NEW ZEALAND DATA SHEET

1. PRODUCT NAME

XIGDUO ® XR 5mg/1000mg, modified release tablet
XIGDUO ® XR 10mg/500mg, modified release tablet
XIGDUO ® XR 10mg/1000mg, modified release tablet

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 HCl extended-release.

XIGDUO XR 10 mg/500 mg: Each film-coated tablet contains 10 mg dapagliflozin as dapagliflozin propanediol and 500 mg metformin HCl extended-release.

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

For the full list of excipients see section 6.1 - List of Excipients.

3. PHARMACEUTICAL FORM

XIGDUO XR 5 mg/1000 mg tablets are pink to dark pink, biconvex, oval shaped, film-coated tablets debossed with "1071" and "5/1000" on one side and plain on the other side.

XIGDUO XR 10 mg/500 mg tablets are pink, biconvex, capsule shaped, film-coated tablets debossed with "1072" and "10/500" on one side and plain on the other side.

XIGDUO XR 10 mg/1000 mg tablets are yellow to dark yellow, biconvex, oval shaped, film-coated tablets debossed with "1073" and "10/1000" on one side and plain on the other side.
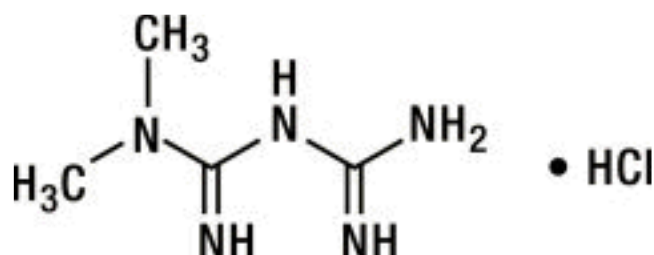
DAPAGLIFLOZIN

Dapagliflozin is described chemically as (1S)-1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-D-glucitol, (S)-propylene glycol, monohydrate.

The chemical structure of dapagliflozin propanediol monohydrate is:
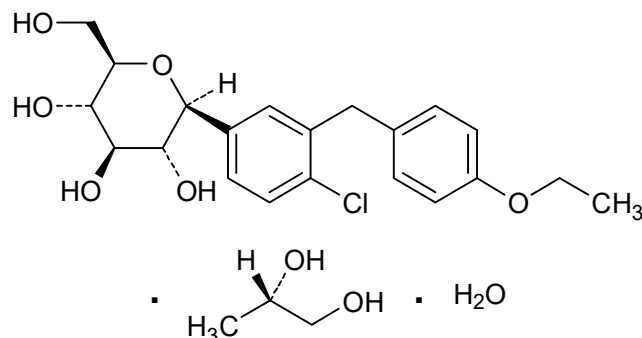
METFORMIN HYDROCHLORIDE

The chemical structure of metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is:

$$H_3C-N(CH_3)-C(=NH)-NH-C(=NH)-NH_2 \cdot HCl$$

4.   CLINICAL PARTICULARS

4.1   THERAPEUTIC INDICATIONS

Glycaemic control

XIGDUO XR is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control when treatment with both dapagliflozin and metformin is appropriate (see sections 5.1 and 4.4 for available data on the combination therapy).

Prevention of hospitalisation for heart failure

Dapagliflozin is indicated in adults with type 2 diabetes mellitus and established cardiovascular disease or risk factors for cardiovascular disease to reduce the risk of hospitalization for heart failure. (see section 5.1 Pharmacodynamic Properties – Clinical Efficacy and Safety).

Prevention of new or worsening nephropathy

Dapagliflozin is indicated in adults with type 2 diabetes mellitus and established cardiovascular disease or risk factors for cardiovascular disease for the prevention of new or worsening nephropathy (see section 5.1 Pharmacodynamic Properties – Clinical Efficacy and Safety).

4.2   DOSE AND METHOD OF ADMINISTRATION

Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment; other risk factors include old age associated with reduced renal function and high doses of metformin above 2 g per day.

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

Initial Therapy

The recommended dose of dapagliflozin is 10 mg once daily. The recommended starting dose of metformin extended-release 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.

Add on combination therapy

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.

When dapagliflozin is used as an add-on therapy with insulin or an insulin secretagogue, a lower dose of insulin or an insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

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 faeces as a soft, hydrated mass that may resemble the original tablet.

Special patient populations

Renal Impairment

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

Mild renal impairment

No dose adjustment of XIGDUO XR is required for patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m^2 by Modified Diet in Renal Disease [MDRD] eGFR equation).

Moderate renal impairment

XIGDUO XR is not recommended for the treatment of diabetes in patients with eGFR persistently below 45 mL/min/1.73 m^2 (see section 4.4 Special Warnings and Precautions for Use). No dose adjustment is required for patients with eGFR ≥ 45 mL/min/1.73 m^2).

Severe renal impairment

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

Dose adjustment for XIGDUO XR – metformin component:

Creatinine clearance between 45-60 mL/min: maximum daily dose of metformin 1000 mg.
Creatinine clearance 60 - 120 ml/min: maximum daily dose of metformin 2000mg.

Hepatic Impairment

Since impaired hepatic function has been associated with some cases of lactic acidosis in patients taking metformin, XIGDUO XR should not be used in patients with clinical or laboratory evidence of hepatic impairment (see section 4.4 Special Warnings and Precautions for Use).

Paediatric and Adolescent

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

Elderly

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 Special Warnings and Precautions for Use).

4.3   CONTRAINDICATIONS

XIGDUO XR is contraindicated in patients with:

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1;

- Metabolic acidosis;

- severe renal impairment (eGFR< 30mL/min/1.73 m^2) (see section 4.4 Special Warnings and Precautions for Use);

- acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, or intravascular administration of iodinated contrast agents (see section 4.4 Special Warnings and Precautions for Use);

- acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, pulmonary embolism, recent myocardial infarction, shock, acute significant blood loss, sepsis, gangrene, pancreatitis;

- during or immediately following surgery where insulin is essential, elective major surgery;

- hepatic impairment;

- acute alcohol intoxication, alcoholism;

- lactation.

4.4   SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

XIGDUO XR should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Lactic acidosis

Metformin hydrochloride

Lactic acidosis is a very 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 Special Warnings and Precautions for Use).

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

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 XR should be discontinued and the patient hospitalized immediately.

Use in Patient with Renal Impairment

XIGDUO XR is not recommended for the treatment of diabetes in patients with eGFR persistently below 45 mL/min/1.73 m^2 as the glycemic efficacy of dapagliflozin is dependent on renal function (see section 4.2 Dose and Method of Administration). 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 once daily.

Initiation of dapagliflozin may transiently increase serum creatinine and decrease eGFR (see section 4.8 Undesirable Effects).

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

Dapagliflozin has not been studied in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2 by MDRD) or end stage renal disease (ESRD).

Metformin is excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function.

Assess renal function prior to initiation of XIGDUO XR and periodically thereafter as follows:
−   at least yearly;

−   prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter;

−   for renal function approaching eGFR 45 mL/min/1.73 m^2 and in elderly patients, at least 2 to 4 times per year. If renal function falls persistently below eGFR < 45 mL/min/1.73 m^2, treatment with XIGDUO XR should be discontinued.

Acute conditions associated with hypoxia or impacting renal function

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

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

A patient with type 2 diabetes mellitus 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 in either form occurs, XIGDUO XR must be stopped immediately and other appropriate corrective measures initiated.

Use in patients with hepatic impairment

Dapagliflozin

There is limited experience in clinical trials in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment. Dapagliflozin should not be used in patients with severe hepatic impairment (see sections 4.2 and 5.2).

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.

Radiologic studies with intravascular iodinated contrast materials

Metformin hydrochloride

Intravascular administration of iodinated contrast agents in radiological studies can lead to an acute decrease in renal function and has 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.

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.

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.

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.

Treatment of ketoacidosis generally requires insulin, fluid and carbohydrate replacement.

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.

In patients where the decision is made to restart XIGDUO XR after an episode of ketoacidosis, any potential risk for DKA should be managed by the physician. If a patient taking dapagliflozin requires major surgery, the need for interruption of treatment should be considered taking into account local guidelines.

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.

Use with Medications Known to Cause Hypoglycaemia

Dapagliflozin

Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with XIGDUO XR (see section 5.1 Pharmacodynamic Properties).

Metformin hydrochloride

Hypoglycaemia 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 sulphonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication, are particularly susceptible to hypoglycaemic effects. Hypoglycaemia may be difficult to recognise in the elderly and in people who are taking beta-adrenergic blocking drugs.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors (see section 4.8 Undesirable Effects). This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise.

Patients treated with XIGDUO XR who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, malaise should be evaluated for necrotising fasciitis.' 'Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis.

If Fournier's gangrene is suspected, XIGDUO XR should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Paediatric use

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

Use in elderly

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.

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 glycaemic 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 from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients.

Urinary tract infections

There have been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis in patients receiving SGLT2 inhibitors.

Cardiac failure

There is limited clinical experience with dapagliflozin in patients with NYHA class IV.

4.5   INTERACTION WITH OTHER MEDICINES 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 neither inhibited CYP 1A2, 2A6, 2B6, 2C8, 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 metabolised by these enzymes and

drugs which 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 interaction studies conducted in healthy subjects, using mainly a single dose design, 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 Normalised Ratio [INR]).

Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension .

4.5.5 Interactions between metformin hydrochloride and other drugs

Cationic drugs

Cationic drugs (e.g. 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.

Glibenclamide

In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glibenclamide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glibenclamide 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 glibenclamide blood levels and pharmacodynamic effects makes the clinical significance of this interaction uncertain.

Frusemide

A single-dose, metformin-frusemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Frusemide 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 frusemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in frusemide renal clearance. No information is available about the interaction of metformin and frusemide 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 hyperglycaemia and may lead to loss of glycaemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, oestrogens, 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 hypoglycaemia.

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 is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulphonamides, chloramphenicol, and probenecid, as compared to the sulphonylureas, which are extensively bound to serum proteins.

