0501400/9

Saxagliptin/Dapagliflozin

QTERN®

5 mg/10 mg Film-Coated Tablet

Oral Hypoglycemic Agent

1. NAME OF THE MEDICINAL PRODUCT

Saxagliptin/Dapagliflozin Fixed-Dose Combination, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Saxagliptin/dapagliflozin tablets:

- 5 mg/10 mg tablet contains: saxagliptin hydrochloride 5.95 mg equivalent to saxagliptin 5 mg and dapagliflozin propanediol monohydrate 12.3 mg equivalent to dapagliflozin 10 mg

For excipients see section 6.1.

3. PHARMACEUTICAL FORM

- Saxagliptin/Dapagliflozin (QTERN) 5 mg/10 mg tablet contains saxagliptin 5 mg and dapagliflozin 10 mg. It is light brown to brown, biconvex, 0.8 cm round, film-coated tablet, with 5/10 printed on one side, and "1122" printed on the other side, in blue ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Saxagliptin/Dapagliflozin (QTERN) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus (T2DM).

4.2 Posology and method of administration

The recommended dose of Saxagliptin/Dapagliflozin (QTERN) is one saxagliptin 5 mg/dapagliflozin 10 mg tablet taken once daily at any time of the day, with or without food. Tablet is to be swallowed whole.

Special Populations

Patients with renal impairment:
No dosage adjustment is recommended based on renal function.

The glycaemic efficacy of dapagliflozin is dependent on renal function. Renal function should be evaluated prior to initiation of Saxagliptin/Dapagliflozin (QTERN) and periodically thereafter. Saxagliptin/Dapagliflozin (QTERN) should not be used in patients with an estimated glomerular filtration rate (eGFR) persistently < 45 mL/min/1.73m^2 as calculated by the Modification of Diet in Renal Disease (MDRD) formula or in patients with end- stage renal disease (ESRD) (see section 4.4).

Patients with hepatic impairment
Saxagliptin/Dapagliflozin (QTERN) may be used in patients with hepatic impairment. The safety and efficacy of Saxagliptin/Dapagliflozin (QTERN) have not been specifically studied in patients with severe hepatic impairment (see section 5.2).

Paediatric and adolescent patients
Safety and effectiveness of Saxagliptin/Dapagliflozin (QTERN) in pediatric and adolescent patients (< 18 years of age) have not been established.

Geriatric patients:
Because elderly patients are more likely to have decreased renal function, care should be taken in the elderly based on renal function (see section 5.1).

4.3 Contraindications

Saxagliptin/Dapagliflozin (QTERN) is contraindicated in patients with a history of any serious hypersensitivity reaction to the active substances or to any of the excipients, including anaphylaxis or angioedema following exposure to any dipeptidyl peptidase-4 (DPP-4) inhibitor (see section 4.4).

4.4 Special warnings and special precautions for use

4.4.1 Use in patients with renal impairment

The glycaemic efficacy of dapagliflozin is dependent on renal function.

Saxagliptin/Dapagliflozin (QTERN) should not be used in patients with an eGFR persistently < 45 mL/min/1.73 m^2 by MDRD or end-stage renal disease (ESRD). Saxagliptin/Dapagliflozin (QTERN) 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) and, therefore, should not be used in these populations. Renal function should be evaluated prior to initiation of Saxagliptin/Dapagliflozin (QTERN) and periodically thereafter (see section 4.2).

4.4.2 Ketoacidosis

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. Saxagliptin/Dapagliflozin (QTERN) is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with Saxagliptin/Dapagliflozin (QTERN) 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 Saxagliptin/Dapagliflozin (QTERN) should be considered and the patient should be promptly evaluated.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin dose reduction, reduced caloric intake or increased insulin requirements due to infections, illness or surgery and alcohol abuse. Saxagliptin/Dapagliflozin (QTERN) should be used with caution in these patients.

4.4.3 Use with medications known to cause hypoglycaemia

Saxagliptin/Dapagliflozin (QTERN) has not been studied in combination with insulin. Insulin and insulin secretagogues, such as sulfonylureas, are known to cause hypoglycaemia. Both saxagliptin and dapagliflozin can individually increase the risk of hypoglycaemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycaemia if used in combination with Saxagliptin/Dapagliflozin (QTERN) (see section 5.1).

4.4.4 Hypersensitivity reactions

During postmarketing experience, the following adverse reactions have been reported with use of saxagliptin, serious hypersensitivity reactions, including anaphylaxis and angioedema. If a serious hypersensitivity reaction to saxagliptin is suspected, discontinue Saxagliptin/Dapagliflozin (QTERN), assess for other potential causes for the event, and institute alternative treatment for diabetes (see section 4.3 and section 4.8).

4.4.5 Pancreatitis

During postmarketing experience for saxagliptin, there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, Saxagliptin/Dapagliflozin (QTERN) should be discontinued (see section 4.8).

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial, the incidence of adjudicated pancreatitis events was 0.3% in both saxagliptin-treated patients and placebo-treated patients in the intent-to-treat population (see section 4.8).

4.4.6 Cardiac Failure

In the SAVOR trial an increase in the rate of hospitalisation for heart failure was observed in the saxagliptin treated patients compared to placebo, although a causal relationship has not been established. Caution is warranted if saxagliptin is used in patients who have known risk factors for hospitalisation for heart failure, such as a history of heart failure or moderate to severe renal

impairment. Patients should be advised of the characteristic symptoms of heart failure, and to immediately report such symptoms. (see section 5.1).

4.4.7 Arthralgia

Joint pain, which may be severe, has been reported in postmarketing reports for DPP4 inhibitors. Patients experienced relief of symptoms after discontinuation of the medication and some experienced recurrence of symptoms with reintroduction of the same or another DPP4 inhibitor. Onset of symptoms following initiation of

drug therapy may be rapid or may occur after longer periods of treatment. If a patient presents with severe joint pain, continuation of drug therapy should be individually assessed (see section 4.8).

4.4.8 Necrotizing fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotizing fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors. 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. Be aware that either uro-genital infection or perineal abscess may precede necrotizing fasciitis. If Fournier's gangrene is suspected, Saxagliptin/Dapagliflozin (QTERN) should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

4.4.9 Bullous pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalisation have been reported with DPP4 inhibitor use, including saxagliptin. In reported cases, patients typically responded to topical or systemic immunosuppressive treatment and discontinuation of the DPP4 inhibitor. If a patient develops blisters or erosions while receiving Saxagliptin/Dapagliflozin (QTERN) and bullous pemphigoid is suspected, Saxagliptin/Dapagliflozin (QTERN) should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Saxagliptin and Dapagliflozin

The lack of pharmacokinetic interaction between saxagliptin and dapagliflozin was demonstrated in a drug-drug interaction study between saxagliptin and dapagliflozin. No dose adjustment of either saxagliptin or dapagliflozin is needed when the two drugs are co-administered.

See saxagliptin and dapagliflozin subsections for drug interactions. In summary, there are no clinically meaningful drug interactions expected for either saxagliptin or dapagliflozin.

Saxagliptin

The metabolism of saxagliptin is primarily mediated by cytochrome (CYP)450 3A4/5 (CYP3A4/5).

In *in vitro* studies, saxagliptin and its major metabolite neither inhibited CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9, or CYP3A4. Therefore, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolised by these enzymes. Saxagliptin is neither a significant inhibitor of P-glycoprotein (P-gp) nor an inducer of P-gp.

The *in vitro* protein binding of saxagliptin and its major metabolite in human serum is below measurable levels. Thus, protein binding would not have a meaningful influence on the pharmacokinetics of saxagliptin or other drugs.

Effect of other drugs on saxagliptin

In interaction studies conducted in healthy subjects, using either single dose or multiple once daily design, the pharmacokinetics of saxagliptin, its major metabolite, or the exposure to the total active components of saxagliptin (parent + metabolite), were not meaningfully altered by metformin (a hOCT-1 and hOCT-2 substrate), glyburide (a CYP2C9 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), digoxin (a P-glycoprotein [P-gp] substrate), simvastatin (a CYP3A4/5 substrate), diltiazem (a moderate inhibitor of CYP3A4/5), ketoconazole (a potent inhibitor of CYP3A4/5 and P-gp), rifampin (a potent inhibitor of CYP3A4/5 and P-gp), omeprazole (a CYP2C19 (major) and CYP3A4 substrate, an inhibitor of CYP2C19, and an inducer of MRP-3), aluminum hydroxide + magnesium hydroxide + simethicone combination (antacid and antigas formulations), or famotidine (an inhibitor of human organic cation transporter [hOCT]-1, hOCT-2, and hOCT-3). Therefore, meaningful interaction of saxagliptin with other substrates of hOCT-1, hOCT-2, P-gp, CYP2C8, CYP2C9, CYP-2C19, CYP3A4/5, and with other inhibitors of hOCT-1, hOCT-2, hOCT-3, CYP3A4/5, CYP2C19, P-gp, and with other inducers of CYP3A4, P-gp, MRP-3, would not be expected.

