 Treatment effects for the primary and secondary endpoints in patients with and without established CV disease



Renal composite defined as: sustained confirmed ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 and/or ESRD (dialysis ≥90 days or kidney transplantation, sustained confirmed eGFR <15 mL/min/1.73m^2) and/or renal or CV death. Time to first event was analyzed in a Cox proportional hazards model.

CI=confidence interval

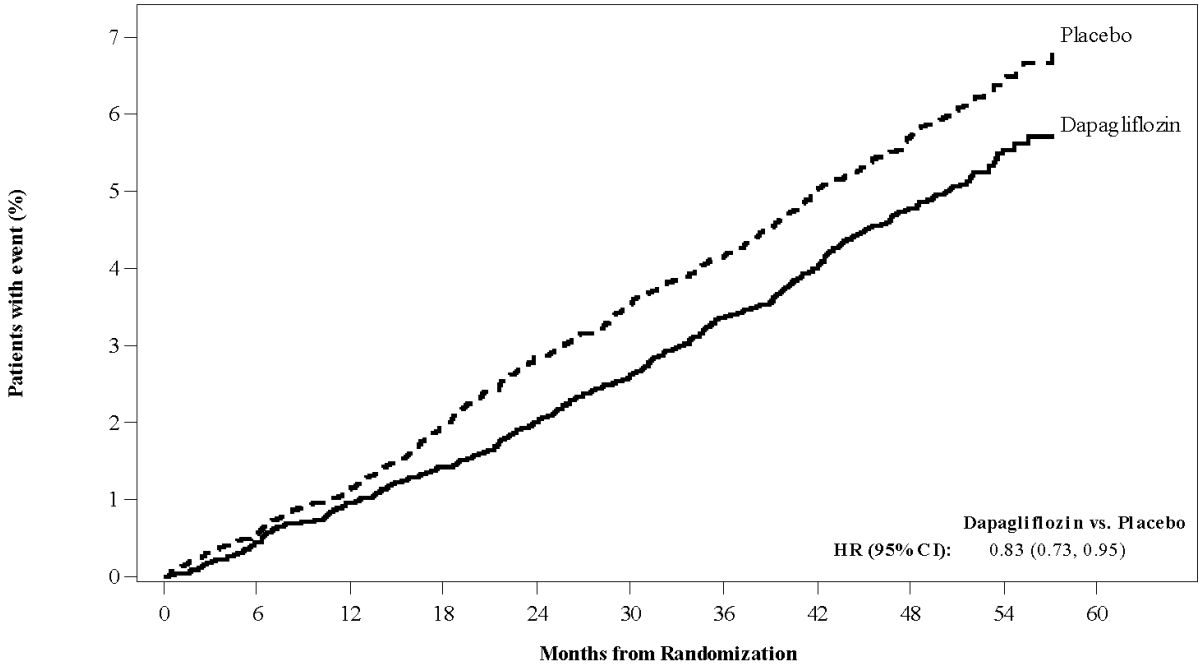
Heart failure or cardiovascular death

Dapagliflozin 10 mg was superior to placebo in preventing the primary composite endpoint of hospitalization for heart failure or CV death (HR 0.83 [95% CI 0.73, 0.95]; p=0.005) (Figure 10).

Exploratory analyses of the single components suggest that the difference in treatment effect was driven by hospitalization for heart failure (HR 0.73 [95% CI 0.61, 0.88]) (Figure 8), with no clear difference in CV death (HR 0.98 [95% CI 0.82 to 1.17]).

The treatment benefit of dapagliflozin over placebo was observed both in patients with and without established CV disease (Figure 9), with and without heart failure at baseline, and was consistent across key subgroups, including age, gender, renal function (eGFR), and region.

Figure 10 Time to first occurrence of hospitalization for heart failure or cardiovascular death



Patients at risk

Dapagliflozin:	8582	8517	8415	8322	8224	8110	7970	7497	5445	1626
Placebo:	8578	8485	8387	8259	8127	8003	7880	7367	5362	1573

Patients at risk is the number of patients at risk at the beginning of the period.

CI Confidence interval, HR Hazard ratio

Major adverse cardiovascular events

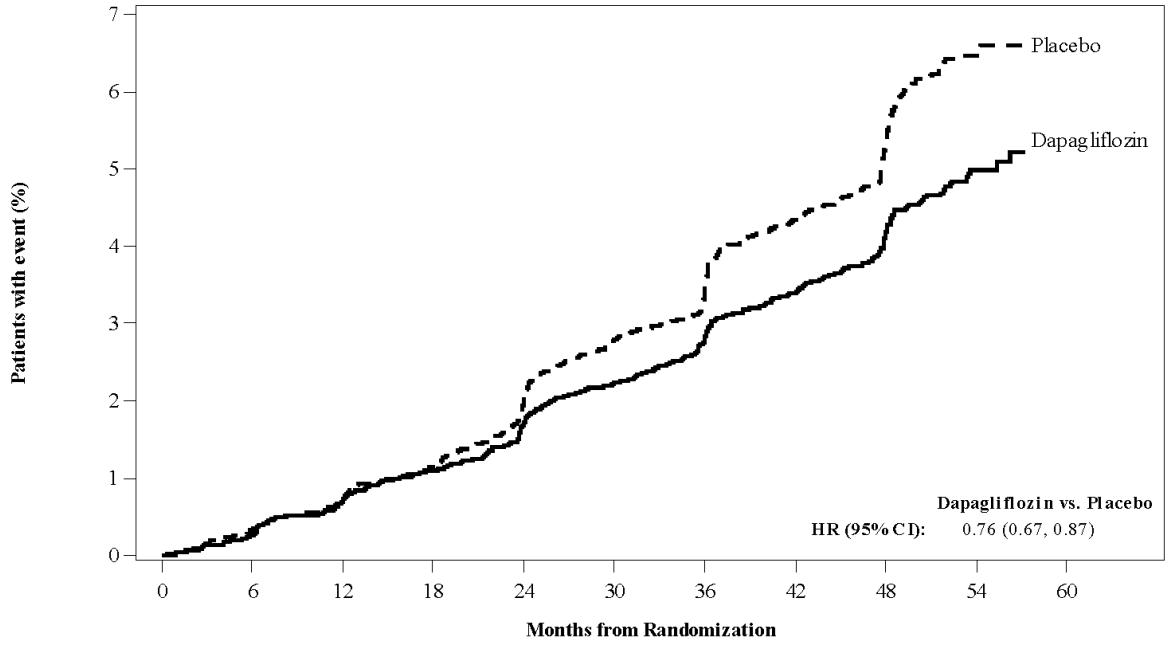
Dapagliflozin demonstrated cardiovascular safety (tested as non-inferiority versus placebo for the composite of CV death, myocardial infarction or ischemic stroke [MACE]; one-sided p <0.001).