Other interactions

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

Effect on Laboratory Tests

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

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

4.6   FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Category D

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 Preclinical Safety Data).

There are no adequate and well-controlled studies of XIGDUO XR or its individual components in pregnant women. When pregnancy is detected, treatment with XIGDUO XR should be discontinued.

Dapagliflozin

In conventional studies of embryo-foetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the period of organogenesis in humans. An increased incidence of embryofoetal lethality, decreased foetal weight and an increased incidence of foetal visceral and skeletal anomalies were seen in rats at maternotoxic doses (oral doses greater than or equal to 150 mg/kg/day). The no observed effect level for embryofoetal effects in rats was an oral dose of 75 mg/kg/day (1530 times the exposure in patients at the maximum recommended human dose [MRHD]). No developmental toxicities were observed in rabbits at oral doses up to 180 mg/kg/day (1265 times the exposure in patients at the MRHD).

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 3 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 foetal concentrations demonstrated a partial placental barrier to metformin.

Breast-feeding

XIGDUO XR must not be used by breastfeeding women.

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.

Studies in rats have shown excretion of dapagliflozin in milk. 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. 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.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND TO USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed with XIGDUO XR or dapagliflozin.

It should be taken into account that dizziness has been reported in studies with dapagliflozin.

4.8 UNDESIRABLE EFFECTS

Clinical Experience

Dapagliflozin and metformin hydrochloride

Data from a prespecified pool of patients from 8 short-term, placebo-controlled studies of dapagliflozin co-administered 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 haemoglobin A1c (HbA1c) was 8.4%, and renal function was normal or mildly impaired in 90% of patients and moderately impaired in 10% of patients.

Dapaglifozin

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 Pharmacodynamic Properties – Clinical Efficacy and Safety.

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, 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 post-marketing 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]
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 post-marketed 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'.

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 more frequently reported 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 CV outcomes 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.

Necrotising fasciitis of the perineum (Fournier's gangrene)

In the dapagliflozin cardiovascular outcomes study with 17,160 patients with type 2 diabetes mellitus and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported on treatment, one in the dapagliflozin-treated group and 5 in the placebo group.

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 CV outcomes 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 CV outcomes 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 Special Warnings and Precautions for Use).

Events Related to Decreased Renal Function

There have been post-marketing reports of acute kidney injury (including acute renal failure) in patients receiving dapagliflozin. In the DECLARE study, there was no increased risk for events of acute kidney injury in dapagliflozin-treated patients compared with the placebo group.

In development, the 13-study, short-term, placebo-controlled pool, use of dapagliflozin was associated with increases in serum creatinine and decreases in eGFR. These changes were observed to reverse after treatment discontinuation.

Metformin hydrochloride

Metformin adverse reactions by system organ class and by frequency category. Frequency categories are based on information available from the metformin Product Information available in Australia.

Gastrointestinal

Very common: Mild gastrointestinal symptoms (such as diarrhoea, nausea, vomiting, abdominal pain and loss of appetite) are the most frequent reactions to metformin (> 1/10), especially during the initial treatment period. These symptoms are generally transient and resolve spontaneously during continued treatment.

Occurrence of gastrointestinal symptoms, once a patient is stabilised on any dose of metformin, could be due to lactic acidosis or other serious disease.

Systemic/metabolic

Very rare: Lactic acidosis (see section 4.4 Special Warnings and Precautions for Use) is a very rare (< 1/10,000) but serious metabolic complication that can occur due to metformin accumulation during treatment with metformin.

The onset of lactic acidosis is often subtle and accompanied only by non-specific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence and non-specific abdominal distress. There may be associated hypothermia, hypotension and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia).

Lactic acidosis is a medical emergency that must be treated in hospital. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted.

Nervous System Disorders

Common: Taste disturbance (3%) is common.

Dermatological

Very rare: Skin reactions such as erythema, pruritus and urticaria have been reported, but the incidence is very rare (< 1/10,000).

Haematological

Common: A decrease of vitamin B12 absorption with a decrease in serum levels has been observed in patients treated long term with metformin. Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia. Therefore, serum B12 levels should be appropriately monitored or periodic parenteral B12 supplementation considered.

Hepatobiliary Disorders

Isolated reports: Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation, have been reported.

In clinical trials in children and adolescents with type 2 diabetes, the profile of adverse reactions was similar to that observed in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/.

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 hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the MRHD) were administered for 2 weeks in healthy subjects and type 2 diabetes patients, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension 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 haemodialysis has not been studied.

Metformin hydrochloride

High dose 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 haemodialysis. Events of hypoglycaemia have been reported with overdoses of metformin, although a causal association has not been established.

For advice on the management of overdose contact the National Poisons Centre on 0800 POISON (0800 764 766).

5.   PHARMACOLOGICAL PROPERTIES

MECHANISM OF ACTION

XIGDUO XR combines two anti-hyperglycaemic 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, a 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 glycaemic 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 is believed to increase tubuloglomerular feedback and reduce 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. Secondary effects of SGLT2 inhibition with dapagliflozin also include a modest reduction in blood pressure, reduction in body weight, and an increase in hematocrit.

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 post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. 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 glucose, dapagliflozin has a low propensity to cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. 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 the weight reduction was 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 approximately 1000-3000 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

Metformin hydrochloride

Metformin is an antihyperglycaemic 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 sulphonylureas, metformin does not produce hypoglycaemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see section 4.4 Special Warnings and Precautions for Use) and does not cause hyperinsulinaemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.1   PHARMACODYNAMIC PROPERTIES

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 dose of dapagliflozin. Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10mg/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 18.3 to 48.3 µmol/L.

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)
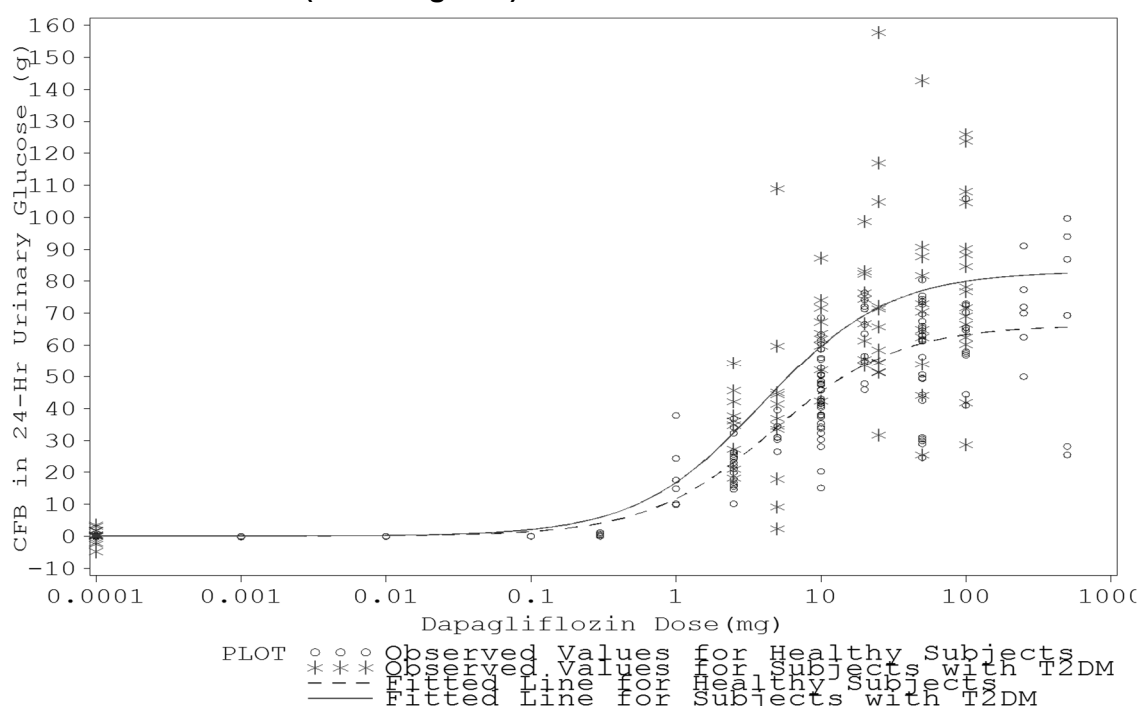
Cardiac Electrophysiology

Dapagliflozin

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.

Clinical Efficacy and Safety

Glycaemic Efficacy

There have been no clinical efficacy studies conducted with XIGDUO XR; however, bioequivalence of XIGDUO XR with coadministered dapagliflozin and metformin hydrochloride extended release tablets was demonstrated.

Addition of Dapagliflozin to Metformin.

The coadministration of dapagliflozin and metformin has been studied in patients with type 2 diabetes inadequately controlled on metformin alone or in combination with a sulphonylurea, or insulin, in treatment-naive patients inadequately controlled on diet and exercise alone, and compared with a sulphonylurea in combination with metformin in patients with inadequate glycaemic control on metformin alone. 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).

Initial Combination Therapy with Metformin

638 patients randomised to one of three treatment arms following a 1-week lead-in period received: 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 the maximum and median dose achieved being 2000 mg. The patients were treatment-naïve, defined as either never having received diabetes medication or having had such for less than 24 weeks since the diagnosis of diabetes, not for more than 14 days during the 12 weeks prior to enrolment, and not at all during the 4 weeks prior to enrolment.

The combination treatment of dapagliflozin 10 mg plus metformin provided significant improvements in haemoglobin A1c (HbA1c) and FPG, compared with either of the monotherapy treatments and significant improvements in body weight compared with metformin alone (Table 2). Dapagliflozin 10 mg as monotherapy also provided significant improvements in FPG and 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 glycaemic control during the 24 week double-blind treatment period (adjusted for baseline HbA1c) was higher on treatment with metformin plus placebo (13.5%) than on dapagliflozin 10 mg plus placebo and dapagliflozin 10 mg plus metformin (7.8%, and 1.4%).