Effect of saxagliptin on other drugs

In interaction studies conducted in healthy subjects, using either single dose or multiple once daily design, saxagliptin did not meaningfully alter the pharmacokinetics of metformin (a hOCT-1 and hOCT-2 substrate), glyburide (a CYP2C9 substrate), pioglitazone (a CYP2C8 substrate), digoxin (a P-gp substrate), simvastatin (a CYP3A4/5 substrate), diltiazem (a moderate inhibitor of CYP3A4/5), or ketoconazole (a potent inhibitor of CYP3A4/5 and P-gp). Therefore, saxagliptin is not a clinical meaningful inhibitor of hOCT-1, hOCT-2, P-gp transporter pathway, and CYP2C8, CYP2C9, CYP3A4/5 mediated metabolic pathway.

Oral Contraceptives: Coadministration of multiple once-daily doses of saxagliptin (5 mg) and [1]Ortho-Cyclen® (0.035 mg ethinyl estradiol/0.250 mg norgestimate), a combined oral contraceptive for 21 days, did not alter the steady state pharmacokinetics of the primary active estrogen component, ethinyl estradiol, or the primary active progestin component, norelgestromin. When saxagliptin was coadministered with Ortho-Cyclen®, the plasma AUC of norgestrel, an active metabolite of norelgestromin, was increased by 13% and the plasma C_{max} of norgestrel was increased by 17%. This small magnitude change in AUC and C_{max} of norgestrel is not considered to be clinically meaningful. Based on these findings, saxagliptin would not be

[1] Copyright of Janssen Pharmaceuticals, Inc. 1998

expected to meaningfully alter the pharmacokinetics of an estrogen/progestin combined oral contraceptive.

Dapagliflozin

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

In *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP1A2, 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 that inhibit or induce these enzymes are not expected to alter the metabolic clearance of dapagliflozin. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

Effect of other drugs on dapagliflozin

In interaction studies conducted in healthy subjects, using mainly single dose design, the pharmacokinetics of dapagliflozin were not meaningfully 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-gp 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.

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

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolizing enzymes) or mefenamic acid (an inhibitor of uridine 5'-diphospho-glucuronosyltransferase [UGT]1A9), 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. No dose adjustment of dapagliflozin is recommended when dapagliflozin is coadministered with rifampicin or with mefenamic acid.

Effect of dapagliflozin on other drugs

In interaction studies conducted in healthy subjects, using mainly a single dose design, dapagliflozin did not meaningfully alter the pharmacokinetics of metformin (an hOCT-1 and hOCT-2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate, sitagliptin (an hOAT-3 substrate, and P-gp substrate), glimepiride (a CYP2C9 substrate), hydrochlorothiazide, bumetanide, valsartan, 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 a single dose of dapagliflozin (20 mg) and simvastatin (40 mg) (a CYP3A4 substrate), did not affect the Cmax of simvastatin but increased the AUC by 20%, which was not considered to be clinically relevant.

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 (a CYP2C19 substrate) as measured by the prothrombin time (International Normalized Ratio [INR]).

Other interactions

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

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 Pregnancy and lactation

Pregnancy

Saxagliptin/dapagliflozin combination
There are no adequate and well-controlled studies of Saxagliptin/Dapagliflozin (QTERN) or its mono-components in pregnant women. Saxagliptin/Dapagliflozin (QTERN) should not be used during pregnancy. If pregnancy is detected, treatment with Saxagliptin/Dapagliflozin (QTERN) should be discontinued.

Dapagliflozin
In the time period corresponding to the second and third trimesters 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.

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

Saxagliptin
Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

Lactation
Saxagliptin/dapagliflozin combination
It is not known whether Saxagliptin/Dapagliflozin (QTERN) or its mono-components and/or their metabolites are excreted in human milk. Saxagliptin/Dapagliflozin (QTERN) must not be used by a nursing woman.

Dapagliflozin
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, although the long-term functional consequences of these effects are unknown. These periods of exposure coincide with a critical window of renal maturation in rats. As functional maturation of the kidneys in humans continues in the first 2 years of life, dapagliflozin-associated dilated renal pelvis and tubules noted in juvenile rats could constitute potential risk for human renal maturation during the first 2 years of life. Additionally, the negative effects on body-weight gain associated with lactational exposure in weanling juvenile rats suggest that dapagliflozin must be avoided during the first 2 years of life (see Section 5.3).

Saxagliptin
Saxagliptin is secreted in the milk of lactating rats.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical trials

Safety profile of saxagliptin/dapagliflozin combination

The safety of combined use of 5 mg saxagliptin and 10 mg dapagliflozin has been evaluated in 1169 adult subjects with type 2 diabetes (T2DM) in an integrated safety pool of three phase 3 active/placebo controlled clinical trials for up to 52 weeks (see section 5.1). The 3-study pooled safety analysis of 1169 adults is referred in this document as pooled safety analysis: saxagliptin and dapagliflozin plus metformin (492 subjects; data pooled from studies CV181169, CV181168, and MB102129); saxagliptin plus metformin (336 subjects data pooled from studies CV181169 and MB102129); and dapagliflozin + metformin (341 subjects data pooled from studies CV181169 and CV181168).

Tabulated list of adverse reactions for saxagliptin/dapagliflozin combination

The adverse reactions are presented in Table 1. The adverse reactions are listed by system organ class (SOC) and absolute frequency.

Common frequency for Table 1 is defined as ≥ 2% to < 10% and very common frequency as ≥ 10%.

Table 1. Adverse reactions reported in ≥2% subjects treated with 5 mg Saxagliptin and 10 mg Dapagliflozin

System Organ Class	Very common Preferred Term	Common Preferred Term	Not known
Infections and infestations	Upper respiratory tract infection[1*]	Urinary tract infection[2*]	Necrotizing fasciitis of the perineum

		Genital infection[3] Gastroenteritis[**]	(Fournier's Gangrene)[6]
Gastrointestinal Disorders		Diarrhoea Vomiting[**]	
Musculoskeletal and Connective Tissue Disorders		Back Pain Arthralgia	
Nervous System Disorders		Headache	
Metabolism and Nutrition Disorders		Dyslipidaemia[4*]	
Renal and Urinary Disorders		Polyuria[5**]	

[*] Adverse reactions reported in ≥5% of treated subjects in the pooled safety analysis include: upper respiratory tract infection, urinary tract infection, and dyslipidaemia.

[**] Gastroenteritis, vomiting, and polyuria were reported in ≥2% of subjects treated with either monocomponent and ≥1% more than placebo.

[1] Upper respiratory tract infection includes the following preferred terms reported: nasopharyngitis, influenza, upper respiratory tract infection, pharyngitis, rhinitis, sinusitis, pharyngitis bacterial, tonsillitis, acute tonsillitis, laryngitis, viral pharyngitis, and viral upper respiratory tract infection.

[2] Urinary tract infection includes the following preferred terms reported: urinary tract infection, Escherichia urinary tract infection, prostatitis, and pyelonephritis.

[3] Genital infection includes the following preferred terms reported: vulvovaginal mycotic infection, balanoposthitis, genital infection fungal, vaginal infection, and vulvovaginitis.

[4] Dyslipidaemia includes the following preferred terms reported: dyslipidaemia, hyperlipidaemia, hypertriglyceridaemia, and hypercholesterolaemia.

[5] Polyuria includes the following preferred terms reported: polyuria, and pollakiuria.

[6] See section 4.4.8.

Diabetic ketoacidosis was identified with a frequency of rare (≥ 1/10,000 to < 1/1000), based on annual rate, in a large cardiovascular outcomes study with dapagliflozin in patients with type 2 diabetes.

Additional clinical trials for up to 52 weeks in adult subjects compared the combination therapy of saxagliptin 5 mg and dapagliflozin 10 mg plus metformin to active/placebo comparators of basal insulin, sitagliptin, 1-6 mg glimepiride (a sulphonylurea), with all comparator arms on a background of ≥ 1,500 mg metformin. The safety results for these studies continue to demonstrate that the combination of saxagliptin and dapagliflozin plus metformin is well-tolerated and is consistent with the known safety profiles for the pooled safety analysis of saxagliptin 5 mg and dapagliflozin 10 mg combination plus metformin, and its monocomponents.

Postmarketing experience

Saxagliptin

During postmarketing experience, the following adverse reactions have been reported with use of saxagliptin: acute pancreatitis, arthralgia, bullous pemphigoid and hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria. Because these reactions are reported

voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Dapagliflozin

During postmarketing experience, the following adverse reactions have been reported with use of dapagliflozin.

Table 2. Adverse reactions identified during postmarketing use of dapagliflozin

System Organ Class Preferred Term	Frequency
Skin and subcutaneous tissue disorders	
Rash*	Unknown**

* Rash includes the following preferred terms, listed in order of frequency in clinical trials: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous.

** Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency. 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', meaning (≥ 1/100 to < 1/10).

Description of selected adverse reactions

Genital infections

The reported adverse events of vulvovaginitis, balanitis and related genital infections from pooled safety analysis were reflective of the safety profile of dapagliflozin. AEs of genital infection were reported in 3.0% in the saxagliptin and dapagliflozin plus metformin group, 0.9% of saxagliptin plus metformin group and 5.9% of subjects in the dapagliflozin plus metformin group. The majority of the genital infections were reported in females (84% of subjects with a genital infection), and were mild or moderate in intensity, of single occurrence, and most patients continued on therapy.

Urinary tract infections

In the pooled safety analysis, UTIs were balanced across the 3 treatment groups: 5.7% in the saxagliptin and dapagliflozin plus metformin group, 7.4% in the saxagliptin plus metformin group and 5.6% in the dapagliflozin plus metformin group. The majority of the urinary tract infection adverse events were reported in females (81% of subjects with UTI), and were mild or moderate in intensity, of single occurrence, and most patients continued on therapy.