There were numerically fewer MACE events in the dapagliflozin group compared with the placebo group (HR 0.93 [95% CI 0.84, 1.03]; p=0.172) (Figure 8).

Nephropathy

Dapagliflozin reduced the incidence of events of the composite of confirmed sustained eGFR decrease, ESRD, renal or CV death (HR 0.76 [95% CI 0.67, 0.87]; nominal p<0.001, Figure 11). The difference between groups was driven by reductions in events of the renal components; sustained eGFR decrease, ESRD and renal death (Figure 8), and was observed both in patients with and without CV disease (Figure 9).

Figure 11 Time to first occurrence of sustained eGFR decrease, ESRD, renal or CV death



Patients at risk

Dapagliflozin:	8582	8533	8436	8347	8248	8136	8009	7534	5472	1637
Placebo:	8578	8508	8422	8326	8200	8056	7932	7409	5389	1589

Patients at risk is the number of patients at risk at the beginning of the period.

Renal composite endpoint defined as sustained confirmed eGFR decrease ≥40% to eGFR <60 mL/min/1.73m^2 and/or ESRD and/or renal or CV death.

CI Confidence interval; HR Hazard ratio.

When evaluating the renal components, there were 127 and 238 events of new or worsening nephropathy (sustained eGFR decrease, ESRD or renal death) in patients in the dapagliflozin and placebo groups, respectively. The HR for time to nephropathy was 0.53 (95% CI 0.43, 0.66) for dapagliflozin versus placebo.

Beneficial effects of dapagliflozin on renal outcomes were also observed for albuminuria, e.g.,

- In patients without pre-existing albuminuria, dapagliflozin reduced the incidence of sustained albuminuria (UACR >30 mg/g) compared with placebo (HR 0.79 [95% CI 0.72, 0.87], nominal p<0.001).
- In patients without pre-existing macroalbuminuria, new onset of macroalbuminuria (UACR >300 mg/g) was reduced in the dapagliflozin group compared with the placebo group (HR 0.54 [95% CI 0.45, 0.65], nominal p<0.001).
- In patients with pre-existing macroalbuminuria, regression of macroalbuminuria was greater in the dapagliflozin group compared with the placebo group (HR 1.82 [95% CI 1.51, 2.20], nominal p<0.001).

The treatment benefit of dapagliflozin over placebo was observed both in patients with and without existing renal impairment.

Supportive Studies

Dapagliflozin dual energy X-ray absorptiometry in diabetic patients

Due to the mechanism of action of dapagliflozin, a study was done to evaluate body composition and bone mineral density in 182 patients with type 2 diabetes. Treatment with dapagliflozin 10 mg added on to metformin IR over a 24-week period provided significant improvements compared with placebo plus metformin, respectively, in body weight (mean change from baseline: −2.96 kg vs −0.88 kg); waist circumference (mean change from baseline: −2.51 cm vs −0.99 cm), and body-fat mass as measured by DXA (mean change from baseline −2.22 kg vs −0.74 kg) rather than lean tissue or fluid loss. Dapagliflozin plus metformin treatment showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment (mean change from baseline: −322.6 cm^3 vs −8.7 cm^3) in an MRI substudy. Week 24 was analyzed using last observation carried forward (LOCF) analysis including data after rescue.

At Week 24, 2 patients (2.2%) in the placebo plus metformin group and no patients in the dapagliflozin 10 mg plus metformin group were rescued for lack of glycemic control.

At Week 50 and Week 102, improvements were sustained in the dapagliflozin 10 mg added on to metformin group compared with the placebo plus metformin group for body weight (adjusted mean change from baseline at Week 50: −4.39 kg vs −2.03 kg; adjusted mean change from baseline at Week 102: −4.54 kg vs −2.12 kg), waist circumference (adjusted mean change from baseline at Week 50: −5.0 cm vs −3.0 cm; adjusted mean change from baseline at Week 102: −5.0 cm vs −2.9 cm), and body-fat mass as measured by DXA at Week 102 (mean change from baseline: −2.80 kg vs −1.46 kg) based on the longitudinal repeated measures analysis including data after rescue. In an MRI substudy at Weeks 50 and 102, dapagliflozin plus metformin treatment showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment (adjusted mean change from baseline at Week 50: −120.0 cm^3 vs 61.5 cm^3; adjusted mean change from baseline at Week 102: −214.9 cm^3 vs −22.3 cm^3).

The proportion of patients at Week 50 (unadjusted for baseline HbA1c) and Week 102 (adjusted for baseline HbA1c) who were rescued or discontinued for lack of glycemic control was higher in

the placebo plus metformin group (6.6% and 33.2%, respectively) than in the dapagliflozin 10 mg plus metformin group (2.2% and 13.5%, respectively).

In an extension of this study to Week 50, there was no change in bone mineral density (BMD) for the lumbar spine, femoral neck, or total hip seen in either treatment group (mean decrease from baseline for all anatomical regions <0.5%). There was also no change in BMD in either treatment group up to Week 102 (mean decrease from baseline for all anatomical regions <1.0%). There were no clinically meaningful changes in markers of bone resorption or bone formation.

Metformin UKPDS Study

The prospective randomized (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patient-years),p=0.0023, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/1000 patient-years), p=0.0034;
- a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-years, p=0.017;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-years, (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1000 patient-years (p=0.021);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1000 patient-years, diet alone 18 events/1000 patient-years, (p=0.01).

Clinical safety - dapagliflozin

Volume depletion

Events suggestive of volume depletion (including reports of dehydration, hypovolemia, or hypotension) were reported in 1.1% and 0.7% of patients who received dapagliflozin 10 mg and placebo, respectively, in the 13-study, short-term, placebo-controlled pool. Serious events occurred in ≤0.2% of patients across the 21 active- and placebo-controlled studies (dapagliflozin as monotherapy or in combination with other antidiabetic therapies) and were balanced between dapagliflozin 10 mg and comparator.

In the CV outcomes study, the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 81 (0.9%) and 70 (0.8%) in the dapagliflozin and placebo group, respectively. Events were generally balanced between treatment groups across subgroups of age, diuretic use, blood pressure and ACEi/ARB use. In patients with eGFR <60 mL/min/1.73 m2 at baseline, there were 19 events of SAEs suggestive of volume depletion in the dapagliflozin group and 13 events in the placebo group

Hypoglycemia

The incidence of hypoglycemia as seen in controlled clinical studies with dapagliflozin in different combinations is shown in Table 12.