Table 2: 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[‡]) (95% CI)	−0.53[§] (−0.74, −0.32)		
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 (mmol/L)			
Baseline (mean)	10.5	11.0	10.5
Change from baseline (adjusted mean[‡])	−3.4	−2.6	−1.9
Difference from dapagliflozin (adjusted mean[‡]) (95% CI)	−0.8[§] (−1.2, −0.4)		

Table 2: **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	Dapagliflozin 10 mg	Metformin XR
Difference from metformin (adjusted mean[‡]) (95% CI)	−1.4[§] (−1.8, −1.0)	−0.6[¶] (−1.0, −0.3)	
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 randomised 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.

Add-on to Metformin

As add-on treatment to metformin, dapagliflozin 10 mg provided significant improvements in HbA1c at week 24 (Table 3).

Table 3: **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
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)
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 randomised 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 2:   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)
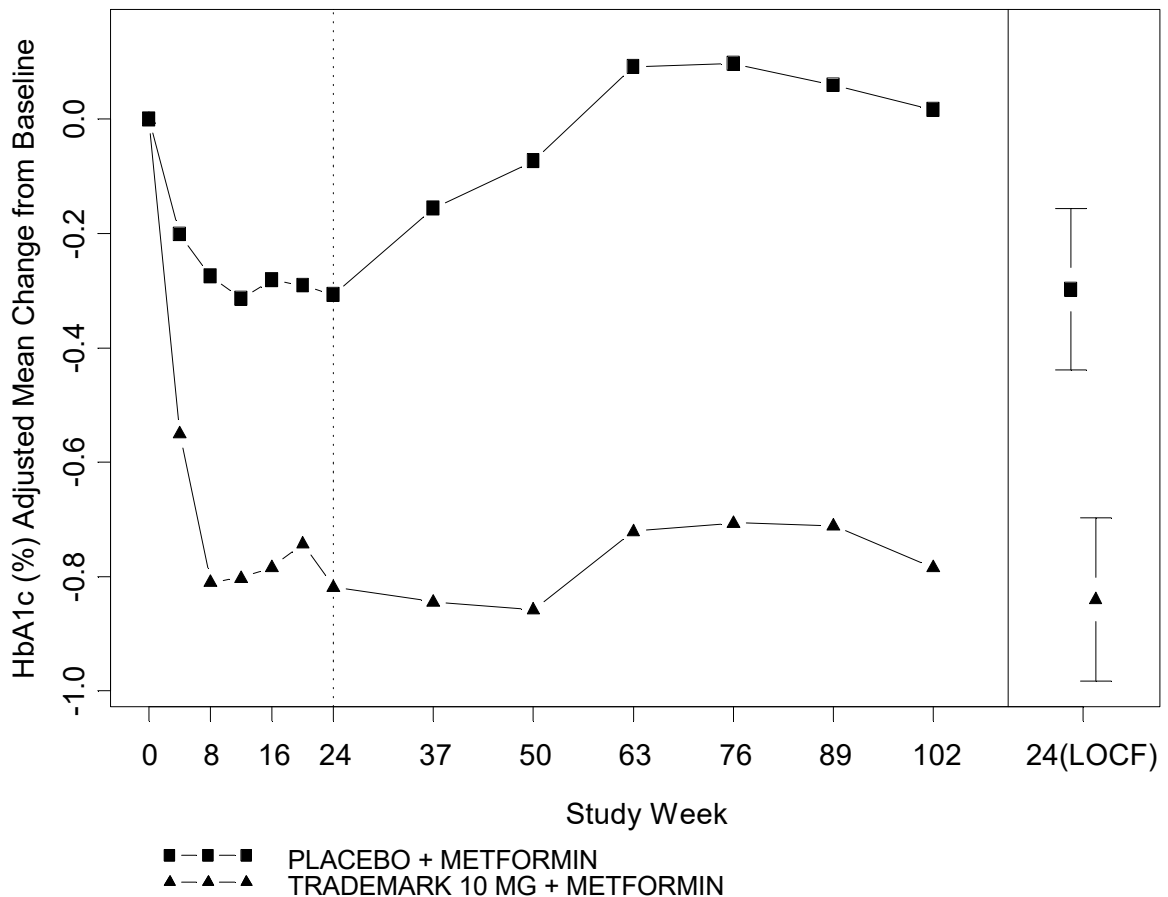
LOCF: Last observation (prior to rescue for rescued subjects) carried forward
Values for 24(LOCF) represent adjusted mean and 95% confidence intervals based on an ANCOVA model
Values for other weeks represent adjusted means based on a longitudinal repeated measures model

Active Glipizide Controlled Study Add-on to Metformin

In a 52 week, active-controlled non-inferiority study (with a 52 week and 104 week extension periods), dapagliflozin was evaluated as add on therapy to metformin compared with a sulphonylurea (glipizide) as add on therapy to metformin in subjects with inadequate glycaemic control (HbA1c > 6.5% and ≤ 10%). The results showed a similar mean reduction in HbA1c from baseline to Week 52, compared to glipizide, thus demonstrating non-inferiority (Table 4). At Week 104, adjusted mean change from baseline in HbA1c was -0.32% for dapagliflozin and -0.14% for glipizide. At Week 208, the secondary endpoint of adjusted mean change from baseline in HbA1c was 0.10% for dapagliflozin and 0.20% for glipizide (see Figure 3). At 52, 104 and 208 weeks, a significantly lower proportion of subjects in the group treated with dapagliflozin (3.5%, 4.3% and 5.0%, respectively) experienced at least one event of hypoglycaemia compared to the group treated with glipizide (40.8%, 47.0% and 50.0%, respectively). The proportion of subjects remaining in

the study at Week 104 and Week 208 was 56.2% and 39% respectively for the group treated with dapagliflozin and 50.0% and 34.6% for the group treated with glipizide.

Table 4: **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‡) (95% CI)	0.00¶ (−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‡) (95% CI)	−4.65§ (−5.14, −4.17)	2.5%

*LOCF: last observation carried forward.
† Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.
‡ Least squares mean adjusted for baseline value.
§ p-value <0.0001.
¶ non-inferior to glipizide + metformin

Figure 3   **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)**
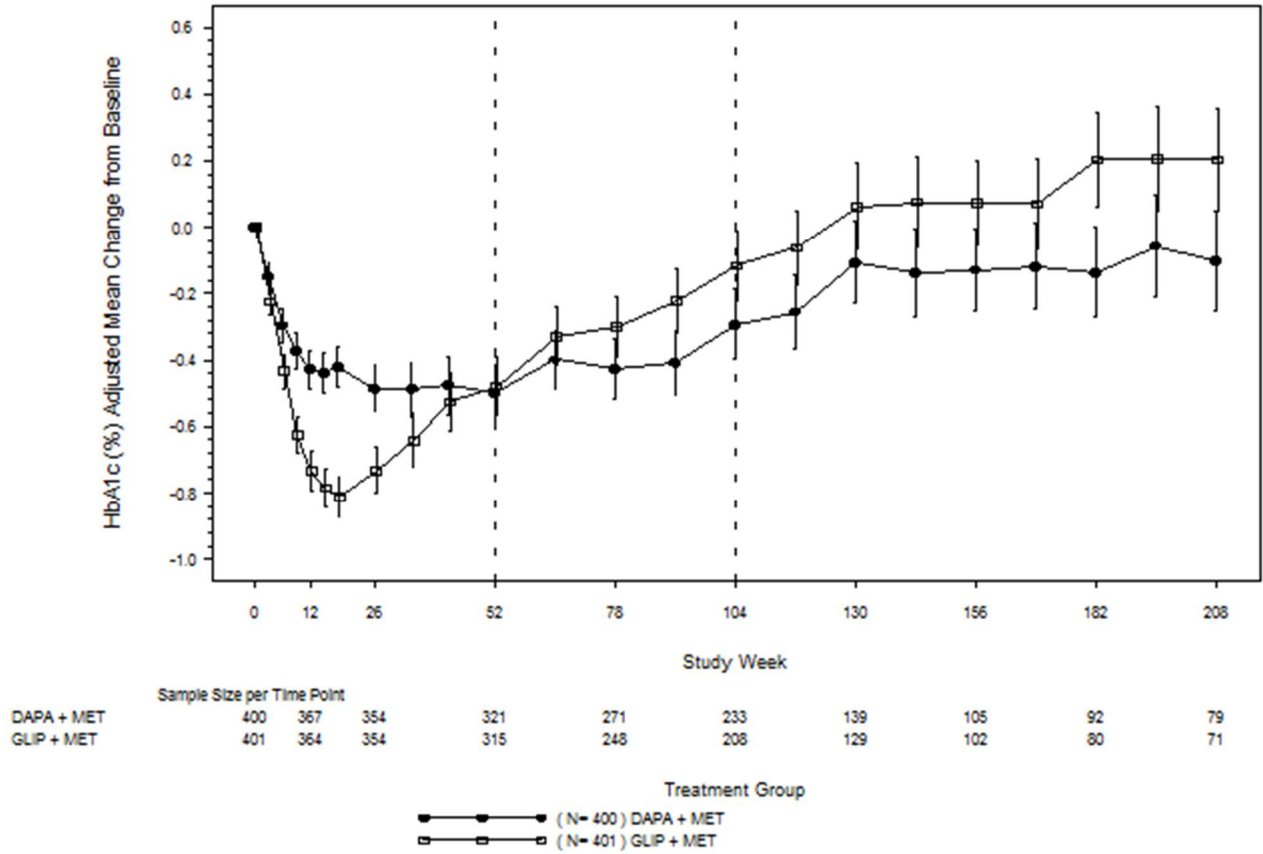
Subjects in the full analysis set.
Mean value based on repeated measures analysis model:
post-baseline = baseline treatment week week*treatment week*baseline.

Error bars represent 95% confidence intervals for the adjusted mean change from baseline.
Treatment symbols shifted horizontally to prevent error bar overlapping.

Combination therapy with Other Anti-hyperglycaemic Agents

Dapagliflozin as an add on with either sitagliptin (with or without metformin) or insulin resulted in statistically significant reductions in HbA1c at 24 weeks compared with subjects receiving placebo (p<0.0001; Tables 5,6 and 7).