Diabetic ketoacidosis (DKA)

In a large cardiovascular outcomes study with dapagliflozin in patients with type 2 diabetes, where 8574 patients received dapagliflozin 10 mg and 8569 patients received placebo, 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 127 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).

Laboratory findings

Decrease in lymphocyte count
Saxagliptin
In a pool of 5 placebo-controlled studies, a small mean decrease in absolute lymphocyte count was observed, approximately 100 cells/microL relative to placebo. Mean absolute lymphocyte counts remained stable with daily dosing up to 102 weeks in duration. The decrease in mean absolute lymphocyte count was not associated with clinically relevant adverse reactions.

Lipids
Data from the saxagliptin and dapagliflozin plus metformin treatment arms of 3 Phase 3 trials, demonstrated trends of mean percent increases from baseline in Total-C, (ranging from 0.4% to 3.8%), LDL-C (ranging from 2.1 to 6.9 %) and HDL-C (ranging 2.3 to 5.2%) along with mean percent decreases from baseline in triglycerides (ranging from -3.0% to -10.8%).

4.9 Overdose

There is no information available on overdose with Saxagliptin/Dapagliflozin (QTERN). In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its major metabolite are removed by haemodialysis (23% of dose over four hours). The removal of dapagliflozin by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

Mechanism of Action

Saxagliptin/Dapagliflozin combination
Saxagliptin/Dapagliflozin (QTERN) combines saxagliptin and dapagliflozin with distinct and complementary mechanisms of action to improve glycaemic control. Saxagliptin, through the selective inhibition of dipeptidyl peptidase 4 (DPP4), enhances glucose-mediated insulin secretion (incretin effect). Dapagliflozin, a selective inhibitor of sodium-glucose co-transporter 2 (SGLT2), inhibits renal glucose reabsorption independently of insulin. Actions of both drugs are regulated by the plasma glucose level. The combination of both agents delivers clinically meaningful reductions in HbA1c for improved glycaemic control in patients with T2DM. While saxagliptin has a neutral effect on weight, urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric and weight loss.

Saxagliptin

Saxagliptin is a highly potent, selective, reversible, competitive, DPP-4 inhibitor. Saxagliptin demonstrates selectivity for DPP4 versus other DPP enzymes, including DPP8 and DPP9. Saxagliptin has extended binding to the DPP4 active site, prolonging its inhibition of DPP4. Saxagliptin exerts its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Concentrations of these active intact incretin hormones are increased by saxagliptin, thereby increasing and prolonging the actions of these hormones.

Incretin hormones are released by the intestine throughout the day and concentrations are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are elevated GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production.

Concentrations of GLP-1 are reduced in patients with type 2 diabetes, but saxagliptin increases active GLP-1 and GIP, potentiating these mechanisms. By increasing and prolonging active incretin concentrations, saxagliptin increases insulin release and decreases glucagon concentrations in the circulation in a glucose-dependent manner.

Saxagliptin improves glycaemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes through improvements in alpha and beta cell function as reflected by the actions described below.

Fasting glucose-dependent insulin secretion: Saxagliptin increases pancreatic beta-cell responsiveness to glucose in the fasting state and leads to enhanced insulin secretion and glucose disposal in the presence of elevated glucose concentrations.

Postprandial glucose-dependent insulin secretion: Saxagliptin increases pancreatic beta-cell responsiveness to glucose in the postprandial state and leads to enhanced postprandial insulin secretion and glucose disposal.

Postprandial glucagon secretion: In type 2 diabetes, paradoxical increases in glucagon secretion from alpha cells following meals stimulate hepatic glucose production and contribute to glycaemic dysregulation. Saxagliptin moderates glucagon secretion and lowers postprandial glucagon concentrations.

Dapagliflozin

Dapagliflozin is a highly potent, selective, and reversible inhibitor of sodium-glucose cotransporter 2 (SGLT2) that improves glycaemic control in patients with 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. 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 postprandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24- hour dosing interval, and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal 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 weight reduction is body-fat loss, including visceral fat, rather than lean tissue, or fluid loss as demonstrated by dual energy x-ray absorptiometry (DXA) and magnetic resonance imaging.

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

5.1 Pharmacodynamic properties

Pharmacodynamic effects

Saxagliptin

In patients with type 2 diabetes, administration of saxagliptin inhibited DPP-4 enzyme activity throughout a 24-hour period. The inhibition of plasma DPP-4 activity by saxagliptin for at least 24 hours after oral administration of saxagliptin is due to high potency, high affinity, and extended binding to the active site. After an oral glucose load, this produced in a 2- to 3-fold increase in circulating levels glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), decreased glucagon concentrations, and increased beta-cell responsiveness, resulting in higher insulin and C-peptide concentrations. The rise in insulin from pancreatic beta-cells and the decrease in glucagon from pancreatic alpha-cells were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

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.

Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in patients with type 2 diabetes mellitus for 12 weeks. This glucose elimination rate approached the maximum glucose excretion observed at 20 mg/day of

dapagliflozin. Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

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

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from -48.3 to -18.3 micromoles/L (-0.87 to -0.33 mg/dL).

Clinical efficacy

Glycaemic control

Treatment with saxagliptin and dapagliflozin (combination or add-on therapy) at all doses produced clinically relevant and statistically significant improvements in HbA1c compared to the active comparator or placebo study arms.

Concomitant therapy with saxagliptin 5 mg and dapagliflozin 10 mg in patients inadequately controlled on metformin

A total of 534 adult patients with type 2 diabetes mellitus and inadequate glycaemic control on metformin alone (HbA1c ≥ 8% and ≤ 12%), participated in a 24-week randomised, double-blind, active comparator-controlled superiority study comparing the combination of saxagliptin 5 mg and 10 mg dapagliflozin added concomitantly to metformin, versus saxagliptin (DPP4 inhibitor) or dapagliflozin (SGLT2 inhibitor) added to metformin. Patients were randomised to one of three double-blind treatment groups to receive saxagliptin 5 mg and dapagliflozin 10 mg added to metformin XR, saxagliptin 5 mg and placebo added to metformin XR, or dapagliflozin 10 mg and placebo added to metformin XR.

The saxagliptin 5 mg and dapagliflozin 10 mg group achieved significantly greater reductions in HbA1c versus either the saxagliptin group or dapagliflozin group at 24 weeks (see Table 3 and Figure 1).

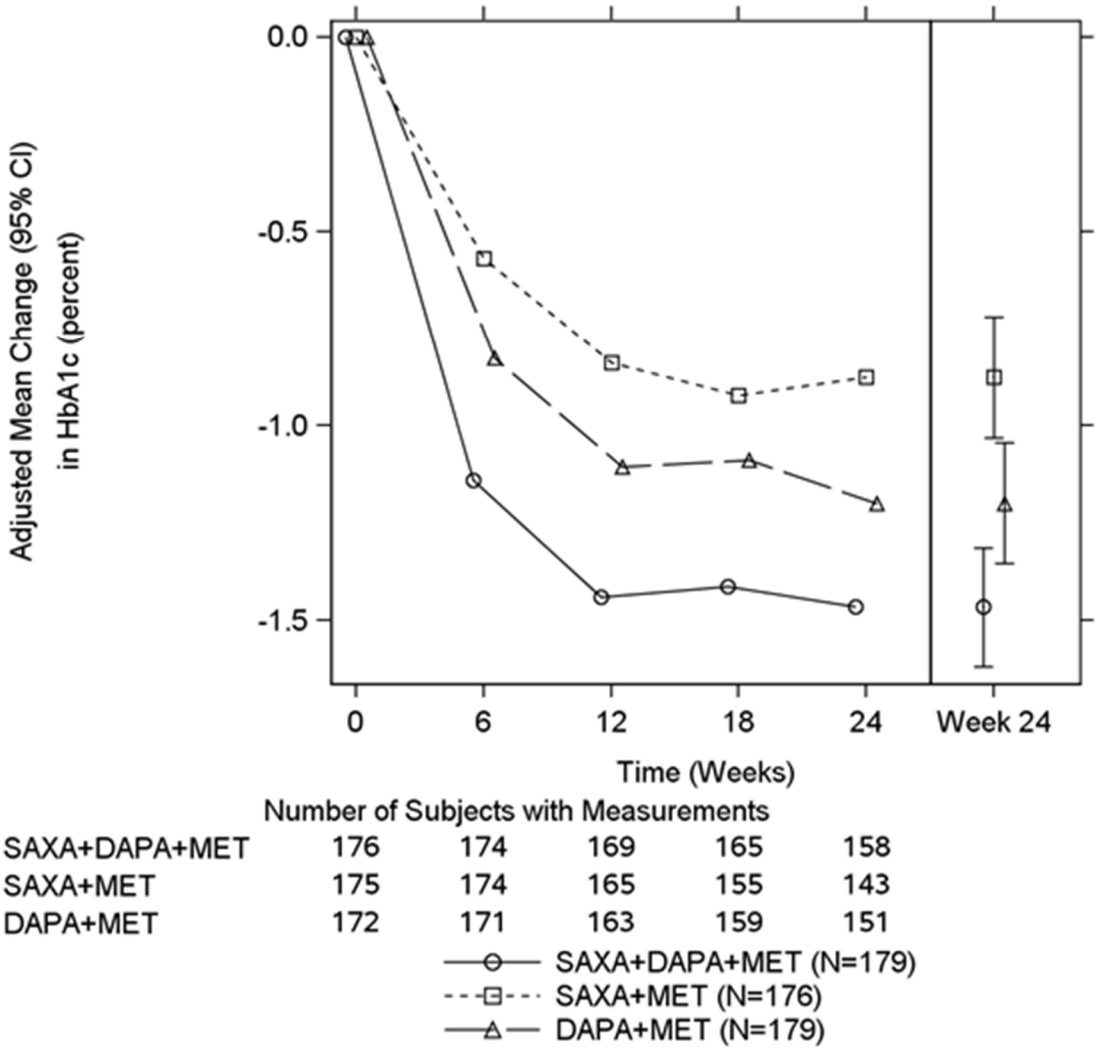
Table 3. HbA1c at Week 24 in active-controlled study comparing the combination of saxagliptin 5 mg and dapagliflozin 10 mg added concurrently to metformin with either saxagliptin 5 mg or dapagliflozin 10 mg added to metformin