Table 12 Incidence of Major[a] and Minor[b] Hypoglycemia in Controlled Clinical Studies

	Placebo/ Active control	**Dapagliflozin 10 mg**
CV Outcomes Trial (48 months median exposure)		
All	**N=8569**	**N=8574**
Major [n(%)]	83 (1.0)	58 (0.7)
Patients treated with insulin	**N=4606**	**N=4177**
Major [n(%)]	64 (1.4)	52 (1.2)
Patients treated with a sulfonylurea	**N=4521**	**N=4118**
Major [n(%)]	23 (0.5)	14 (0.3)
Monotherapy* (24 weeks)	**N=75**	**N=70**
Major [n (%)]	0	0
Minor [n (%)]	0	0
Add-on to Metformin* (24 weeks)	**N=137**	**N=135**
Major [n (%)]	0	0
Minor [n (%)]	0	1 (0.7)

	Placebo/ Active control	Dapagliflozin 10 mg
Active Control Add-on to Metformin versus Glipizide (52 weeks)	**N=408**	**N=406**
Major [n (%)]	3 (0.7)	0
Minor [n (%)]	147 (36.0)	7 (1.7)
Add-on to Glimepiride (24 weeks)	**N=146**	**N=151**
Major [n (%)]	0	0
Minor [n (%)]	3 (2.1)	9 (6.0)
Add-on to Metformin and a Sulfonylurea (24 Weeks)	**N=109**	**N=109**
Major [n (%)]	0	0
Minor [n (%)]	4 (3.7)	14 (12.8)
Add-on to Pioglitazone (24 weeks)	**N=139**	**N=140**
Major [n (%)]	0	0
Minor [n (%)]	0	0
Add-on to DPP4 inhibitor (24 weeks)	**N=226**	**N=225**
Major [n (%)]	0	1 (0.4)
Minor [n (%)]	3 (1.3)	4 (1.8)
Add-on to Insulin with or without other OADs[c] (24 weeks)	**N=197**	**N=196**
Major [n (%)]	1 (0.5)	1 (0.5)
Minor [n (%)]	67 (34.0)	79 (40.3)

[a] Major episodes of hypoglycemia were defined as symptomatic episodes requiring external (third party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <54 mg/dL and prompt recovery after glucose or glucagon administration.

[b] Minor episodes of hypoglycemia were defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement <63 mg/dL that does not qualify as a major episode.

[c] OAD = oral antidibetic therapy.

Events Related to Decreased Renal Function

In the 13-study, short-term, placebo-controlled pool, mean serum creatinine levels increased a small amount at Week 1 (mean change from baseline: 0.041 mg/dL dapagliflozin 10 mg *vs.* -0.008 mg/dL placebo) and decreased toward baseline by Week 24 (mean change from baseline: 0.019 mg/dL dapagliflozin 10 mg *vs.* 0.008 mg/dL placebo). There were no further changes through Week 102.

In the CV outcomes study, there were fewer patients with marked laboratory abnormalities of creatinine, creatinine clearance, eGFR, and UACR in the dapagliflozin group compared with the placebo group. Fewer renal events (e.g., decreased renal creatinine clearance, renal impairment, increased blood creatinine, and decreased glomerular filtration rate) were reported in the dapagliflozin group compared with the placebo group: 422 (4.9%) and 526 (6.1%), respectively. There were fewer patients with events reported as acute kidney injury in the dapagliflozin group compared with the placebo group: 125 (1.5%) and 175 (2.0%), respectively. There were fewer patients with SAEs of renal events in the dapagliflozin group compared with the placebo group: 80 (0.9%) and 136 (1.6%), respectively.

Laboratory findings-dapagliflozin

Hematocrit

In the pool of 13 placebo-controlled studies, increases from baseline in mean hematocrit values were observed in dapagliflozin-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. At Week 24, the mean changes from baseline in hematocrit were 2.30% in the dapagliflozin 10 mg group versus –0.33% in the placebo group. At Week 102, the mean changes were 2.68% versus –0.46%, respectively. By Week 24, hematocrit values >55% were reported in 1.3% of dapagliflozin 10-mg–treated patients versus 0.4% of placebo-treated patients. Results were similar during the short-term plus long-term phase (the majority of patients were exposed to treatment for more than one year).

Serum inorganic phosphorus

In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in dapagliflozin 10-mg-treated patients compared with placebo-treated patients (mean increases of 0.13 mg/dL vs −0.04 mg/dL, respectively). Similar results were seen at Week 102. Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia (≥5.6 mg/dL if age 17-65 or ≥5.1 mg/dL if age ≥66) were reported in dapagliflozin 10 mg group versus placebo at Week 24 (1.7% vs 0.9%, respectively) and during the short-term plus long-term phase (3.0% vs 1.6%, respectively). The clinical relevance of these findings is unknown.

Lipids

In the pool of 13 placebo-controlled studies, small changes from baseline in mean lipid values were reported at Week 24 in dapagliflozin-10-mg–treated patients compared with placebo-treated patients. Mean percent change from baseline at Week 24 for dapagliflozin 10 mg versus placebo, respectively, was as follows: total cholesterol, 2.5% versus 0.0%; HDL cholesterol, 6.0% versus 2.7%; LDL cholesterol, 2.9% versus −1.0%; triglycerides, −2.7% versus −0.7%. Mean percent change from baseline at Week 102 for dapagliflozin 10 mg versus placebo, respectively, was as follows: total cholesterol, 2.1% versus −1.5%; HDL cholesterol, 6.6% versus 2.1%; LDL cholesterol, 2.9% versus −2.2%; triglycerides, −1.8% versus −1.8%. The ratio between LDL cholesterol and HDL cholesterol decreased for both treatment groups at Week 24.

In the CV outcomes study, no clinical important differences in total cholesterol, HDL cholesterol, LDL cholesterol or triglycerides were seen.

Glycemic control in special populations

Use in patients with type 2 diabetes and hypertension

Dapagliflozin

In two 12-week, placebo-controlled studies, a total of 1062 patients with inadequately controlled type 2 diabetes and hypertension were treated with dapagliflozin 10 mg or placebo. Patients with inadequately controlled hypertension (seated systolic blood pressure ≥140 and <165 mmHg, seated diastolic blood pressure ≥85 and <105 mmHg, and a 24-hour mean blood pressure of ≥130/80 mmHg) despite pre-existing stable treatment with an ACEi or ARB (alone [Study 1] or in combination with an additional antihypertensive [Study 2]) as well as inadequate glycemic control (HbA1c ≥7.0% and ≤10.5%) despite pre-existing stable treatment with OADs (including metformin

immediate- or extended-release) or insulin (alone or in combination) prior to entry, were eligible for these studies. During the studies, no adjustments in antidiabetic and antihypertensive medications were allowed. Across the 2 studies, 527 patients were treated with dapagliflozin 10 mg and 535 with placebo. Approximately 90% of patients treated with dapagliflozin 10 mg or placebo also received metformin immediate- or extended release in addition to other OADs. Patients treated with dapagliflozin 10 mg or placebo also received the following medications for blood pressure control, which were balanced between treatment groups: ACEis (64%), ARBs (36%), thiazide diuretics (16%), calcium channel blockers (9%), and beta-blockers (6%).