Table 5: Results of a 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Sitagliptin (Stratum with Metformin)

Efficacy Parameter	Dapagliflozin 10 mg + Sitagliptin +Metformin N=113[†]	Placebo + Sitagliptin +Metformin 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)	
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)	

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

Table 6. Results of a 24-Week Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin and a Sulphonylurea

Efficacy Parameter	Dapagliflozin 10 mg + Metformin[a] + Sulphonylurea N=108[†]	Placebo +Metformin[a] + Sulphonylurea 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)	
Subjects (%) achieving HbA1c < 7% (LOCF)[*]		
Adjusted for baseline	31.8[§]	11.1
Body Weight (kg) LOCF[*]		
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)	

a   Metformin (immediate- or extended-release formulations) ≥1500 mg/day plus maximum tolerated dose, which must be at least half maximum dose, of a sulphonylurea for at least 8 weeks prior to enrollment.
^   HbA1c analysed using Longitudinal Repeated Measures (LRM) analysis
*   LOCF: last observation (prior to rescue for rescued patients) carried forward.
†   Randomised 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.

Table 7: **Results of 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Combination with Insulin (alone or with oral glucose-lowering medicinal products)**

Efficacy Parameter	Dapagliflozin 10 mg + insulin ± oral glucose-lowering medicinal products^	Placebo + insulin ± oral glucose-lowering medicinal products^
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)	
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%
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)	

*   LOCF: last observation (prior to or on the date of the first insulin up-titration, if needed) carried forward.

†   All randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double blind period.

‡   Least squares mean adjusted for baseline value and presence of oral glucose lowering-medicinal product.

§   p-value <0.0001 versus placebo+ insulin ± oral glucose-lowering medicinal product.

**   p-value <0.05 versus placebo+ insulin ± oral glucose-lowering medicinal product.

^   Fifty percent of subjects were on insulin therapy monotherapy at baseline: 50% were on 1 or 2 oral glucose-lowering medicinal product(s) in addition to insulin: Of this latter group 80% were on metformin alone, 12 % were on metformin plus sulphonylurea therapy and the rest were on other oral glucose-lowering medicinal products

††   Up-titration of insulin regimens (including short acting, intermediate and basal insulin) was only allowed if subjects met pre-defined FPG criteria.

The reductions in HbA1c observed at Week 24 were sustained in add on combination studies and up to 104 week data (insulin, see Figure 4). At Week 48 when added to sitagliptin (with or without metformin), the adjusted mean change from baseline for dapagliflozin 10 mg and placebo was -0.30% and 0.38%, respectively. For the add on to metformin study, HbA1c reductions were sustained through Week 102 (-0.78% and 0.02% adjusted mean change from baseline for 10 mg and placebo, respectively, see also Figure 4). At Week 104 for insulin (with or without additional oral glucose lowering medicinal products), the HbA1c reductions were -0.71% and -0.06% adjusted mean change from baseline for dapagliflozin 10 mg and placebo, respectively. At Weeks 48 and 104, the

insulin dose remained stable compared to baseline in subjects treated with dapagliflozin 10 mg at an average dose of 76 IU/day (see Figure 5). In the placebo group there was a mean increase of 10.5 IU/day and 18.3 IU/day from baseline (mean average dose of 84 and 92 IU/day) at Weeks 48 and 104, respectively. The proportion of subjects remaining in the study at Week 104 was 72.4% for the group treated with dapagliflozin 10 mg and 54.8% for the placebo group.

Figure 4: **HbA1c (%) Adjusted Mean Change from Baseline Over Time Short-term and Long-term Treatment Period in a 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.**
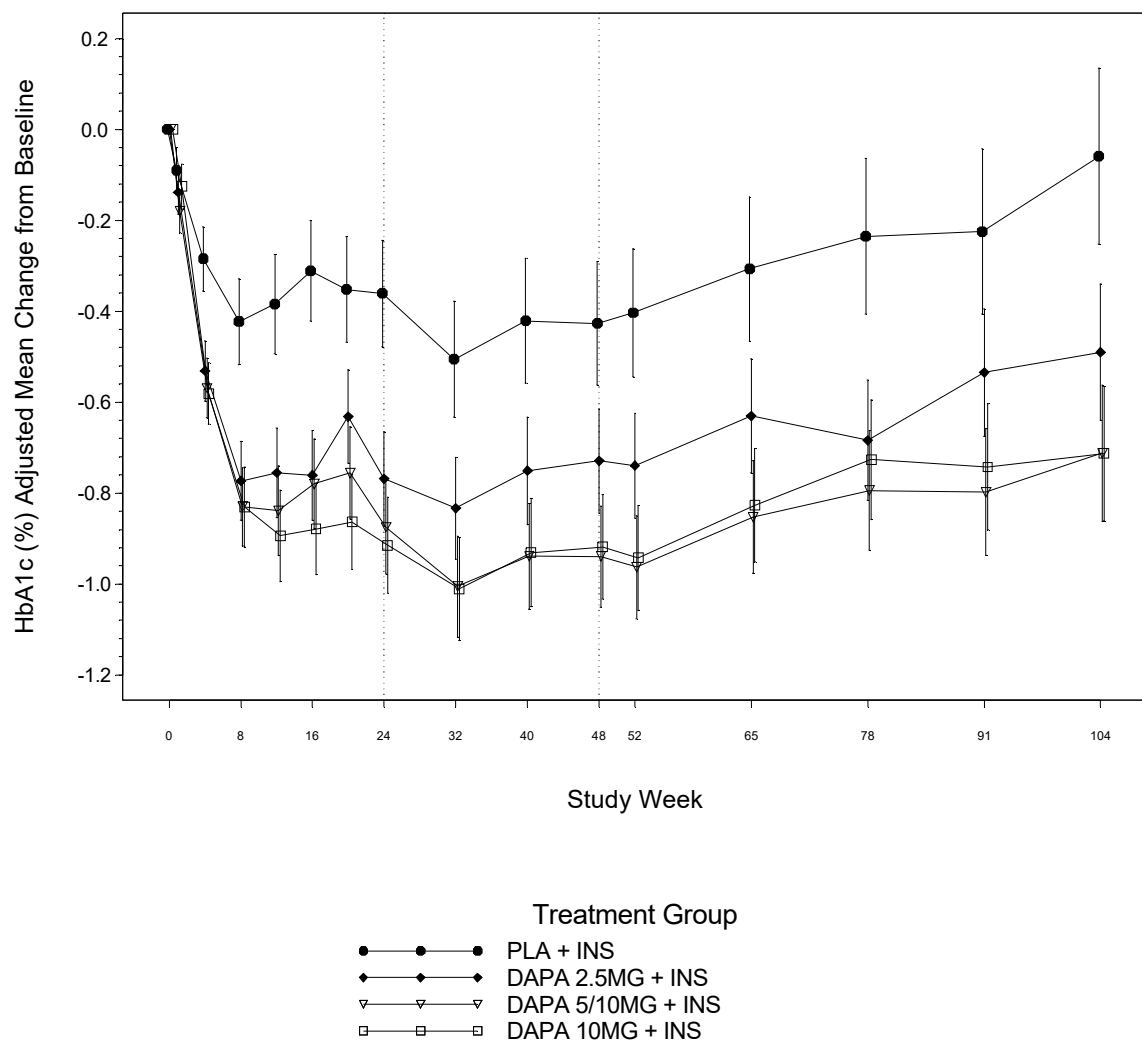
Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Figure 5: **Mean Daily Insulin Dose (IU/day) Adjusted Mean Change from Baseline Over Time in a Placebo-controlled Study of Dapagliflozin in Combination with Insulin with or without up to 2 Oral Anti-diabetic Therapies Short-term and Long-term Treatment Period Including Data After Insulin Up-titration**
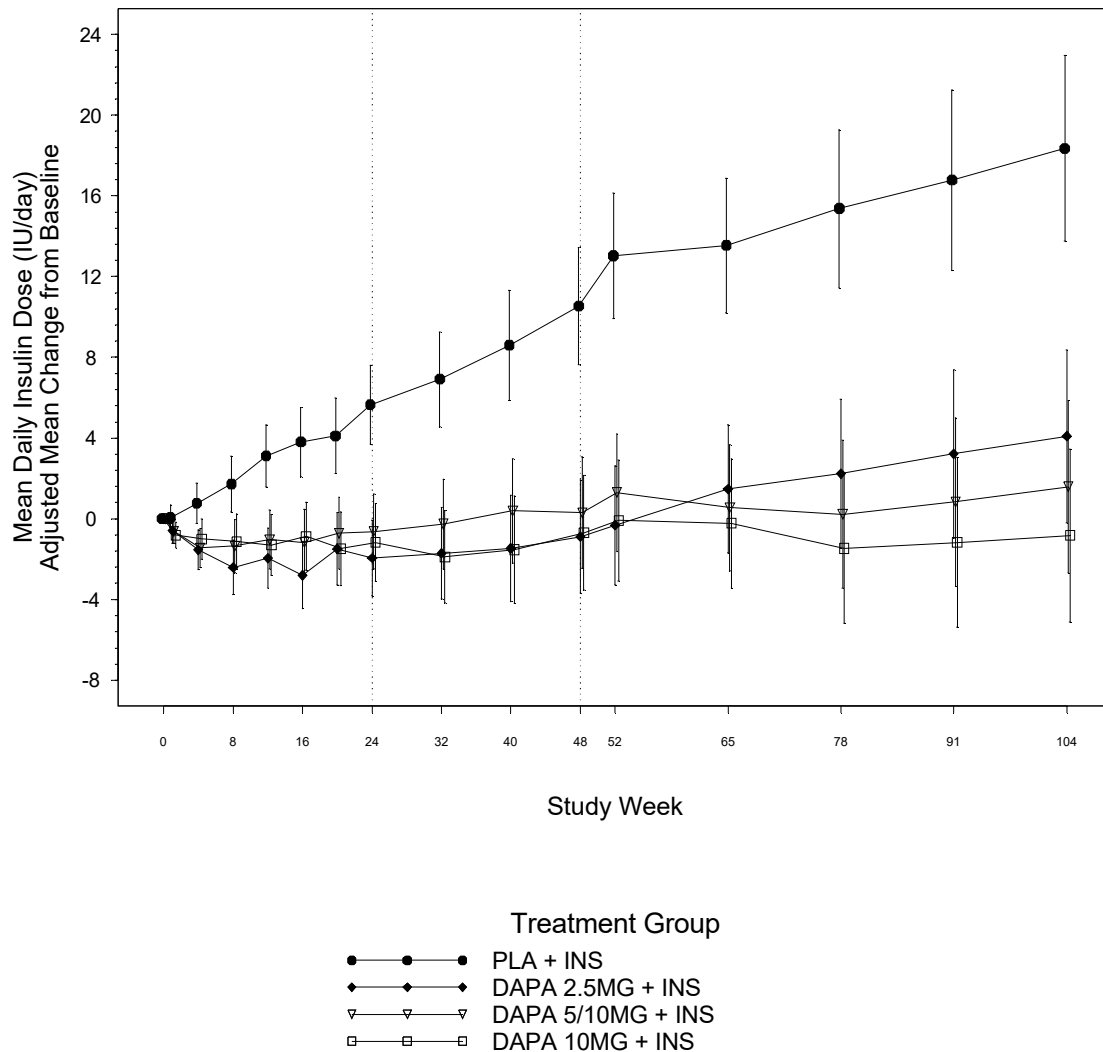
Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Fasting plasma glucose