Efficacy Parameter	**Saxagliptin 5 mg + Dapagliflozin 10 mg + Metformin**	**Saxagliptin 5 mg + Metformin**	**Dapagliflozin 10 mg + Metformin**
N[2]	**179**	**176**	**179**
HbA1c (%) at Week 24[1]			
Baseline (mean)	8.93	9.03	8.87

Change from baseline (adjusted mean[3]) (95% CI)	−1.47 (−1.62, −1.31)	−0.88 (−1.03, −0.72)	−1.20 (−1.35, −1.04)
Difference from saxagliptin + metformin (adjusted mean[3]) (95% CI)	−0.59[4] (−0.81, −0.37)	-	-
Difference from dapagliflozin + metformin (adjusted mean[3]) (95% CI)	−0.27[5] (−0.48, −0.05)	-	-

1. LRM = Longitudinal repeated measures (using values prior to rescue).
2. Randomised and treated patients
3. Least squares mean adjusted for baseline value.
4. p-value < 0.0001.
5. p-value=0.0166.

Figure 1. Change from baseline in HbA1c – 24-Week double blind period in randomised subjects*



N is the number of randomised subjects with at least one dose of double-blind medication during short-term double-blind treatment. Mean refers to mean change from baseline based on a mixed model with treatment, baseline value, week, week-by-treatment interaction, and week-by-baseline interaction as independent variables. Error bars represent 95% confidence intervals for the adjusted mean change from baseline. Plot uses data values from study subjects prior to rescue.

The majority of patients in this study had a baseline HbA1c of > 8% (Table 4). The combination of saxagliptin 5 mg and dapagliflozin 10 mg added to metformin treatment consistently demonstrated greater reductions in HbA1c irrespective of baseline HbA1c compared with saxagliptin 5 mg or dapagliflozin 10 mg alone added to metformin. In a separate pre-specified subgroup analysis, mean reductions from baseline in HbA1c were generally greater for patients with higher baseline HbA1c values.

Table 4. HbA1c subgroup analysis by baseline HbA1c at Week 24 in randomised subjects

Treatments	Adjusted mean change from baseline by baseline HbA1c		
	< 8.0%	**≥ 8% to < 9.0%**	**≥ 9.0%**
Saxagliptin 5 mg + Dapagliflozin 10 mg + Metformin Adjusted mean change from baseline (95% CI)	–0.80 (n=37) (–1.12, –0.47)	–1.17 (n=56) (–1.44, –0.90)	–2.03 (n=65) (–2.27, –1.80)
Saxagliptin 5 mg + Metformin Adjusted mean change from baseline (95% CI)	–0.69 (n=29) (–1.06, –0.33)	–0.51 (n=51) (–0.78, –0.25)	–1.32 (n=63) (–1.56, –1.09)
Dapagliflozin 10 mg + Metformin Adjusted mean change from baseline (95% CI)	–0.45 (n=37) (–0.77, –0.13)	–0.84 (n=52) (–1.11, –0.57)	–1.87 (n=62) (–2.11, –1.63)

n = number of subjects with non-missing baseline and a Week 24 value.

Proportion of patients achieving HbA1c < 7%
Forty-one point four percent (41.4%) (95% CI [34.5, 48.2]) of patients (CV181169) in the saxagliptin 5 mg and dapagliflozin 10 mg combination group achieved HbA1c levels of less than 7% compared to 18.3% (95% CI [13.0, 23.5]) patients in the saxagliptin 5 mg group and 22.2% (95% CI [16.1, 28.3]) patients in the dapagliflozin 10 mg group at week 24.

Proportion of subjects achieving HBA1c < 7% based on baseline HbA1c
A greater number of responders were reported in the saxagliptin 5 mg plus dapagliflozin 10 mg plus metformin group compared to either saxagliptin 5 mg plus metformin or dapagliflozin 10 mg plus metformin (Table 5).

Table 5. HbA1c subgroup analysis by the proportion of subjects achieving HbA1c < 7% at Week 24

Treatments	Proportion of subjects achieving HbA1c < 7% based on baseline HbA1c		
	< 8.0%	**≥ 8% to < 9.0%**	**≥ 9.0%**
Saxagliptin 5 mg + Dapagliflozin 10 mg + Metformin Percent (adjusted for	65.1	49.7	23.5

baseline Hb1Ac): X/N# (95% CI)	(n=26/40 (50.6, 79.7)	(n=30/58) (37.0, 62.4)	(n=18/79) (14.3, 32.6)
Saxagliptin 5 mg + Metformin Percent (adjusted for baseline Hb1Ac): X/N# (95% CI)	58.1 (n=16/30) (40.8, 75.5)	10.5 (n=6/61) (3.0, 17.9)	8.5 (n=7/84) (2.6, 14.4)
Dapagliflozin 10 mg + Metformin Percent (adjusted for baseline Hb1Ac): X/N# (95% CI)	42.1 (n=18/40) (27.1, 57.0)	19.0 (n=11/58) (8.9, 29.1)	14.6 (n=11/75) (6.6, 22.6)

X is the number of responders.
N# is the number of randomised subjects with non-missing baseline and Week 24 last observation carried forward (LOCF) values.

Concomitant therapy of saxagliptin 5 mg and dapagliflozin 10 mg in comparison to glimepiride in patients inadequately controlled on metformin

A 52-week randomised, double-blind, active-controlled, parallel-group study with a blinded 104-week extension compared orally once daily saxagliptin 5 mg and dapagliflozin 10 mg co-administered in combination with metformin to once daily glimepiride (a sulphonylurea) up-titrated 1-6 mg plus placebo with metformin (≥ 1500 mg per day) in T2DM patients with inadequate glycaemic control (HbA1c ≥ 7.5% and ≤ 10.5%) on metformin alone. Patients on glimepiride/placebo dose were up-titrated starting at 1 mg per day over 12 weeks to optimal glycaemic effect (FPG < 6.1 mmol/dL [110 mg/dL]) or the highest tolerable dose during the first 12 weeks. Thereafter, glimepiride/placebo dose were kept constant, except for down-titration to prevent hypoglycaemia.

Saxagliptin 5 mg and dapagliflozin 10 mg plus metformin had a statistically greater mean reduction in HbA1c from baseline at Week 52, compared with glimepiride plus metformin demonstrating superiority (Table 6).

Fewer treatment intensification events occurred in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group (n=3) compared with the glimepiride plus metformin group (n=19). A total of 3 subjects (1.3%) in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group and 18 subjects (8.3%) in the glimepiride plus metformin group were rescued during the treatment period. The most common rescue treatment was insulin (2 subjects [0.9%] in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group and 11 subjects [5.1%] in the glimepiride plus metformin group).

Table 6. Results at Week 52 comparing saxagliptin 5 mg and dapagliflozin 10 mg plus metformin to glimepiride plus metformin

Efficacy Parameter*	**Saxagliptin 5 mg and Dapagliflozin 10 mg + Metformin**	**Glimepiride 1 to 6 mg + Metformin**

HbA1c (%)		
N†	218	212
Baseline (mean)	8.4	8.49
Change from baseline (adjusted mean)‡	-1.35	-0.98
Difference from glimepiride + metformin (95% CI)	-0.37§ (-0.57, -0.18)	

* Mixed model of repeated measure analysis prior to rescue and treatment discontinuation.

† Number of subjects in the randomised subject data set with non-missing baseline assessment and at least one post-baseline assessment. Subjects had a high mean baseline HbA1c of 8.45% and a mean duration of T2DM of 7.8 years across all treatment groups while on a stable metformin dose of at least 1500 mg/day (characteristics of difficult-to-treat patients).

‡ Median exposure to study medication was 365 days for all treatment groups.

§ p-value < 0.001

Proportion of patients achieving HbA1c < 7%

The proportion of patients achieving HbA1c < 7.0% at Week 52 was higher in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group (44.3% 95% CI [37.45, 51.32]) compared to the glimepiride plus metformin group (34.3% 95% CI [27.87, 41.33] p=0.044).