At Week 12 for both studies, dapagliflozin 10 mg plus usual treatment provided significant improvement in HbA1c and a significant reduction in seated systolic blood pressure compared with placebo plus usual treatment (see Table 13). Consistent reductions were seen in mean 24-hour ambulatory systolic blood pressure in patients treated with dapagliflozin 10 mg treatment compared with placebo. There was a small reduction in mean seated diastolic blood pressure in patients treated with dapagliflozin 10 mg that was not statistically significant compared with placebo.

Table 13: Results at Week 12 in 2 Placebo-Controlled Studies of Dapagliflozin in Patients with Type 2 Diabetes and Hypertension

	Study 1		Study 2	
Efficacy Parameter	**Dapagliflozin10 mg + Usual Treatment N=302†**	**Placebo + Usual Treatment N=311†**	**Dapagliflozin10 mg + Usual Treatment N=225†**	**Placebo + Usual Treatment N=224†**
HbA1c (%) (LRM)*				
Baseline (mean)	8.1	8.0	8.1	8.0
Change from baseline (adjusted mean‡)	−0.6	−0.1	−0.6	0.0
Difference from placebo (adjusted mean‡) (95% CI)	−0.5§ (−0.6, −0.3)		−0.6§ (−0.8, −0.5)	
Seated SBP (mmHg) (LRM) *				
Baseline (mean)	149.8	149.5	151.0	151.3

	Study 1		Study 2	
Efficacy Parameter	**Dapagliflozin 10 mg + Usual Treatment N=302†**	**Placebo + Usual Treatment N=311†**	**Dapagliflozin 10 mg + Usual Treatment N=225†**	**Placebo + Usual Treatment N=224†**
Change from baseline (adjusted mean‡)	−10.4	−7.3	−11.9	−7.6
Difference from placebo (adjusted mean‡) (95% CI)	−3.1¶ (−4.9, −1.2)		−4.3¶ (−6.5, −2.0)	

* LRM: longitudinal repeated measures analysis.

† All randomized patients who took at least one dose of double-blind study medication during the short-term, double-blind period.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001.

¶ p-value <0.05.

LOCF: last observation carried forward.

Use in patients with type 2 diabetes and cardiovascular disease

Dapagliflozin

In two 24-week, placebo-controlled studies with 80-week extension periods, a total of 1887 patients with type 2 diabetes and CVD were treated with dapagliflozin 10 mg or placebo.

Patients with established CVD and inadequate glycemic control (HbA1c ≥7.0% and ≤10.0%), despite pre-existing, stable treatment with OADs or insulin (alone or in combination) prior to entry, were eligible for these studies and were stratified according to age (<65 years or ≥65 years), insulin use (no or yes), and time from most recent qualifying cardiovascular event (>1 year or <1 year prior to enrollment). Across the 2 studies, 942 patients were treated with dapagliflozin 10 mg and 945 with placebo. Ninety-six percent (96%) of patients treated with dapagliflozin 10 mg across the 2 studies had hypertension at entry, the majority for more than 10 years duration; the most common qualifying cardiovascular events were coronary heart disease (75%) and stroke (22%). Approximately 19% of patients received loop diuretics at entry and 15% had congestive heart failure (2% had NYHA Class III). Approximately 37% of patients treated with dapagliflozin 10 mg also received metformin plus one additional OAD (sulfonylurea, thiazolidinedione, DPP4 inhibitor,

or other OAD with or without insulin at entry), 39% received insulin plus at least one OAD, and 18% received insulin alone.

At Week 24 for both studies, when added to pre-existing antidiabetic treatments, treatment with dapagliflozin 10 mg provided significant improvement to coprimary endpoints of HbA1c and composite clinical benefit compared with placebo. Composite clinical benefit was defined as the proportion of patients with an absolute drop from baseline of 0.5% in HbA1c, and a relative drop from baseline of at least 3% in total body weight, and an absolute drop from baseline of at least 3 mmHg in seated systolic blood pressure (Table 14). Significant reductions in total body weight and seated systolic blood pressure were also seen in patients treated with dapagliflozin 10 mg compared with placebo.

In a separate analysis of patients on metformin alone (with or without insulin) in these two studies, similar improvements in HbA1c and percent body weight reduction to those seen in the total study population were seen in patients treated with dapagliflozin 10 mg plus metformin alone compared with placebo plus metformin alone at Week 24. A mean reduction in seated systolic blood pressure was observed, consistent with that seen in the total study population, in patients treated with dapagliflozin 10 mg plus metformin alone compared with placebo plus metformin alone at Week 24 in study 1, but not in study 2.

At Week 52 and Week 104 for Study 1, adjusted mean change from baseline in HbA1c, seated systolic blood pressure, and adjusted percent change from baseline in body weight were −0.44% and −0.41%, −3.40 mmHg and −2.64 mmHg, and −2.89% and −3.53%, respectively, for patients treated with dapagliflozin 10 mg plus usual treatment based on the longitudinal repeated measures analysis. Corresponding numbers for patients treated with placebo plus usual treatment were 0.22% and 0.50%, 0.18 mmHg and 1.54 mmHg, and −0.29% and −0.02%. At Week 52 and Week 104, percent composite clinical benefit was still higher in the dapagliflozin 10 mg group (6.6% and 3.8%) than in the placebo group (0.7% and 0.5%).

At Week 24, Week 52, and Week 104 for Study 1, the proportion of patients who were rescued for lack of glycemic control (adjusted for baseline HbA1c) was higher in the placebo plus usual treatment group (24.0%, 51.8%, and 57.3%, respectively) than in the dapagliflozin 10 mg plus usual treatment group (7.9%, 24.6%, and 31.8%, respectively).

At Week 52 and Week 104 for Study 2, adjusted mean change from baseline in HbA1c, seated systolic blood pressure, and adjusted percent change from baseline in body weight were −0.47% and −0.37%, −3.56 mmHg and −1.96 mmHg, and −3.20% and −3.51%, respectively, for patients treated with dapagliflozin 10 mg plus usual treatment based on the longitudinal repeated measures analysis. Corresponding numbers for patients treated with placebo plus usual treatment were 0.03% and −0.18%, −0.91 mmHg and −0.37 mmHg, and −1.12% and −0.65%. At Week 52 and Week 104, percent composite clinical benefit was still higher in the dapagliflozin 10 mg group (10.6% and 4.2%) than in the placebo group (3.1% and 1.1%).