Treatment with dapagliflozin 10 mg as an add on to either metformin, metformin and a sulphonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant reductions in fasting plasma glucose (-1.90 to -1.20 mmol/L) compared to placebo (-0.33 to 0.21 mmol/L) at 24 weeks. This effect was observed at Week 1 of treatment and maintained in studies extended through Week 104.

<u>Concomitant Initiation of Dapagliflozin and Prolonged-Release Exenatide in patients Inadequately Controlled on Metformin</u>

A total of 694 adult patients with type 2 diabetes mellitus and inadequate glycaemic control (HbA1c ≥8.0 and ≤12.0%) on metformin alone (≥1,500 mg/day) participated in this 28-week randomised, double-blind, active-controlled trial to compare the concomitant initiation of dapagliflozin 10 mg once daily and extended release exenatide 2 mg once weekly on a background of metformin versus extended release exenatide 2 mg once weekly (GLP-1 receptor agonist) alone and dapagliflozin 10 mg once daily alone when added to metformin. Following a 1-week placebo lead-in period, patients were randomised equally to one of three double-blind treatment groups to receive either dapagliflozin 10 mg and extended release exenatide, dapagliflozin 10 mg and placebo or extended release exenatide and placebo. During the treatment period, patients continued on the same type and dose of metformin as when they entered the study. Randomisation was stratified by HbA1c at baseline (<9.0% or ≥9.0%).

The primary endpoint was the change in HbA1c from baseline to Week 28 (Fig 6). Compared to dapagliflozin 10 mg alone and prolonged-release exenatide alone, concomitant initiation of dapagliflozin 10 mg and prolonged-release exenatide resulted in statistically significant reductions in HbA1c from baseline at Week 28 (Table 7).

Figure 6: Change in HbA1c over Time, LS Mean (SE) – 28-Week Treatment Period (Intent-to-Treat Analysis Set)
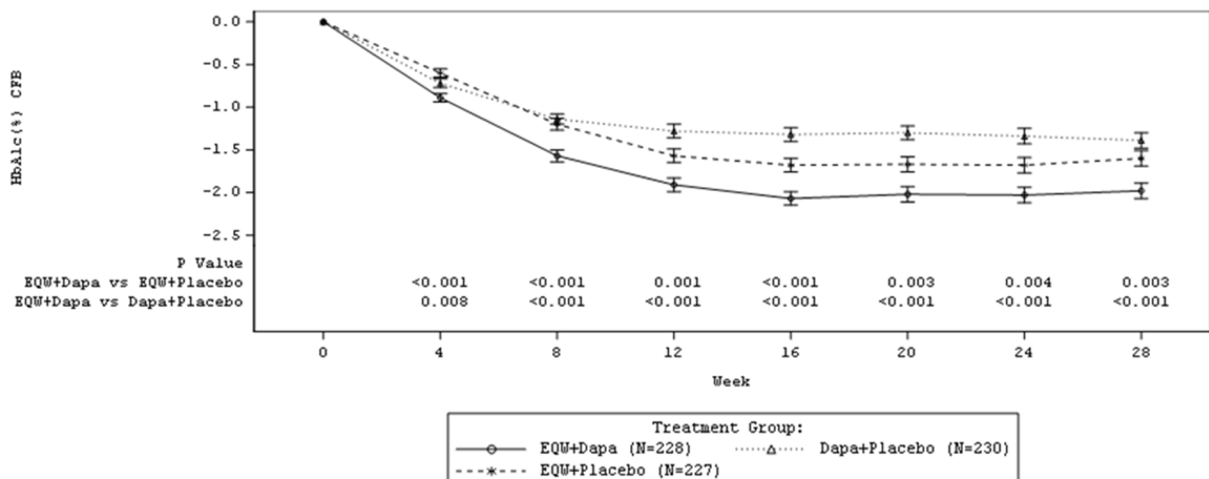
CFB=change from baseline; EQW=exenatide 2 mg once weekly; Dapa=dapagliflozin 10 mg once daily.
Baseline is defined as Week 0.

Table 8. **Results of a 28-Week Active-Controlled Trial of Dapagliflozin 10 mg and prolonged-Release Exenatide 2 mg Concomitant Add-On to Metformin**

	Dapagliflozin 10 mg QD + Extended release exenatide 2 mg QW	Dapagliflozin 10 mg QD + Placebo QW	Prolonged-release exenatide 2 mg QW + Placebo QD
Intent-to-Treat population (N) [c]	**228**	**230**	**227**
HbA1c (%)			
Baseline (mean)[a]	9.29	9.25	9.26
Change from baseline	-1.98	-1.39	-1.60
Mean difference in change from baseline vs. dapagliflozin (95% CI)	-0.59* (-0.84 -0.34)		
Mean difference in change from baseline vs. Extended release exenatide QW (95% CI)	-0.38** (-0.63 -0.13)		
Percent of patients achieving HbA1c <7.0%[b]	44.7%	19.1%	26.9%
Body weight (kg)			
Baseline (mean)[a]	92.13	90.87	89.12
Change from baseline	-3.55	-2.22	-1.56
Mean difference in change from baseline vs. dapagliflozin (95% CI)	-1.33 ** (-2.12 -0.55)		
Mean difference in change from baseline vs. Extended release exenatide (95% CI)	-2.00* (-2.79 -1.20)		
FPG (mmol/L)			
Baseline (mean)[a]	10.9	10.5	10.5
Change from baseline	-3.7	-2.7	-2.5
Mean difference in change from baseline vs. dapagliflozin (95% CI)	-0.92* (-1.36 -0.49)		
Mean difference in change from baseline vs. Extended release exenatide (95% CI)	-1.12* (-1.55 -0.68)		
2-hour PPG (mg/dL)			
Standard meal test population (n)	198	199	188
Baseline (mean)[a]	14.9	14.5	14.8
Change from baseline	-4.9	-3.4	-3.3

Table 8.   Results of a 28-Week Active-Controlled Trial of Dapagliflozin 10 mg and prolonged-Release Exenatide 2 mg Concomitant Add-On to Metformin

Mean difference in change from baseline vs. dapagliflozin (95% CI)	-1.49* (-2.04 -0.93)		
Mean difference in change from baseline vs. Extended release exenatide (95% CI)	-1.54* (-2.10 -0.98)		
Seated systolic blood pressure (mmHg)			
Baseline (mean)[a]	130.7	129.5	129.3
Change from baseline	-4.3	-1.8	-1.2
Mean difference in change from baseline vs. dapagliflozin (95% CI)	-2.4[#] (-4.5 -0.4)		
Mean difference in change from baseline vs. Extended release exenatide (95% CI)	-3.0** (-5.2 -0.9)		

QD=once daily, QW=once weekly, N=number of patients in treatment group, CI=confidence interval, FPG= fasting plasma glucose, PPG= postprandial glucose.

[a] Adjusted least squares means (LS Means) and treatment group difference(s) in the change from baseline values at Week 28 are modeled using a mixed model with repeated measures (MMRM) including treatment, region, baseline HbA1c stratum (< 9.0% or ≥ 9.0%), week, and treatment by week interaction as fixed factors, and baseline value as a covariate.

[b] Categories are derived from continuous measurements. All patients with missing endpoint data are imputed as non-responders. Treatment comparison is based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline HbA1c (< 9.0% or ≥ 9.0%). P-values are from the general association statistics.

[c] Patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA1c assessment.

*p < 0.001, **p < 0.01, #p < 0.05.

P values are all adjusted p values for multiplicity.

Analyses exclude measurements post rescue therapy and post premature discontinuation of study medication discontinuation, except for systolic blood pressure analysis, which includes measurements post rescue therapy but excludes data post premature discontinuation of study medication discontinuation.

Concomitant initiation therapy of dapagliflozin 10 mg and prolonged-release exenatide resulted in a greater proportion of patients achieving HbA1c ≤6.5% at Week 28 (30.3%) compared to dapagliflozin alone (10.4%) and prolonged-release exenatide alone (18.5%). The mean baseline HbA1c was 9.3%.

Post prandial glucose

Treatment with dapagliflozin 10 mg as an add on to sitagliptin (with or without metformin) resulted in reductions in 2 hour post prandial glucose at 24 weeks that were maintained up to Week 48.