Systolic blood pressure

The decrease in systolic blood pressure (SBP) at Week 52 in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group (-2.6 mmHg 95% CI [-4.4, -0.8]) was greater than in the glimepiride plus metformin group (1.0 mmHg 95% CI [-0.9, 2.9]). The difference in mean SBP between treatment groups was -3.6 mmHg (95% CI [-6.3, -1.0] p=0.007).

Body weight

Treatment with saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group resulted in significant difference in mean body weight change at Week 52 compared to glimepiride plus metformin. The adjusted mean change from baseline was -3.11 kg (95% CI [-3.65, -2.57]) for the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group, and 0.95 kg (95% CI [0.38, 1.51]) for the glimepiride plus metformin group. The difference in mean body weight between treatment groups was -4.06 kg (95% CI [-4.84, -3.28] p < 0.001).

Concomitant therapy of saxagliptin 5 mg and dapagliflozin 10 mg in comparison to insulin glargine in patients inadequately controlled on metformin with or without a sulphonylurea

A 24-week randomised, open-label, active-controlled, parallel group study with a 28-week extension compared orally once daily saxagliptin 5 mg and dapagliflozin 10 mg co-administered with metformin with or without a sulphonylurea to titrated subcutaneous insulin glargine co-administered with metformin with or without a sulphonylurea in T2DM patients with inadequate glycemic control (HbA1c ≥ 8.0% and ≤ 12.0%).

Saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without a SU group met the predefined criteria for non-inferiority in HbA1c reduction from baseline compared to insulin glargine plus metformin with or without a SU group after 24 weeks of open-label treatment.

Table 7. Results at Week 24 comparing saxagliptin 5 mg and dapagliflozin 10 mg to insulin glargine

Efficacy Parameter*	**Saxagliptin 5 mg and dapagliflozin 10 mg**	**Insulin glargine plus metformin**

	plus metformin with or without a sulphonylurea	with or without a sulphonylurea
HbA1c (%)		
N[†‡]	319	312
Baseline (mean)	9.04	9.04
Change from baseline (adjusted mean[‡])	-1.67	-1.54
Difference from insulin glargine + metformin with or without a SU (adjusted mean[‡]) (95% CI)	-0.13 (-0.30, 0.03)	-

* MMRM model with terms for strata, treatment, baseline HbA1c, week, treatment-by-week interaction and baseline HbA1c-by-week interaction. Values recorded after rescue or collected more than 8 days after the last dose date were excluded from the analysis.

† Subjects had a high mean baseline HbA1c of 9.05% and a mean duration of T2DM of 9.41 years across treatment groups while on a stable metformin dose of at least 1500 mg/day (characteristics of difficult-to-treat patients).

‡ Median exposure to study medication was 169 days in both treatment groups.

Hypoglycaemia events with glucose ≤ 3.9 mmol/L [70 mg/dL]

A substantially lower proportion of patients in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without a SU group (11.4% of N=324) experienced at least one event of hypoglycaemia (glucose ≤ 3.9 mmol/L [70 mg/dL] with symptoms) at Week 24) than the titrated insulin glargine plus metformin with or without a SU group (24.5% of N=319). There were 57 events of hypoglycaemia in 26 patients with SU and 16 events in 11 patients without SU in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group; there were 233 events of hypoglycaemia in 52 patients with SU and 65 events in 26 patients without SU in the insulin glargine plus metformin group.

Continuous glucose monitoring

For expressing numbers as mmol/L

After 2 weeks of open-label treatment, patients in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without a SU group demonstrated a mean decrease from baseline in 24-hour mean glucose as measured by 24-hour continuous glucose monitoring (CGM) of -2.69 mmol/L (95% CI [-2.97, -2.42]) compared to the insulin glargine plus metformin with or without a SU group -1.58 mmol/L (95% CI [-1.86, -1.31]). The difference in the least squared mean change between the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without a SU group and insulin glargine plus metformin with or without a SU group was -1.11 mmol/L (95% CI [-1.50, -0.72]) $p<0.0001$).

For expressing numbers as mg/dL

After 2 weeks of open-label treatment, patients in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without a sulphonylurea group demonstrated a mean decrease from baseline in 24-hour mean glucose as measured by 24-hour continuous glucose monitoring (CGM) of -48.5 mg/dL (95% CI [-53.5, -43.6]) compared to the insulin glargine plus metformin with or without a SU group -28.5 mg/dL (95% CI [-33.5, -23.6]). The difference in the least squared mean change between the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without a SU group and the insulin glargine plus metformin with or without a SU group was -19.99 mg/dL (95% CI [-26.98, -13.00]) $p<0.0001$).

Body weight
Treatment with saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without a SU group resulted in significant difference in body weight change at Week 24, mean change from baseline -1.50 kg (95% CI [-1.89, -1.11]) versus 2.14 kg (95% CI [1.75, 2.54]) in the insulin glargine plus metformin with or without a SU group. The difference in mean body weight between treatment groups was -3.64 kg (95% CI [-4.20, -3.09] p<0.001).

Proportion of patients achieving HbA1c < 7%
The adjusted percent (95% CI) of patients achieving a therapeutic glycaemic response (HbA1c < 7%) at Week 24 was 33.2% (28.0, 38.8) in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU group and 33.5% (28.3, 39.3) in the insulin glargine plus metformin with or without SU group (difference -0.4% 95% CI [-7.42, 6.54]). Non-inferiority of saxagliptin 5 mg and dapagliflozin 10 mg plus metformin with or without SU compared with the insulin glargine plus metformin with or without SU group was demonstrated (non-inferiority defined by lower bound of 95% CI > 10%).

Add-on therapy with dapagliflozin in patients inadequately controlled on saxagliptin plus metformin
A 24-week randomised, double-blind, placebo-controlled study with the sequential addition of dapagliflozin 10 mg to saxagliptin (DPP4 inhibitor) 5 mg and metformin compared to the addition of placebo to saxagliptin 5 mg and metformin in patients with inadequate glycaemic control (HbA1c ≥ 7% and ≤ 10.5% at Week –2). A total of 818 subjects were enrolled prior to the open-label period in the study; 483 subjects entered the open-label period (349 in stratum A and 134 in stratum B). Stratum A consisted of subjects with inadequate glycaemic control with (HbA1c ≥ 8.0% and ≤ 11.5%) at the screening visit (Weeks –18 to –17) on stable metformin therapy alone (≥ 1500 mg per day). Stratum B consisted of subjects with inadequate glycaemic control (HbA1c ≥ 7.5% and ≤ 10.5%) at the screening visit on a maximum dose of a DPP4 inhibitor for at least 8 weeks prior to the screening visit (Week –10) in addition to a stable metformin therapy (≥ 1500 mg per day). Subjects in the open-label period were switched to saxagliptin 5 mg plus the nearest multiple of metformin 500 mg tablets with a ~HbA1c ≥ 7.5% and < 9% at Week–2. Eighty-three percent (83%) [402/483 subjects] completed the open-label period of which 320 subjects (79.6%) were randomised equally into either the dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin treatment group or placebo plus saxagliptin plus metformin treatment group for the double-blind treatment period of 24 weeks, with 92.5% and 95.6% completion of the respective groups. Mean duration of diabetes was 7.6 years at randomised baseline. Patients who completed the initial 24-week study period were eligible to enter a controlled 28-week long-term study extension (52 weeks). The safety profile of dapagliflozin 10 mg added to saxagliptin 5 mg plus metformin in the long-term treatment period was consistent with that previously observed in the clinical trial experience for the concomitant therapy study and that observed in the 24-week treatment period in this study.

The group with dapagliflozin 10 mg sequentially added to saxagliptin 5 mg and metformin achieved statistically significant (p-value < 0.0001) greater reductions in HbA1c versus the group with placebo sequentially added to saxagliptin 5 mg plus metformin group at 24 weeks (see Table 8). The effect in HbA1c observed at Week 24 was sustained at Week 52. Adjusted mean change from baseline in HbA1c was −0.74% (95% CI [−0.90, −0.57]) for patients treated with dapagliflozin 10 mg plus saxagliptin 5 mg with metformin versus 0.07% (95% CI [−0.13,

0.27]) for patients treated with saxagliptin 5 mg with metformin based on the longitudinal repeated measures analysis excluding data after rescue.

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

A 24-week randomised, double-blind, placebo-controlled study with the sequential addition of saxagliptin 5 mg to dapagliflozin 10 mg and metformin compared to the addition of placebo to dapagliflozin 10 mg (SGLT2 inhibitor) and metformin in subjects with T2DM with inadequate glycaemic control (HbA1c ≥ 7% and ≤ 10.5%) on metformin and dapagliflozin. A total of 857 subjects were enrolled prior to the open-label period in the study with an HbA1c ≥ 8% to ≤ 11.5% with stable dose of metformin ≥ 1500 mg per day at Weeks –18 to –17. Four hundred and eighty-four (484) subjects in the open-label period were switched to dapagliflozin 10 mg plus the nearest multiple of metformin 500 mg tablets (Week –10) with a HbA1c ≥ 7% to ≤ 10.5% at Week–2. Eighty-nine point four percent (89.4%) [431/482 subjects] completed the open-label period of which 153 subjects (48.6%) were randomised to the saxagliptin added dapagliflozin plus metformin treatment group, and 162 (51.4%) subjects were randomised to the placebo added to dapagliflozin plus metformin treatment group for the double-blind treatment period of 24 weeks, with 92.8% and 96.3% completion of the respective groups. Mean duration of diabetes was 7.7 years at randomised baseline. Patients who completed the initial 24-week study period were eligible to enter a controlled 28-week long-term study extension (52 weeks). The safety profile of saxagliptin added to dapagliflozin plus metformin in the long-term treatment period was consistent with that previously observed in the clinical trial experience for the concomitant therapy study and that observed in the 24-week treatment period in this study. This add-on treatment was generally well-tolerated over 52 weeks of treatment with no new or increased safety signals observed that have not been previously reported for each medication as monotherapy.