At Week 24, Week 52, and Week 104 for Study 2, the proportion of patients who were rescued for lack of glycemic control (adjusted for baseline HbA1c) was higher in the placebo plus usual treatment group (22.3%, 43.6%, and 50.5%, respectively) than in the dapagliflozin 10 mg plus usual treatment group (7.6%, 18.7%, and 27.5%, respectively).

Table 14: Results at Week 24 (LOCF*) in Two Placebo-Controlled Studies Comparing Dapagliflozin to Placebo in Patients with Type 2 Diabetes and Cardiovascular Disease

	Study 1		Study 2	
Efficacy Parameter	**Dapagliflozin 10 mg + Usual Treatment**	**PLACEBO + Usual Treatment**	**Dapagliflozin 10 mg + Usual Treatment**	**PLACEBO + Usual Treatment**
	N=455[†]	**N=459[†]**	**N=480[†]**	**N=482[†]**
HbA1c (%)				
Baseline mean	8.18	8.08	8.04	8.07
Change from baseline (adjusted mean[‡])	−0.38	0.08	−0.33	0.07
Difference from placebo (adjusted mean[‡]) (95% CI)	−0.46[§] (−0.56, −0.37)		−0.40[§] (−0.50, −0.30)	
Responders of Composite Clinical Benefit (%)	11.7	0.9	10.0	1.9

	Study 1		Study 2	
Efficacy Parameter	**Dapagliflozin 10 mg + Usual Treatment**	**PLACEBO + Usual Treatment**	**Dapagliflozin 10 mg + Usual Treatment**	**PLACEBO + Usual Treatment**
Difference from placebo (adjusted %)	9.9[§]		7.0[§]	
Components of Composite Endpoint (%)				
Patients with absolute reduction HbA1c ≥0.5% (adjusted %)	46.2	19.7	42.2	21.2
Patients with body weight decrease of at least 3% from baseline (adjusted %)	40.0	13.9	41.3	15.4
Patients with absolute reduction in SBP ≥3 mmHg (adjusted %)	49.1	41.6	46.2	40.9
Body Weight (kg)				
Baseline mean	92.63	93.59	94.53	93.22
Change from baseline (adjusted percent[‡])	−2.56	−0.30	−2.53	−0.61
Difference from placebo (adjusted percent[‡]) (95% CI)	−2.27[§] (−2.64, −1.89)		−1.93[§] (−2.31, −1.54)	
Body weight decrease of at least 5% in patients with baseline BMI ≥27 kg/m^2 (%)	16.5[§]	4.0	18.4[§]	4.8
Seated SBP (mmHg)				
Change from baseline at Week 24 (adjusted mean[‡])	−2.99	−1.03	−2.70	0.32
Difference from placebo (adjusted mean[‡]) (95%CI)	−1.95[¶]		−3.02[¶]	

	Study 1		Study 2	
Efficacy Parameter	**Dapagliflozin 10 mg + Usual Treatment**	**PLACEBO + Usual Treatment**	**Dapagliflozin 10 mg + Usual Treatment**	**PLACEBO + Usual Treatment**
	(−3.56, −0.34)		(−4.59, −1.46)	
Change from baseline seated SBP (mmHg) at week 8 in patients with baseline SBP ≥130 mmHg (adjusted mean‡)	-	-	−5.33¶	−1.89

* LOCF: last observation carried forward.

† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001.

¶ p-value <0.05.

At Week 24, patients treated with dapagliflozin 10 mg in the predefined age groups (<65 and ≥65 years of age) also showed significant improvements in the coprimary endpoints of HbA1c and composite clinical benefit compared with placebo in both studies. A significant reduction in total body weight was also seen in both age groups and a significant reduction of seated systolic blood pressure in patients <65 years treated with dapagliflozin 10 mg compared with placebo at Week 24. These effects were maintained at Week 52 and Week 104. The safety profile of dapagliflozin in these studies was consistent with that of dapagliflozin in the general clinical study population through 104 weeks of treatment (see section 4.8).

Use in patients with type 2 diabetes and Renal Impairment

Dapagliflozin

Patients with mild renal impairment (eGFR >60 to <90 mL/min/1.73 m^2)

In the clinical trial program over 3000 patients with mild renal impairment were treated with dapagliflozin. Efficacy was assessed in a pooled analysis across 9 dapagliflozin clinical studies consisting of 2226 patients with mild renal impairment. The mean change from baseline in hemoglobin A1c (HbA1c) and the placebo-corrected mean HbA1c change at 24 weeks was −1.03% and −0.54%, respectively for dapagliflozin 10 mg (n=562). The safety profile in patients with mild renal impairment is similar to that in the overall population.

Patients with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2)

The glycemic efficacy and safety of dapagliflozin was evaluated in two dedicated studies of patients with moderate renal impairment and in two subgroup analyses of pooled clinical studies.

In a randomized, double blind, placebo-controlled trial a total of 321 adult patients with type 2 diabetes mellitus and eGFR ≥45 to <60 mL/min/1.73 m2 (moderate renal impairment subgroup CKD 3A), with inadequate glycemic control on current treatment regimen, were treated with dapagliflozin 10 mg or placebo. At Week 24, dapagliflozin 10 mg (n=159) provided significant improvements in HbA1c, FPG, Body Weight and SBP compared with placebo (n=161) (Table 15). The mean change from baseline in HbA1c and the placebo-corrected mean HbA1c change was −0.37% and −0.34%, respectively. The mean change from baseline in FPG and the placebo-corrected mean FPG was -21.46 mg/dL and -16.59 mg/dL, respectively. The mean body weight reduction (percentage) and the placebo-corrected mean body weight reduction was -3.42% and -1.43%, respectively. The mean reduction in seated systolic blood pressure (SBP) and the placebo-corrected mean reduction in SBP was -4.8 mmHg and -3.1 mmHg, respectively.