Body weight

Dapagliflozin 10 mg as an add on to metformin, metformin and a sulphonylurea, sitagliptin (with metformin) or insulin resulted in a statistically significant body weight reduction at 24 weeks (Tables 3, 5 and 6) with placebo-corrected reductions of 1.97 kg (2.43 %), 2.07 kg (2.25 %) and 1.68 kg (1.83 %), respectively. These effects were sustained in longer-term trials (see Figure 7 for add-on to insulin). At 48 weeks, the difference for dapagliflozin as add on to sitagliptin (with or without metformin) compared to placebo was -2.22 kg. At 102 weeks, the differences for dapagliflozin as add on to metformin compared to placebo, or as add on to insulin (at 104 weeks) compared to placebo were -2.14 and -2.88 kg, respectively.

As an add on therapy to metformin in an active controlled non inferiority study, dapagliflozin resulted in a statistically significant body weight reduction compared with glipizide of 4.65 kg at 52 weeks (Table 4) , that was sustained at 104 and 208 weeks (-5.06 kg and -4.38 kg respectively) (see Figure 8).

Figure 7: Total Body Weight (kg) Adjusted Mean Change from Baseline Over Time in a Placebo-controlled Study of Dapagliflozin in Combination with Insulin with or without up to 2 Oral Anti-diabetic Therapies Short-term and Long-term Treatment Period Including Data After Insulin Up-titration
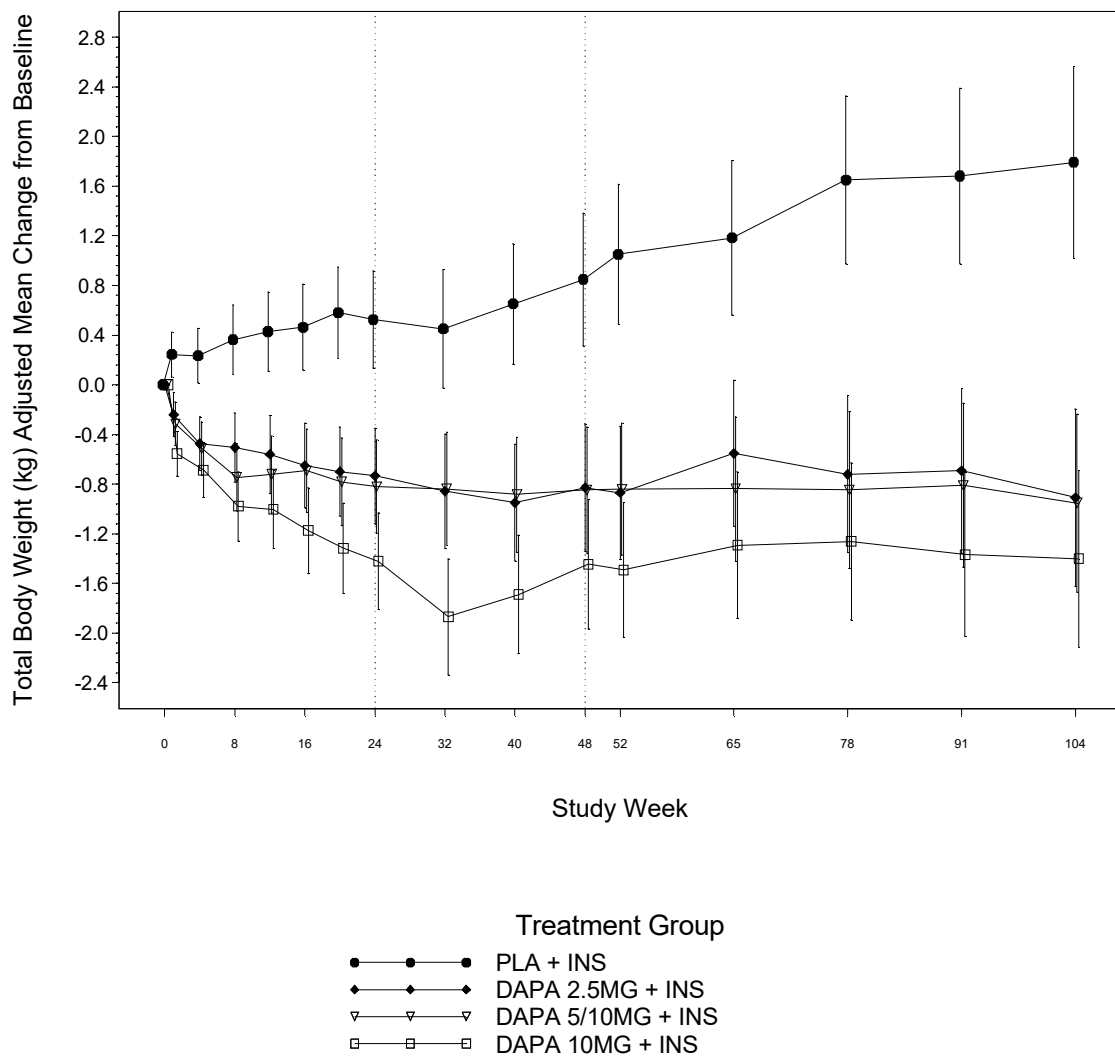
Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Figure 8: **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, Excluding Data after Rescue)**
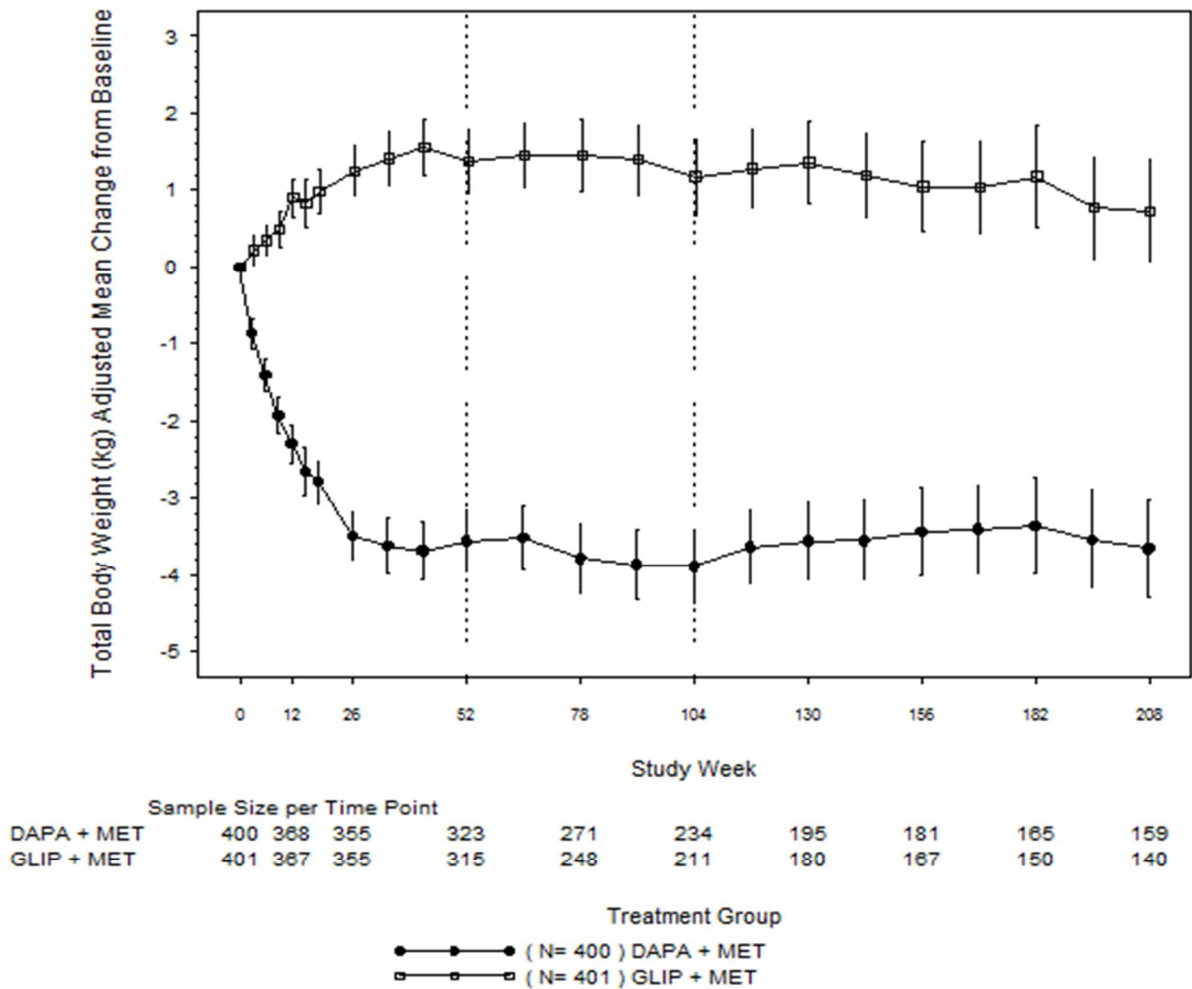
Subjects in the full analysis set.
Mean value based on repeated measures analysis model:
post-baseline = baseline treatment week rescue week*treatment week*baseline.
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