The group with saxagliptin 5 mg sequentially added to dapagliflozin 10 mg and metformin achieved statistically significant (p-value < 0.0001) greater reductions in HbA1c versus the group with placebo sequentially added to dapagliflozin 10 mg plus metformin group at 24 weeks (see Table 8). The effect in HbA1c observed at Week 24 was sustained at Week 52. At week 52, the difference in adjusted HbA1c mean change from baseline between the 2 treatment groups was -0.42% (95% CI [-0.64, -0.20]).

Table 8. HbA1c change from baseline at Week 24 excluding data after rescue for randomised subjects–studies MB102129 and CV181168

Efficacy Parameter	Sequential add-on clinical trials				
	Study MB102129			Study CV181168	
	Dapagliflozin 10 mg add to Saxagliptin 5 mg + Metformin	Placebo + Saxagliptin 5 mg + Metformin		Saxagliptin 5 mg added to Dapagliflozin 10 mg + Metformin	Placebo + Dapagliflozin 10 mg + Metformin
N[†]	160	160		153	162

HbA1c (%) at Week 24*					
Baseline (mean)	8.24	8.16		7.95	7.85
Change from baseline (adjusted mean‡) (95% CI)	−0.82 (−0.96, 0.69)	−0.10 (−0.24, 0.04)		−0.51 (−0.63, −0.39)	−0.16 (−0.28, −0.04)
Difference in HbA1c effect Adjusted mean (95% CI) p-value	−0.72 (−0.91, −0.53) < 0.0001			−0.35 (−0.52, −0.18) < 0.0001	

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

† Randomised and treated patients.

‡ Least squares mean adjusted for baseline value.

Proportion of patients achieving of HbA1c < 7%

The proportion of patients achieving HbA1c < 7.0% at Week 24 was higher in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group 36.1% (95% CI [29.1, 43.2]) compared to the placebo plus saxagliptin plus metformin group 11.6% (95% [6.3,17.0]). The effect in HbA1c observed at Week 24 was sustained at Week 52. The proportion of patients achieving HbA1c < 7.0% at Week 52 was 29.4% (95% CI [22.7, 36.2]) in the dapagliflozin 10 mg plus saxagliptin 5 mg plus metformin group, compared to 12.6% (95% CI [7.4, 17.9]) in the placebo plus saxagliptin 5 mg plus metformin group. The proportion of patients achieving HbA1c < 7% at Week 24 was higher in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group 35.3% (95% CI [28.2, 42.2]) compared to the placebo plus dapagliflozin plus metformin group 23.1% (95% CI [16.9, 29.3]). The effect in HbA1c observed at Week 24 was sustained at Week 52. The proportion of patients achieving HbA1c < 7.0% at Week 52 was 29.3% (95% CI [22.5, 36.1]) in the saxagliptin 5 mg and dapagliflozin 10 mg plus metformin group, compared to 13.1% (95% CI [8.1, 18.2]) in the placebo plus dapagliflozin 10 mg plus metformin group.

Body weight

In the saxagliptin 5 mg add-on study, both treatment groups had similar small mean changes in body weight at Week 24 from baseline: -0.69 kg (95% CI [−1.23, −0.16]) for the saxagliptin 5 mg plus dapagliflozin 10 mg plus metformin group and -0.56 kg (95% CI [−1.01, −0.12]) for the placebo plus dapagliflozin 10 mg plus metformin group. In the dapagliflozin 10 mg add-on study, the adjusted changes from baseline at Week 24 in body weight were -1.91 kg (95% CI [−2.34, −1.48]) in the dapagliflozin 10 mg plus saxagliptin 5 mg plus metformin group and -0.41 kg (95% CI [−0.86, 0.04]) in the placebo plus saxagliptin 5 mg plus metformin group. The effect in body weight observed at Week 24 was sustained at Week 52. Adjusted mean change from baseline in body weight was –2.13 kg (95% CI [−2.70, −1.56]) for patients treated with dapagliflozin 10 mg plus saxagliptin 5 mg with metformin versus –0.37 kg (95% CI [−1.01, 0.26]) for patients treated with saxagliptin 5 mg with metformin based on the longitudinal repeated measures analysis excluding data after rescue.

Blood pressure
Consistent with its mild diuretic effect, the pre-specified analysis of dapagliflozin-containing treatments in the studies CV181169 and MB102129 and CV181168 were associated with decreases from baseline in systolic and diastolic blood pressure. Treatment with saxagliptin 5 mg/dapagliflozin 10 mg combination resulted in change from baseline for systolic blood pressure ranging from –1.3 to –2.2 mmHg and for diastolic blood pressure ranging from –0.5 to –1.2 mmHg. The modest lowering effects on BP were consistent over time and a similar number of subjects had systolic BP < 130 mmHg or diastolic BP < 80 mmHg at Week 24 across the treatment groups.

Glycaemic control in special population

Use in elderly patients with type 2 diabetes mellitus

Saxagliptin
Of the total number of subjects (N=4148) in six, double-blind, controlled clinical safety and efficacy studies of saxagliptin, 634 (15.3%) patients were 65 years and over, of which 59 (1.4%) patients were 75 years and over.

No overall differences in safety or effectiveness were observed between subjects 65 years and older, 75 years and older, and younger subjects.

Dapagliflozin
In the pool of 21 double-blind, controlled, clinical safety and efficacy studies of 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. 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.

Use in patients with type 2 diabetes mellitus and hypertension

In two 12-week, placebo-controlled studies, a total of 1062 patients with inadequately controlled type 2 diabetes and hypertension were treated with dapagliflozin 10 mg or placebo. Patients with inadequately controlled hypertension (seated systolic blood pressure ≥ 140 and < 165 mmHg, seated diastolic blood pressure ≥ 85 and < 105 mmHg, and a 24-hour mean blood pressure of ≥ 130/80 mmHg) despite pre-existing stable treatment with an angiotensin-converting enzyme inhibitor (ACE) or angiotensin receptor blocker (ARB) (alone [Study 1] or in combination with an additional antihypertensive [Study 2]) as well as inadequate glycaemic control (HbA1c ≥ 7.0% and ≤ 10.5%) despite pre-existing stable treatment with OADs or insulin (alone or in combination) prior to entry, were eligible for these studies. During the studies, no adjustments in antidiabetic and antihypertensive medications were allowed. Across the 2 studies, 527 patients were treated with dapagliflozin 10 mg and 535 with placebo. Patients treated with dapagliflozin 10 mg or placebo also received the following medications for blood pressure control, which were balanced between treatment groups: ACES (64%), ARBS (36%), thiazide diuretics (16%), calcium channel blockers (9%), and beta-blockers (6%).

At Week 12 for both studies, dapagliflozin 10 mg plus usual treatment provided significant improvement in HbA1c and significant reduction in seated systolic blood pressure compared with

placebo plus usual treatment (see Table 9). Consistent reductions were seen in mean 24-hour ambulatory systolic blood pressure in patients treated with dapagliflozin 10 mg treatment compared with placebo. There was a small reduction in mean seated diastolic blood pressure in patients treated with dapagliflozin 10 mg that was not statistically significant compared with placebo.

Table 9. Results at Week 12 in 2 placebo-controlled studies of dapagliflozin in patients with type 2 diabetes and hypertension

	Study 1		Study 2	
Efficacy Parameter	**Dapagliflozin 10 mg + Usual Treatment N=302†**	**Placebo + Usual Treatment N=311†**	**Dapagliflozin 10 mg + Usual Treatment N=225†**	**Placebo + Usual Treatment N=224†**
HbA1c (%) (LRM)*				
Baseline (mean)	8.1	8.0	8.1	8.0
Change from baseline (adjusted mean‡)	−0.6	−0.1	−0.6	0.0
Difference from placebo (adjusted mean‡) (95% CI)	−0.5§ (−0.6, −0.3)		−0.6§ (−0.8, −0.5)	
Seated Systolic Blood Pressure (mmHg) (LRM)*				
Baseline (mean)	149.8	149.5	151.0	151.3
Change from baseline (adjusted mean‡)	−10.4	−7.3	−11.9	−7.6
Difference from placebo (adjusted mean‡) (95% CI)	−3.1¶ (−4.9, −1.2)		−4.3¶ (−6.5, −2.0)	

* LRM: longitudinal repeated measures analysis.
† All 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.
¶ p-value < 0.05.
# LOCF: last observation carried forward.

Use in patients with type 2 diabetes mellitus and renal impairment

Dapagliflozin

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

The glycaemic efficacy and safety of dapagliflozin was evaluated in two dedicated studies of patients with moderate renal impairment.