Table 15: Results at Week 24 in a Placebo-Controlled Study of dapagliflozin Treatment in Diabetic Patients with Moderate Renal Impairment (Class 3A, eGFR ≥45 to <60 mL/min/1.73 m^2)

Efficacy Parameter	**Dapagliflozin 10 mg N=159**	**Placebo N=161**
HbA1c (%)		
Baseline (mean)	8.35	8.03
Change from baseline (adjusted mean*)	-0.37§	-0.03
Difference from placebo (adjusted mean*) (95% CI)	-0.34§ (-0.53, -0.15)	
FPG (mg/dL)		
Baseline (mean)	183.04	173.28
Change from baseline (adjusted mean*)	-21.46§	-4.87

Efficacy Parameter	Dapagliflozin 10 mg N=159	Placebo N=161
Difference from placebo (adjusted mean*) (95% CI)	-16.59§ (-26.73, -6.45)	
Body Weight (percentage)		
Baseline (mean)	92.51	88.30
% Change from baseline (adjusted mean*)	-3.42§	-2.02
Difference from placebo (adjusted mean*) (95% CI)	-1.43§ (-2.15, -0.69)	
Seated Systolic Blood Pressure (mmHg)		
Baseline (mean)	135.7	135.0
Change from baseline (adjusted mean*)	-4.8¶	-1.7
Difference from placebo (adjusted mean*) (95% CI)	-3.1¶ (-6.3, 0.0)	

* Least squares mean adjusted for baseline value.

§ p-value <0.001.

¶ p-value <0.05.

The safety profile of dapagliflozin in the study was consistent with that in the general population of patients with type 2 diabetes. Mean eGFR decreased initially during the treatment period in the dapagliflozin group and subsequently remained stable during the 24-week treatment period (dapagliflozin: -3.39 mL/min/1.73 m^2 and placebo: -0.90 mL/min/1.73 m^2). At 3 weeks after termination of dapagliflozin, the mean change from baseline in eGFR in the dapagliflozin group was similar to the mean change in the placebo group (dapagliflozin: 0.57 mL/min/1.73 m^2 and placebo: -0.04 mL/min/1.73 m^2).

Efficacy in patients with moderate renal impairment was assessed in a pooled analysis across 9 clinical studies (366 patients, 87% with eGFR ≥45 to <60 mL/min/1.73 m^2); this pool did not include the two dedicated studies of diabetic patients with moderate renal impairment. The

mean change from baseline in HbA1c and the placebo-corrected mean HbA1c change at 24 weeks was −0.87% and −0.39%, respectively, for dapagliflozin 10 mg (n=85).

Safety in patients with moderate renal impairment was assessed in a pooled analysis of 12 clinical studies (384 patients, 88% with eGFR ≥45 to <60 mL/min/1.73 m^2); this pool did not include the two dedicated studies of diabetic patients with moderate renal impairment. At Week 24, safety was similar to that seen in the overall program of clinical studies except for a higher proportion of patients reporting at least one event related to renal impairment or failure (7.9% dapagliflozin 10 mg *versus* 5.6% placebo). Of these events, increased serum creatinine was the most frequently reported (6.7% dapagliflozin 10 mg *versus* 2.8% placebo). Increases in mean parathyroid hormone (PTH) and serum phosphorus observed with dapagliflozin in the overall program of clinical studies were also seen in the pooled analysis. In the short-term plus long-term safety pool up to 102 weeks, the safety profile remained similar.

The efficacy and safety of dapagliflozin was also assessed in a study of 252 diabetic patients with eGFR ≥30 to <60 mL/min/1.73 m^2 (moderate renal impairment subgroup CKD 3A and CKD 3B). dapagliflozin treatment did not show a significant placebo corrected change in HbA1c in the overall study population (CKD 3A and CKD 3B combined) at 24 weeks. In an additional analysis of the subgroup CKD 3A, dapagliflozin 10 mg (n=32) provided a placebo-corrected mean HbA1c change at 24 weeks of −0.33%. At Week 52, dapagliflozin was associated with changes from baseline in mean eGFR (dapagliflozin 10 mg −4.46 mL/min/1.73 m^2 and placebo −2.58 mL/min/1.73 m^2) At Week 104, these changes persisted (eGFR: dapagliflozin 10 mg −3.50 mL/min/1.73 m^2 and placebo −2.38 mL/min/1.73 m^2) With dapagliflozin 10 mg, this eGFR reduction were evident at Week 1 and remained stable through Week 104, while placebo-treated patients had a slow continuous decline through Week 52 that stabilized through Week 104. At Week 52 and persisting through Week 104, greater increases in mean PTH and serum phosphorus were observed in this study with dapagliflozin 10 mg compared to placebo, where baseline values of these analytes were higher. Elevations of potassium of ≥6 mEq/L were more common in patients treated with placebo (12.0%) than those treated with dapagliflozin 5 mg and 10 mg (4.8% for both groups) during the cumulative 104-week treatment period. The proportion of patients discontinued for elevated potassium, adjusted for baseline potassium, was higher for the placebo group (14.3%) than for the dapagliflozin groups (6.9% and 6.7% for the 5 mg and 10 mg groups, respectively).Overall, there were 13 patients with an adverse event of bone fracture reported in this study up to Week 104 of which 8 occurred in the dapagliflozin 10 mg group, 5

occurred in the dapagliflozin 5 mg group, and none occurred in the placebo group. Eight (8) of these 13 fractures were in patients who had eGFR 30 to 45 mL/min/1.73 m^2 and 10 of the 13 fractures were reported within the first 52 weeks. There was no apparent pattern with respect to the site of fracture. No imbalance in bone fractures was observed in the safety analysis of the 12-study pool data and no bone fractures were reported in the dedicated study of patients with eGFR ≥45 to <60 mL/min/1.73 m^2 (CKD 3A).

Use in elderly patients with diabetes

Dapagliflozin

A total of 2403 (26%) of the 9339 treated patients were 65 years and older and 327 (3.5%) patients were 75 years and older in the pool of 21 double-blind, controlled, clinical studies of dapagliflozin assessing the safety and efficacy of dapagliflozin in improving glycemic control, as monotherapy or in combination with other antidiabetic therapies. After controlling for level of renal function (eGFR), there was no conclusive evidence suggesting that age is an independent factor affecting efficacy. Overall, the proportion of patients reporting adverse events was consistent between those ≥65 and <65 years of age.

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently than younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients.

5.2 Pharmacokinetics

XIGDUO XR combination tablets are considered to be bioequivalent to coadministration of corresponding doses of dapagliflozin and metformin hydrochloride XR administered together as individual tablets.

5.2.1 Interaction with food

The administration of XIGDUO XR in healthy subjects after a standard meal compared to the fasted state results in the same extent of exposure for both dapagliflozin and metformin XR. Compared to the fasted state, the standard meal results in 35% reduction and a delay of 1 to 2 hours in the peak plasma concentrations of dapagliflozin. This effect of food is not considered to be clinically meaningful.

5.2.2 Absorption

Dapagliflozin

Dapagliflozin is rapidly and well absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (C_{max}) are usually attained within 2 hours after administration in the fasted state. The C_{max} and AUC values increase proportionally to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%.