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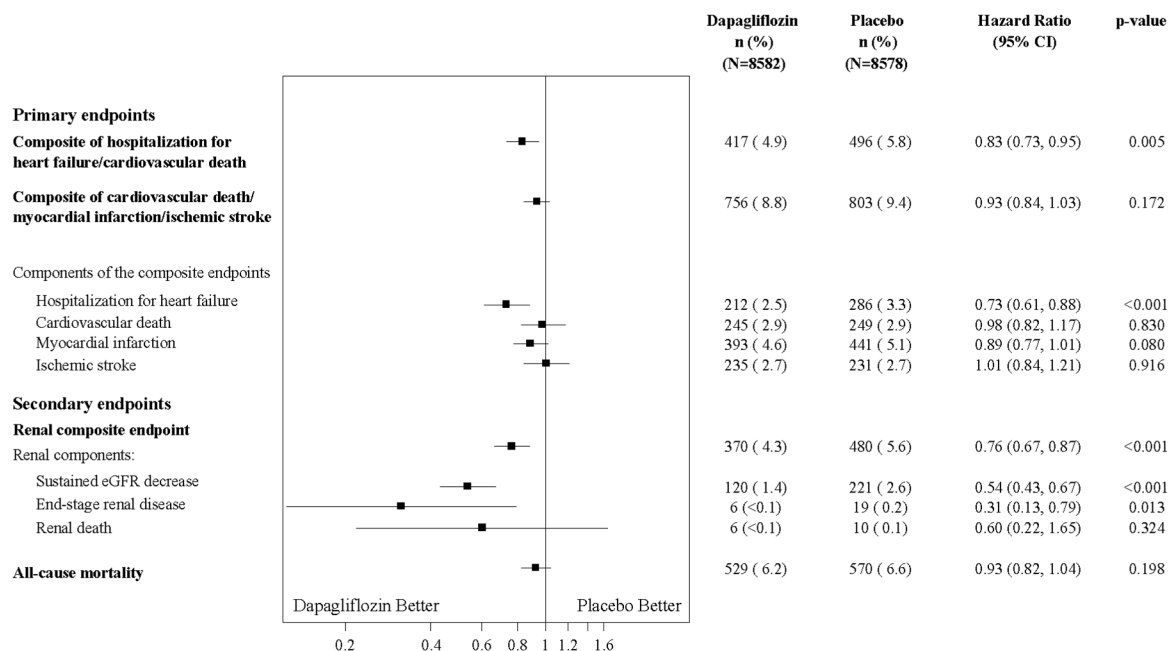
At baseline, 10.0% of patients had a history of heart failure. Mean eGFR was 85.2 mL/min/1.73 m^2, 7.4% of patients had eGFR <60mL/min/1.73 m^2 and 30.3% of patients had micro- or macroalbuminuria (urine albumin to creatinine ration [UACR] ≥30 to ≤300 mg/g or >300 mg/g, respectively).

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 sulphonylurea, 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 9 and 10.

Figure 9: Treatment effects for the primary composite endpoints and their components and the secondary endpoints and components

	Dapagliflozin n (%) (N=8582)	Placebo n (%) (N=8578)	Hazard Ratio (95% CI)	p-value
Primary endpoints				
Composite of hospitalization for heart failure/cardiovascular death	417 (4.9)	496 (5.8)	0.83 (0.73, 0.95)	0.005
Composite of cardiovascular death/ myocardial infarction/ischemic stroke	756 (8.8)	803 (9.4)	0.93 (0.84, 1.03)	0.172
Components of the composite endpoints				
Hospitalization for heart failure	212 (2.5)	286 (3.3)	0.73 (0.61, 0.88)	<0.001
Cardiovascular death	245 (2.9)	249 (2.9)	0.98 (0.82, 1.17)	0.830
Myocardial infarction	393 (4.6)	441 (5.1)	0.89 (0.77, 1.01)	0.080
Ischemic stroke	235 (2.7)	231 (2.7)	1.01 (0.84, 1.21)	0.916
Secondary endpoints				
Renal composite endpoint				
Renal components:	370 (4.3)	480 (5.6)	0.76 (0.67, 0.87)	<0.001
Sustained eGFR decrease	120 (1.4)	221 (2.6)	0.54 (0.43, 0.67)	<0.001
End-stage renal disease	6 (<0.1)	19 (0.2)	0.31 (0.13, 0.79)	0.013
Renal death	6 (<0.1)	10 (0.1)	0.60 (0.22, 1.65)	0.324
All-cause mortality	529 (6.2)	570 (6.6)	0.93 (0.82, 1.04)	0.198

Dapagliflozin Better   Placebo Better

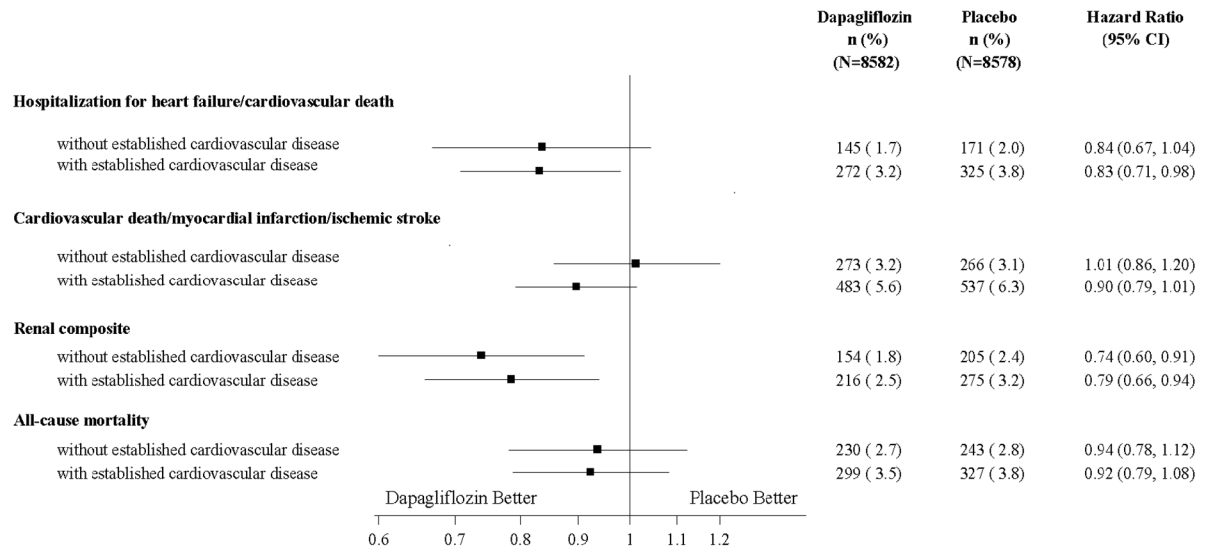0.2   0.4   0.6   0.8   1   1.2   1.6

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/1.73 m^2 and/or ESRD (dialysis ≥90 days or kidney transplantation, sustained confirmed eGFR <15 mL/min/1.73 m^2) and/or renal or CV death.

CI=confidence interval.

Figure 10: Treatment effects for the primary and secondary endpoints in patients with and without established CV disease

	Dapagliflozin n (%) (N=8582)	Placebo n (%) (N=8578)	Hazard Ratio (95% CI)
Hospitalization for heart failure/cardiovascular death			
without established cardiovascular disease	145 (1.7)	171 (2.0)	0.84 (0.67, 1.04)
with established cardiovascular disease	272 (3.2)	325 (3.8)	0.83 (0.71, 0.98)
Cardiovascular death/myocardial infarction/ischemic stroke			
without established cardiovascular disease	273 (3.2)	266 (3.1)	1.01 (0.86, 1.20)
with established cardiovascular disease	483 (5.6)	537 (6.3)	0.90 (0.79, 1.01)
Renal composite			
without established cardiovascular disease	154 (1.8)	205 (2.4)	0.74 (0.60, 0.91)
with established cardiovascular disease	216 (2.5)	275 (3.2)	0.79 (0.66, 0.94)
All-cause mortality			
without established cardiovascular disease	230 (2.7)	243 (2.8)	0.94 (0.78, 1.12)
with established cardiovascular disease	299 (3.5)	327 (3.8)	0.92 (0.79, 1.08)

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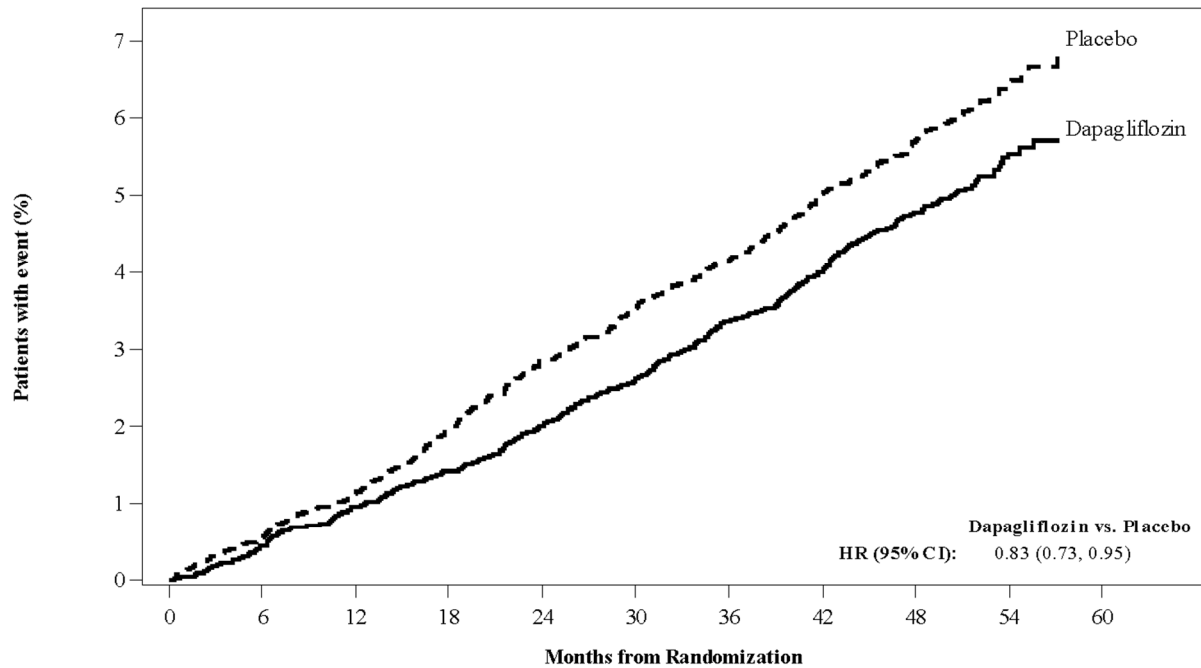CI=confidence interval

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 11).

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 9), 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 10), with and without heart failure at baseline, and was consistent across key subgroups, including age, gender, renal function (eGFR), and region.