In a randomised, 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

10). The mean change from baseline in HbA1c and the placebo-corrected mean HbA1c change was −0.37% and −0.34%, respectively. The mean change from baseline in FPG and the placebo-corrected mean FPG was -21.46 mg/dL and -16.59 mg/dL, respectively. The mean body weight reduction (percentage) and the placebo-corrected mean body weight reduction was -3.42% and -1.43 %, respectively. The mean reduction in seated systolic blood pressure (SBP) and the placebo-corrected mean reduction in SBP was -4.8 mmHg and -3.1 mmHg, respectively.

Table 10. Results at Week 24 in a placebo-controlled study of dapagliflozin treatment in diabetic Patients with moderate renal impairment (Class 3A, eGFR ≥45 to <60 mL/min/1.73 m^2)

Efficacy Parameter	Dapagliflozin 10 mg N=159	Placebo N=161
HbA1c (%)		
Baseline (mean)	8.35	8.03
Change from baseline (adjusted mean*)	-0.37	-0.03
Difference from placebo (adjusted mean*) (95% CI)	-0.34§ (-0.53, -0.15)	
FPG (mg/dL)		
Baseline (mean)	183.04	173.28
Change from baseline (adjusted mean*)	-21.46	-4.87
Difference from placebo (adjusted mean*) (95% CI)	-16.59§ (-26.73, -6.45)	
Body Weight (percentage)		
Baseline (mean)	92.51	88.30
% Change from baseline (adjusted mean*)	-3.42	-2.02
Difference from placebo (adjusted mean*) (95% CI)	-1.43§ (-2.15, -0.69)	
Seated Systolic Blood Pressure (mmHg)		
Baseline (mean)	135.7	135.0
Change from baseline (adjusted mean*)	-4.8	-1.7
Difference from placebo (adjusted mean*) (95% CI)	-3.1¶ (-6.3, 0.0)	

* Least squares mean adjusted for baseline value.
§ p-value ≤0.001.
¶ p-value <0.05.

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

The efficacy and safety of dapagliflozin was also assessed in a study of 252 diabetic patients with eGFR ≥30 to <60 mL/min/1.73 m^2 (moderate renal impairment subgroup CKD 3A and CKD 3B). Dapagliflozin treatment did not show a significant placebo corrected change in HbA1c in the overall study population (CKD 3A and CKD 3B combined) at 24 weeks. In an additional analysis of the subgroup CKD 3A, dapagliflozin 10 mg (n=32) provided a placebo corrected mean HbA1c change at 24 weeks of −0.33%. At Week 52, dapagliflozin was

associated with changes from baseline in mean eGFR (dapagliflozin 10 mg −4.46 mL/min/1.73 m^2 and placebo −2.58 mL/min/1.73 m^2). At Week 104, these changes persisted (eGFR: dapagliflozin 10 mg −3.50 mL/min/1.73 m^2 and placebo −2.38 mL/min/1.73 m^2). With dapagliflozin 10 mg, this eGFR reduction were evident at Week 1 and remained stable through Week 104, while placebo-treated patients had a slow continuous decline through Week 52 that stabilized through Week 104.

Use in patients with type 2 diabetes mellitus and cardiovascular disease

Saxagliptin

Despite active management of concomitant antidiabetic therapy in both study arms in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial, mean HbA1c levels were lower in the saxagliptin group compared to the placebo group at Year 1 (7.6% versus 7.9%, difference of –0.35% [95% CI: –0.38, –0.31]) and at Year 2 (7.6% versus 7.9%, difference of –0.30% [95% CI: –0.34, –0.26]). The proportions of subjects with HbA1c < 7% in the saxagliptin group compared to the placebo group were 38% versus 27% at Year 1 and 38% versus 29% at Year 2.

Compared to placebo, saxagliptin resulted in less need for the initiation of new or increases in current oral diabetes medications or insulin. The improvements in HbA1c and the proportion of subjects reaching HbA1c targets among saxagliptin-treated subjects were observed despite lower rates of upward adjustments in diabetes medications or initiation of new diabetes medications or insulin compared with placebo.

Dapagliflozin

In two 24-week, placebo-controlled studies with 80-week extension periods, a total of 1887 patients with type 2 diabetes and cardiovascular disease (CVD) were treated with dapagliflozin 10 mg or placebo. Patients with established CVD and inadequate glycaemic control (HbA1c ≥ 7.0% and ≤ 10.0%), despite pre-existing, stable treatment with oral antidiabetic therapy (OADs) or insulin (alone or in combination) prior to entry, were eligible for these studies and were stratified according to age (< 65 years or ≥ 65 years), insulin use (no or yes), and time from most recent qualifying cardiovascular event (> 1 year or < 1 year prior to enrollment). Across the 2 studies, 942 patients were treated with dapagliflozin 10 mg and 945 with placebo. Ninety-six percent (96%) of patients treated with dapagliflozin across the 2 studies had hypertension at entry, the majority for more than 10 years duration; the most common qualifying cardiovascular events were coronary heart disease (75%) or stroke (22%). Approximately 19% of patients received loop diuretics at entry and 15% had congestive heart failure (2% had NYHA Class III). Approximately 37% of patients treated with dapagliflozin 10 mg also received metformin plus one additional OAD at entry, (sulfonylurea, thiazolidinedione, DPP4-inhibitor, or other OAD with or without insulin at entry) 38% received insulin plus at least one OAD, and 18% received insulin alone.

Treatment with dapagliflozin 10 mg as add-on to pre-existing antidiabetic treatments over 24 weeks provided significant improvement in coprimary endpoints of HbA1c and composite clinical benefit compared with placebo in this population. Significant reductions in total body weight and seated systolic blood pressure were also seen. These benefits extended up to 104 weeks of treatment. The safety profile of dapagliflozin in these studies was consistent with that of dapagliflozin in the general clinical study population through 104 weeks of treatment.

Cardiovascular outcomes studies in patients with type 2 diabetes mellitus

No cardiovascular outcomes studies have been conducted to evaluate the saxagliptin/dapagliflozin combination.

In an outcome study with saxagliptin an increase in the rate of hospitalisation for heart failure was observed in the saxagliptin-treated patients compared to placebo, although a causal relationship has not been established.

In an outcome study with dapagliflozin a reduced risk of hospitalisation for heart failure was observed in the dapagliflozin treated patients compared to placebo.

The overall effect of Saxagliptin/Dapagliflozin (QTERN) on hospitalisation for heart failure in adults with type 2 diabetes mellitus is unknown.

SAVOR (saxagliptin)

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial, the effect of saxagliptin on the occurrence of major cardiovascular disease (CVD) events was assessed in 16,492 adult patients with type 2 diabetes who had either established CVD or multiple risk factors for vascular disease, including patients with moderate or severe renal impairment. Patients ≥ 40 years of age, diagnosed with type 2 diabetes and with HbA1c ≥ 6.5%, and with either established CVD or multiple CV risk factors were enrolled.

Patients were randomly assigned to placebo (n=8212) or saxagliptin (5 mg or 2.5 mg for patients with moderate or severe renal insufficiency) once daily (n=8280). Randomization to the saxagliptin and placebo groups was stratified by CV risk with 3533 patients (21.4%) with CV risk factors only and 12,959 patients (78.6%) with established CVD and by renal impairment including 13,916 subjects (84.4%) with normal renal function to mild impairment, 2240 subjects (13.6%) with moderate impairment, and 336 subjects (2.0%) with severe renal impairment. Patients with established CVD were defined by a history of ischaemic heart disease, peripheral vascular disease, or ischaemic stroke. Patients with CV risk factors only had age as a CV risk factor (men ≥ 55 years and women ≥ 60 years) plus at least one additional risk factor of dyslipidemia, hypertension, or current cigarette smoking.

The demographics and baseline characteristics of subjects were balanced between the saxagliptin and placebo groups. The study population was 67% male and 33% female with a mean age at randomization of 65 years. Of the 16,492 patients randomised, 8561 (52%) patients were 65 years and over and 2330 (14%) were 75 years and over. Of the 16,492 patients randomised in the SAVOR trial, 8561 (51.9%) patients were 65 years and over and 2330 (14.1%) were 75 years and over. The number of subjects treated with saxagliptin in the SAVOR study that were 65 years and over was 4290 and the number of subjects that were 75 years and over was 1169.

All study subjects had a mean duration of T2DM of 12 years (median=10.3) and a mean HbA1c level of 8.0% (median=7.6%). Overall, 25% of subjects had baseline HbA1c levels < 7%. Subjects were followed for a mean duration of 2 (median = 2.0) years.

Concomitant medication use was similar for the two treatment groups. Overall, the use of diabetes medications was consistent with local treatment practice and the saxagliptin clinical program (metformin 69%, insulin 41%, sulfonylureas 40%, and TZDs 6%). The use of CVD medications was also consistent with local treatment practice (ACE inhibitors or ARBs 79%, statins 78%, aspirin 75%, beta-blockers 62%, and nonaspirin antiplatelet medications 24%). Approximately 6% of subjects were treated with diet and exercise only at baseline. Concomitant medications were managed throughout the trial to local guideline targets for glycaemic control and CV risk reduction in order to minimize differences between the two treatment groups, particularly for glycaemic control.

The primary safety and efficacy endpoint was a composite endpoint consisting of the time-to-first occurrence of any of the following major adverse CV events (MACE): CV death, nonfatal myocardial infarction, or nonfatal ischaemic stroke.