Metformin hydrochloride XR

Following a single oral dose of metformin extended-release, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. At steady state, the AUC and C_{max} are less than dose proportional for metformin extended-release within the range of 500 to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 µg/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively.

5.2.3 Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in various disease states (eg. renal or hepatic impairment).

Metformin hydrochloride

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mg averages 654±358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time.

5.2.4 Metabolism

Dapagliflozin

Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase enzymes. The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin is 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. Dapagliflozin is extensively metabolized primarily to yield dapagliflozin 3-

O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounts for 61% of a 50 mg [^{14}C]-dapagliflozin dose and is the predominant drug-related component in human plasma, accounting for 42% (based on AUC[0-12 h]) of total plasma radioactivity, similar to the 39% contribution by parent drug. Based on AUC, no other metabolite accounts for >5% of the total plasma radioactivity. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP mediated metabolism is a minor clearance pathway in humans.

Metformin hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Metabolism studies with extended-release metformin tablets have not been conducted.

5.2.5 Elimination

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged dapagliflozin. After administration of 50 mg [^{14}C]-dapagliflozin dose, 96% is recovered, 75% in urine and 21% in feces. In feces, approximately 15% of the dose is excreted as parent drug.

Metformin hydrochloride

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

5.2.6 Special populations

Renal impairment

Dapagliflozin

For dosing recommendations for patients with moderate to severe renal impairment see section 4.2. At steady-state (20 mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes and mild, moderate or severe renal impairment (as determined by iohexol clearance) had mean systemic exposures of dapagliflozin that were 32%, 60% and 87% higher, respectively, than those of patients with type 2 diabetes and normal renal function. At dapagliflozin 20 mg once-daily, higher systemic exposure to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal-glucose clearance or 24-hour glucose excretion. The renal-glucose clearance and 24-hour glucose excretion was lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18, and 11 g of glucose/day was excreted by patients with type 2 diabetes mellitus and normal renal function or mild, moderate, or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of hemodialysis on dapagliflozin exposure is not known.

Metformin hydrochloride

In patients with renal impairment, the plasma and blood half-life of metformin is prolonged in proportion to the decrease in renal function.

Hepatic impairment

Dapagliflozin

For dosing recommendations for patients with moderate or severe hepatic impairment see section 4.2. A single dose (10 mg) dapagliflozin clinical pharmacology study was conducted in patients with mild, moderate or severe hepatic impairment (Child-Pugh classes A, B, and C, respectively) and healthy matched controls in order to compare the pharmacokinetic characteristics of dapagliflozin between these populations. There were no differences in the protein binding of dapagliflozin between patients with hepatic impairment compared to healthy subjects. In patients with mild or moderate hepatic impairment mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C), mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively. Dapagliflozin should not be used in

patients with severe hepatic impairment since the safety and efficacy of dapagliflozin have not been specifically studied in this population.

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Age

Dapagliflozin

No dosage adjustment for dapagliflozin from the dose of 10 mg once daily is recommended on the basis of age. The effect of age (young: ≥18 to <40 years [n=105] and elderly: ≥65 years [n=224]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients ≥40 to <65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10.4% lower than in the reference group (90% CI: 87.9, 92.2%) and 25% higher in elderly patients compared to the reference group (90% CI: 123, 129%). These differences in systemic exposure were considered to not be clinically meaningful.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric and adolescent

Dapagliflozin

Pharmacokinetics in the pediatric and adolescent population have not been studied.

Metformin hydrochloride

After administration of a single oral metformin 500 mg tablet with food, geometric mean metformin C_{max} and AUC differed less than 5% between pediatric type 2 diabetic patients (12-16 years of age) and gender- and weight-matched healthy adults (20-45 years of age), all with normal renal function.

Gender

Dapagliflozin

No dosage adjustment from the dose of 10 mg once daily is recommended for dapagliflozin on the basis of gender. Gender was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. The mean dapagliflozin AUC_{ss} in females (n=619) was estimated to be 22% higher than in males (n=634), (90% CI: 117,124).

Metformin hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

Race

Dapagliflozin

No dosage adjustment from the dapagliflozin dose of 10 mg once daily is recommended on the basis of race. Race (White, Black, or Asian) was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. Differences in systemic exposures between these races were small. Compared to Whites (n=1147), Asian subjects (n=47) had no difference in estimated mean dapagliflozin systemic exposures (90% CI range 3.7% lower, 1% higher). Compared to Whites, Black subjects (n=43) had 4.9% lower estimated mean dapagliflozin systemic exposures [90% CI range 7.7% lower, 3.7% lower).

Metformin hydrochloride

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

Body weight

No dose adjustments from the proposed dapagliflozin dose of 10 mg once daily is recommended on the basis of weight.

In a population pharmacokinetic analysis using data from healthy subject and patient studies, systemic exposures in high-body-weight subjects (≥120 kg, n=91) were estimated to be 78.3% (90% CI: 78.2, 83.2%) of those of reference subjects with body weight between 75 and 100 kg. This

difference is considered to be small, therefore, no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with high body weight (≥120 kg) is recommended.

Subjects with low body weights (<50 kg) were not well represented in the healthy subject and patient studies used in the population pharmacokinetic analysis. Therefore, dapagliflozin systemic exposures were simulated with a large number of subjects. The simulated mean dapagliflozin systemic exposures in low-body-weight subjects were estimated to be 29% higher than subjects with the reference group body weight. This difference is considered to be small, and based on these findings no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with low body weight (<50 kg) is recommended.

5.3 Preclinical safety data

5.3.1 Carcinogenesis, mutagenesis, impairment of fertility

Dapagliflozin

Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were equivalent to AUC exposure multiples of approximately 72x (males) and 105x (females) the human AUC at MRHD of 10 mg/day. In rats, AUC exposures were approximately 131x (males) and 186x (females) the human AUC at the MRHD.

Dapagliflozin was negative in the Ames mutagenicity assay and was positive in an in-vitro clastogenicity assay, but only in the presence of S9 activation and at concentrations ≥100 μg/mL. Importantly, dapagliflozin was negative for clastogenicity in vivo in a series of studies evaluating micronuclei or DNA repair in rats at exposure multiples >2100x the human exposure at the MRHD. These studies, along with the absence of tumor findings in the rat and mouse carcinogenicity studies, support that dapagliflozin does not represent a genotoxic risk to humans.

Dapagliflozin-related gene transcription changes were evaluated in kidney, liver, adipose, and skeletal muscle of Zucker Diabetic Fatty (ZDF) rats treated daily with dapagliflozin for 5 weeks. These organs were specifically selected as they represent target organs in the treatment of

diabetes. There was no evidence that dapagliflozin caused transcriptional changes that are predictive of tumor promoters.