Figure 11: 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
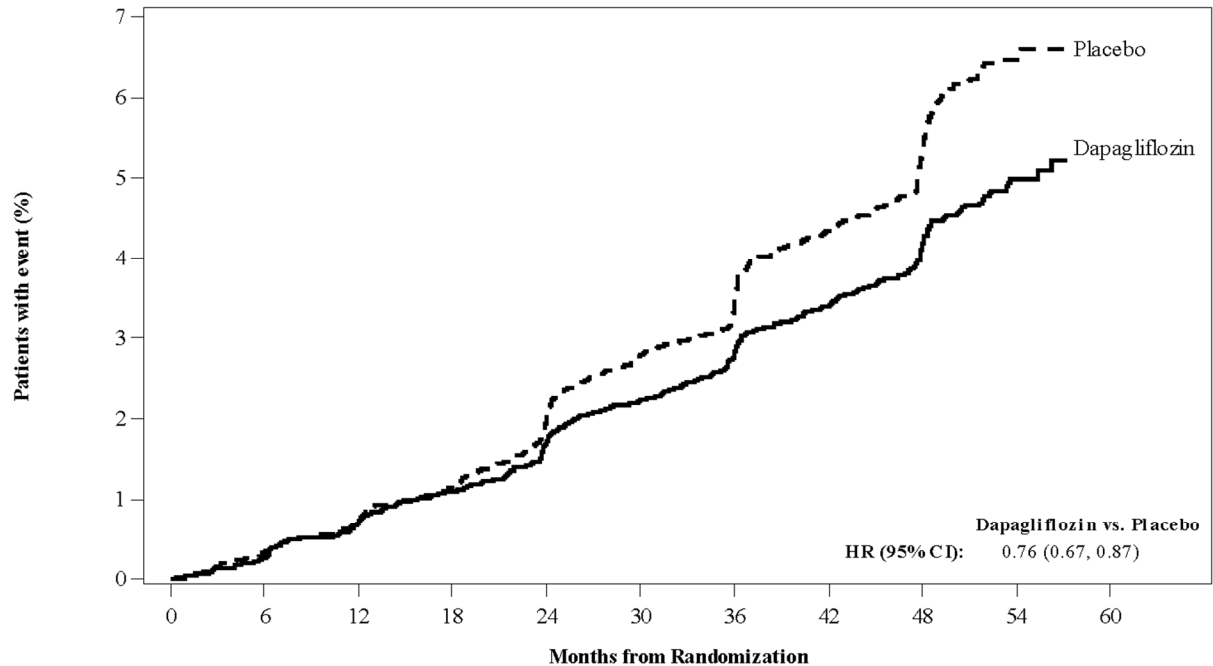
Major adverse cardiovascular events

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) (Figures 9 and 10).

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 12). The difference between groups was driven by reductions in events of the renal components; sustained eGFR decrease, ESRD and renal death (Figure 9), and was observed both in patients with and without CV disease (Figure 10).

Figure 12: Time to first occurrence of sustained eGFR decrease, ESRD, renal or CV death

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

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. Dapagliflozin 10 mg added on to metformin in 182 patients with type 2 diabetes over a 24 week period provided significant improvements compared with placebo plus metformin, respectively, in body weight (mean change from baseline: -2.96 kg v. -0.88 kg); waist circumference (mean change from baseline: -2.51 cm v. -0.99 cm), and body fat mass as measured by DXA (mean change from baseline -2.22 kg v. -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 (change from baseline -322.6 cm^3 vs. -8.7 cm^3) in an MRI substudy. In an ongoing extension of this study to week 50, there was no important change in bone mineral density for the lumbar spine, femoral neck or total hip seen in either treatment group (mean change from baseline for all anatomical regions <0.5%, 7/89 dapagliflozin and 4/91 comparator subjects showed a decrease of 5% or more). These effects were sustained in a further extension of the study to 102 weeks where no important changes in BMD for the lumbar spine, femoral neck or total hip in either treatment group were observed.

Special Populations

Use in patients with renal impairment

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 m^2 (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 16). 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 -1.19 mmol/L and -0.92 mmol/L, 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 9   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 (mmol/L)		
Baseline (mean)	10.16	9.62
Change from baseline (adjusted mean[*])	-1.19[§]	-0.27
Difference from placebo (adjusted mean[*]) (95% CI)	-0.92[§] (-1.48, -0.36)	
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 $\geq$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 $\geq$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).

Blood Pressure

In the pre specified pooled analysis of 13 placebo-controlled studies (see section 4.8 Undesirable Effects), treatment with dapagliflozin 10 mg resulted in a systolic blood pressure change from baseline of –3.7 mmHg and diastolic blood pressure of –1.8 mmHg versus –0.5 mmHg systolic and 0.5 mmHg diastolic blood pressure for the placebo group at Week 24. Similar reductions were observed up to 104 weeks.

In two 12-week, placebo-controlled studies a total of 1,062 patients with inadequately controlled type 2 diabetes and hypertension (despite pre-existing stable treatment with an ACE-I or ARB in one study and an ACE-I or ARB plus one additional antihypertensive treatment in another study) were treated with dapagliflozin 10 mg or placebo. At Week 12 for both studies, dapagliflozin 10 mg plus usual antidiabetic treatment provided

improvement in HbA1c and decreased the placebo-corrected systolic blood pressure on average by 3.1 and 4.3 mmHg, respectively

Clinical Safety

<u>Hypoglycaemia</u>

The incidence of hypoglycemia as seen in controlled clinical studies with dapagliflozin in different combinations is shown in Table 10.

Table 10: 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 sulphonylurea	**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)
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 Sulphonylurea (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 10mg *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.

5.2 PHARMACOKINETIC PROPERTIES

The results of bioequivalence studies in healthy subjects demonstrated that XIGDUO XR combination tablets are bioequivalent to coadministration of corresponding doses of dapagliflozin and metformin hydrochloride modified-release as individual tablets.

The following statements reflect the pharmacokinetic properties of the individual active substances of XIGDUO XR.

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.

Absorption

Dapagliflozin

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

Metformin hydrochloride

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. Although the extent of metformin absorption (as measured by AUC) from the metformin extended-release tablet increased by approximately 50% when given with food, there was no effect of food on C_{max} and T_{max} of metformin. Both high and low fat meals had the same effect on the pharmacokinetics of metformin extended-release.

Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. 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 averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulphonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time.

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 [14C]-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 was 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.

Elimination

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged dapagliflozin. After oral administration of 50 mg [14C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was 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. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Special Populations

Renal Impairment

Dapagliflozin

For dosing recommendations for patients with moderate to severe renal impairment see section 4.2 Dose and Method of Administration. 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-h 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 haemodialysis 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

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. No dose adjustment is required for patients with severe hepatic impairment. However, the benefit:risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed 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.

Elderly Patients

Dapagliflozin

No dosage adjustment for dapagliflozin 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%]. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients >70 years old.

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.

Paediatric and Adolescent

Dapagliflozin

Pharmacokinetics in the paediatric 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 paediatric 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 analysed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycaemic 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 [African descent] 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 (African descent) 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 antihyperglycaemic effect was comparable in whites (n=249), blacks (n=51) and Hispanics (n=24).

Body Weight

Dapagliflozin

No dose adjustment 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

Carcinogenesis, mutagenesis, impairment of fertility

Dapagliflozin

Dapagliflozin did not induce tumours 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 72× (males) and 105× (females) the human AUC at MRHD of 10 mg/day. In rats, AUC exposures were approximately 131× (males) and 186× (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 >2100× the human exposure at the MRHD. These studies, along with the absence of tumour 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 tumour 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 ≥100× human C_{max} at the MRHD. In a mouse xenograft study, dapagliflozin administered daily to male and female nude mice implanted with human TCC tumours did not significantly enhance the size of tumours at exposures up to 75× and up to 0.9× 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 tumour 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 tumours 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 ≤1708× and 998× 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.

Teratogenicity and impairment of early development

<u>Dapagliflozin</u>

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 ≥15× 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 1415× and 137×, 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 ≥ 29× 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 19× the human value at the MRHD.

In additional studies of embryo-foetal 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 1191× the MRHD. In rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day (1441× the MRHD). Doses ≥150 mg/kg/day (≥ 2344× 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-foetal lethality, increased incidences of fetal malformations and skeletal variations, and reduced foetal 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.

<u>Metformin hydrochloride</u>

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 foetal concentrations demonstrated a partial placental barrier to metformin.

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 (≥346×the human exposures at the MRHD) and in dogs for up to 12 months at doses of ≤120 mg/kg/day (≥3200× 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 (≥2100× based on human exposures at the MRHD). Despite achieving exposure multiples of ≥3200× the human exposure at the MRHD, there was no dose-limiting or target-organ toxicities identified in the 12-month dog study.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each film-coated tablet of XIGDUO XR contains the following inactive ingredients:
- carmellose sodium
- hypromellose
- magnesium stearate
- microcrystalline cellulose
- lactose
- crospovidone
- silicon dioxide
- polyvinyl alcohol
- macrogol 3350
- titanium dioxide
- purified talc
- iron oxide red CI77491 (XIGDUO XR 10/500 and XIGDUO XR 5/1000 tablets)
- iron oxide yellow CI77492 (XIGDUO XR 10/1000 tablets).

6.2 INCOMPATABILITIES

Not applicable.

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

The tablets should be stored below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

XIGDUO XR 10/500: Aluminium/aluminium blisters in pack sizes of 7 (not available in NZ) and 28 tablets.
XIGDUO XR 10/1000: Aluminium/aluminium blisters in pack sizes of 7 (not available in NZ) and 28 tablets.
XIGDUO XR 5/1000: Aluminium/aluminium blisters in pack sizes of 14 (not available in NZ) and 56 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. DATE OF FIRST APPROVAL

10 December 2015

9. SPONSOR

AstraZeneca Limited
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10. DATE OF REVISION OF TEXT

7 June 2023

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4 & 4.8	Vitamin B12 decrease/deficiency - New paragraph added to section 4.4 - AE frequency amended in Section 4.8