Dapagliflozin and its primary human metabolite (3-O-glucuronide) did not enhance the in vitro growth of six human urinary bladder transitional cell carcinomas (TCC) cell lines at concentrations ≥100x human C_{max} at the MRHD. In a mouse xenograft study, dapagliflozin administered daily to male and female nude mice implanted with human TCC tumors did not significantly enhance the size of tumors at exposures up to 75x and up to 0.9x clinical exposures at the MRHD for dapagliflozin and its 3-O-glucuronide metabolite, respectively. These studies provide evidence that dapagliflozin and its primary human metabolite do not enhance urinary bladder tumor growth.

In a 15-month phenotyping study, there was no evidence of any difference in survival, body weights, clinical pathology parameters, or histopathologic findings observed between SGLT2 KO mice and their wild-type (WT) counterparts. SGLT2 KO mice had glucosuria, unlike the WT mice. Despite a lifetime of glucosuria, there was no evidence of any alteration of renal function or proliferative changes observed in the kidneys or urinary bladders of SGLT2 KO mice. These data strongly suggest that high levels of urinary glucose do not induce urinary tract tumors or accelerate age-related urinary tract pathology.

In a study of fertility and early embryonic development in rats, doses of 15, 75, or 300/210 mg/kg/day dapagliflozin were administered to males (the 300 mg/kg/day dose was lowered to 210 mg/kg/day after 4 days); and doses of 3, 15, or 75 mg/kg/day were administered to females. Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated males or females at any dose tested (at exposure multiples ≤1708x and 998x the MRHD in males and females, respectively). However, at 300/210 mg/kg/day, seminal vesicle and epididymal weights were reduced; sperm motility and sperm counts were reduced; and there were low numbers of morphologically abnormal sperm.

Metformin hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg based on body-surface-area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no

tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following in vitro tests: Ames test (S. typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body-surface-area comparisons.

5.3.2 Teratogenicity and Impairment of Early Development

Dapagliflozin

Direct administration of dapagliflozin to weanling juvenile rats, and indirect exposure during late pregnancy and lactation (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation), are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥15x the MRHD. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

In a separate study of pre-natal and postnatal development, maternal rats were dosed from gestation day (GD) 6 through PND 21 (also at 1, 15, or 75 mg/kg/day), and pups were indirectly exposed in utero and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups.) Increased incidence or severity of renal pelvic dilatation was again observed in adult offspring of treated dams, although only at 75 mg/kg/day (associated maternal and pup dapagliflozin exposures were 1415x and 137x, respectively, the human values at the MRHD). Additional developmental toxicity was limited to dose-related reductions in pup body weights, and observed only at doses ≥15 mg/kg/day (associated with pup exposures that are ≥29x the human values at the MRHD). Maternal toxicity was evident only at 75 mg/kg/day, and limited

to transient reductions in body weight and food consumption at dose initiation. The no-adverse-effect level (NOAEL) for developmental toxicity, 1 mg/kg/day, is associated with a maternal systemic exposure multiple that is approximately 19x the human value at the MRHD.

In additional studies of embryo-fetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested (20, 60, or 180 mg/kg/day); 180 mg/kg/day is associated with a systemic exposure multiple of approximately 1191x the MRHD. In rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day (1441x the MRHD). Doses ≥150 mg/kg/day (≥2344x the human values at the MRHD) were associated with both maternal and developmental toxicities. Maternal toxicity included mortality, adverse clinical signs, and decrements in body weight and food consumption. Developmental toxicity consisted of increased embryo-fetal lethality, increased incidences of fetal malformations and skeletal variations, and reduced fetal body weights. Malformations included a low incidence of great vessel malformations, fused ribs and vertebral centra, and duplicated manubria and sternal centra. Variations were primarily reduced ossifications.

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

5.3.3 Animal Toxicology

A 3-month rat study was conducted with the combination of dapagliflozin and metformin. No toxicity was observed at AUC exposures 52 and 1.4 times the MRHD for dapagliflozin and metformin, respectively.

Dapagliflozin

Most of the effects observed in pivotal repeat-dose toxicity studies in both rats and dogs were considered to be secondary to pharmacologically mediated increases in urinary glucose and included decreases in body weights and/or body-weight gains, increased food consumption, and increases in urine volumes due to osmotic diuresis. Dapagliflozin was well tolerated when given orally to rats for up to 6 months at doses of ≤25 mg/kg/day (≥346x the human exposures at the

MRHD) and in dogs for up to 12 months at doses of ≤120 mg/kg/day (≥3200x the human exposures at the MRHD). Also, single-dose studies with dapagliflozin indicated that the dapagliflozin 3-O-glucuronide metabolite would have been formed in both rat and dog toxicity studies at exposure levels (AUCs) that are greater than or approximately equal to anticipated human dapagliflozin 3-O-glucuronide exposures following administration of dapagliflozin at the MRHD. In rats, the most noteworthy nonclinical toxicity finding of increased trabecular bone and tissue mineralization (associated with increased serum calcium), was only observed at high-exposure multiples (≥2100x based on human exposures at the MRHD). Despite achieving exposure multiples of ≥3200x the human exposure at the MRHD, there was no dose-limiting or target-organ toxicities identified in the 12-month dog study.

6 PHARMACEUTICAL PROPERTIES

6.1 List of Excipients

Each film-coated tablet of XIGDUO XR contains 5 mg or 10 mg of dapagliflozin and 1000 mg of metformin and the following inactive ingredients:

Dapagliflozin layer for 5 mg and 10 mg FDCs: microcrystalline cellulose, lactose anhydrous, crospovidone, silicon dioxide, and magnesium stearate.

Metformin Layer for 1000 mg FDCs: carboxymethylcellulose sodium, Hypromellose 2208, silicon dioxide, and magnesium stearate.

Coating: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxides (5/1000 and 10/1000).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

24 months

6.4 Storage

This medicinal product does not require any special storage conditions.

Store below 30°C

7. DOSAGE FORMS AND PACKAGING AVAILABLE

XIGDUO XR 5 mg/1000 mg tablets: cartons containing PA/ Alu/ PVC-Alu blisters of 14 or 56 tablets (2 or 8 blisters of 7 film-coated tablets each).

XIGDUO XR 10 mg/1000 mg tablets: cartons containing PA/ Alu/ PVC-Alu blisters of 7 or 28 tablets (1 or 4 blisters of 7 film-coated tablets each).

8. NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER

AstraZeneca (Thailand) Ltd, Bangkok, Thailand

9. DATE OF REVISION PACKAGE INSERT

January 2024