The primary safety objective of this trial was to establish that the upper bound of the 2-sided 95% CI for the estimated risk ratio comparing the incidence of the composite endpoint of CV death, non-fatal MI or non-fatal ischaemic stroke observed with saxagliptin to that observed in the placebo group was < 1.3.

The primary efficacy objective was to determine, as a superiority assessment, whether treatment with saxagliptin, compared with placebo when added to current background therapy, resulted in a significant reduction in the primary MACE endpoint.

The first secondary efficacy endpoint was a composite endpoint consisting of the time-to-first occurrence of MACE plus hospitalisation for heart failure, hospitalisation for unstable angina pectoris, or hospitalisation for coronary revascularisation (MACE plus). The next secondary efficacy endpoint was to determine whether treatment with saxagliptin compared with placebo when added to current background therapy in subjects with T2DM would result in a reduction of all-cause mortality.

The cardiovascular safety of saxagliptin was evaluated in the SAVOR trial which established that saxagliptin did not increase the CV risk (CV death, non-fatal myocardial infarction, or non-fatal ischaemic stroke) in patients with T2DM compared to placebo when added to current background therapy (HR 1.00; 95% CI: 0.89, 1.12; P< 0.001 for non-inferiority).

The primary efficacy endpoint did not demonstrate a statistically significant difference in major adverse coronary events for saxagliptin compared to placebo when added to current background therapy in patients with T2DM.

Table 11. Primary and secondary clinical endpoints by treatment group in the SAVOR study*

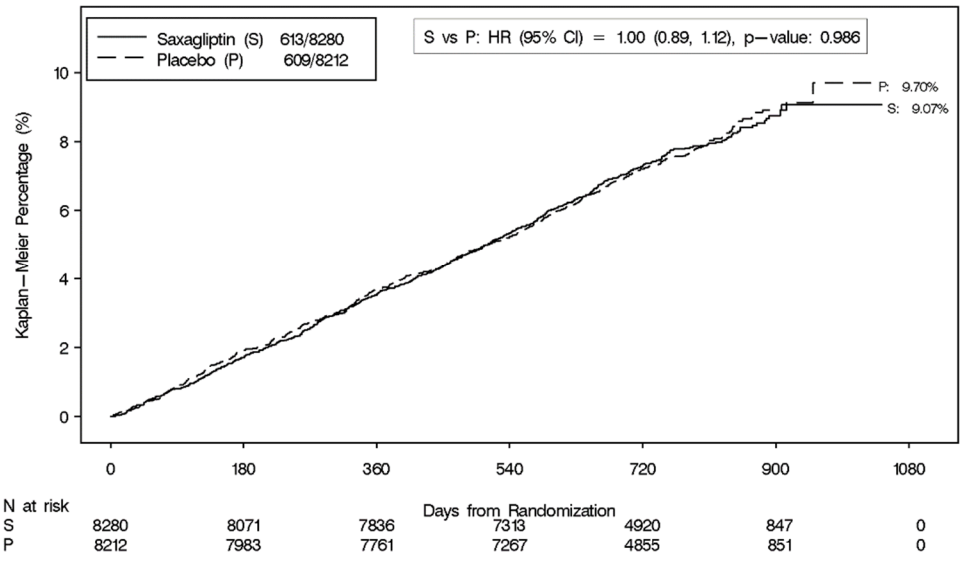
	Saxagliptin (N=8280)		**Placebo (N=8212)**		
Endpoint	**Subjects with events n (%)**	**Event rate per 100 patient-yrs**	**Subjects with events n (%)**	**Event rate per 100 patient-yrs**	**Hazard Ratio (95% CI)†**
Primary composite endpoint: MACE	613 (7.4)	3.76	609 (7.4)	3.77	1.00 (0.89, 1.12)‡,§

Table 11. Primary and secondary clinical endpoints by treatment group in the SAVOR study*

Endpoint	Saxagliptin (N=8280)		Placebo (N=8212)		Hazard Ratio (95% CI)†
	Subjects with events n (%)	Event rate per 100 patient-yrs	Subjects with events n (%)	Event rate per 100 patient-yrs	
Secondary composite endpoint: MACE plus	1059 (12.8)	6.72	1034 (12.6)	6.60	1.02 (0.94, 1.11)¶
All-cause mortality	420 (5.1)	2.50	378 (4.6)	2.26	1.11 (0.96, 1.27)¶

* Intent-to-treat population
† Hazard ratio adjusted for baseline renal function category and baseline CVD risk category.
‡ P-value < 0.001 for noninferiority (based on HR < 1.3) compared to placebo.
§ P-value = 0.99 for superiority (based on HR < 1.0) compared to placebo.
¶ Significance not tested.

Figure 2. Cumulative percent of time to first CV event for primary composite endpoint*



* Intent-to-treat population

Events accumulated consistently over time, and the event rates for saxagliptin and placebo did not diverge notably over time.

One component of the secondary composite endpoint, hospitalisation for heart failure, occurred at a greater rate in the saxagliptin group (3.5%) compared with the placebo group (2.8%), with nominal statistical significance (i.e. without adjustment for testing of multiple endpoints) favoring placebo [HR = 1.27; (95% CI 1.07, 1.51); P=0.007]. Clinically relevant factors predictive of increased relative risk with saxagliptin treatment could not be definitively identified. Subjects at

higher risk for hospitalisation for heart failure, irrespective of treatment assignment, could be identified by known risk factors for heart failure such as baseline history of heart failure or impaired renal function. However, subjects on saxagliptin with a history of heart failure or impaired renal function at baseline were not at an increased risk relative to placebo for the primary or secondary composite endpoints or all-cause mortality.

No increased risk for the primary endpoint was observed between saxagliptin and placebo in any of the following subgroups: CVD, multiple risk factors for CVD, mild, moderate, or severe renal impairment, age, gender, race, region, duration of type 2 diabetes, history of heart failure, baseline HbA1c, albumin/creatinine ratio, baseline antidiabetic medication, or baseline use of statins, aspirin, ACE inhibitors, ARBs, beta-blockers, or antiplatelet medications.

DECLARE (dapagliflozin)

Dapagliflozin Effect on Cardiovascular Events (DECLARE) was an international, multicenter, randomised, 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 dyslipidaemia, 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 randomised patients, 6974 (40.6%) had established CV disease and 10186 (59.4%) did not have established CV disease. 8582 patients were randomised to dapagliflozin 10 mg and 8578 to placebo and were followed for a median of 4.2 years.

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

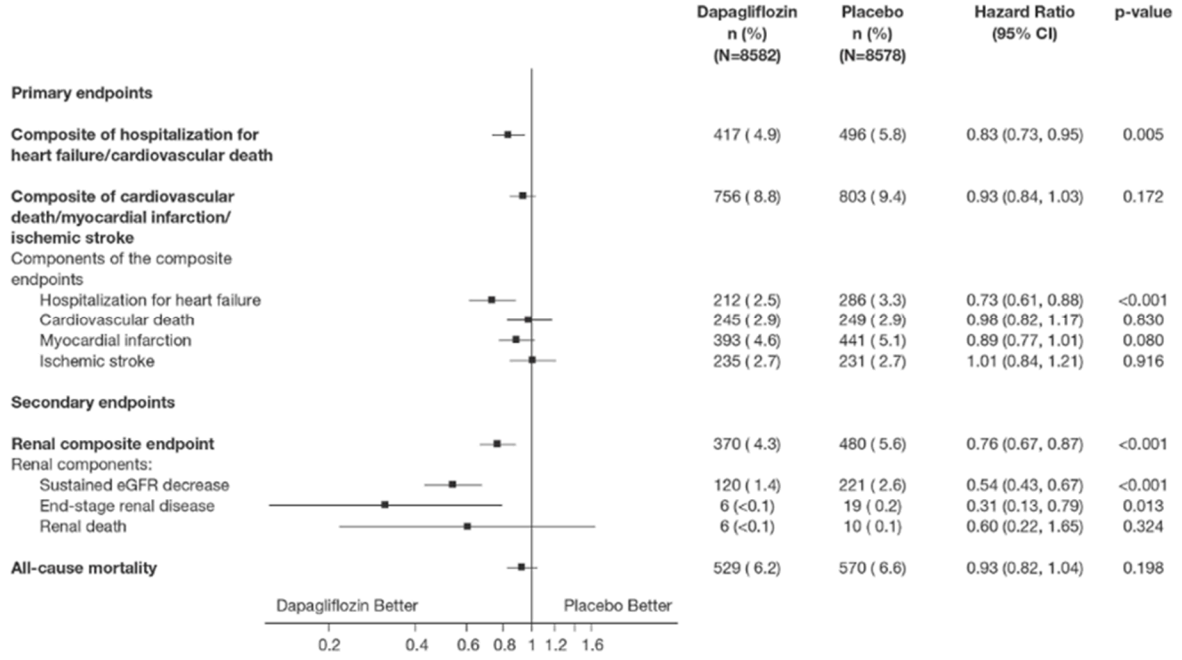
At baseline, 10.0% of patients had a history of heart failure. Mean eGFR was 85.2 mL/min/1.73 m^2, 7.4% of patients had eGFR < 60mL/min/1.73 m^2 and 30.3% of patients had micro- or macroalbuminuria (urine albumin to creatinine ration [UACR] ≥ 30 to ≤ 300 mg/g or > 300 mg/g, respectively).

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

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

Results on primary and secondary endpoints are displayed in Figures 3 and 4.

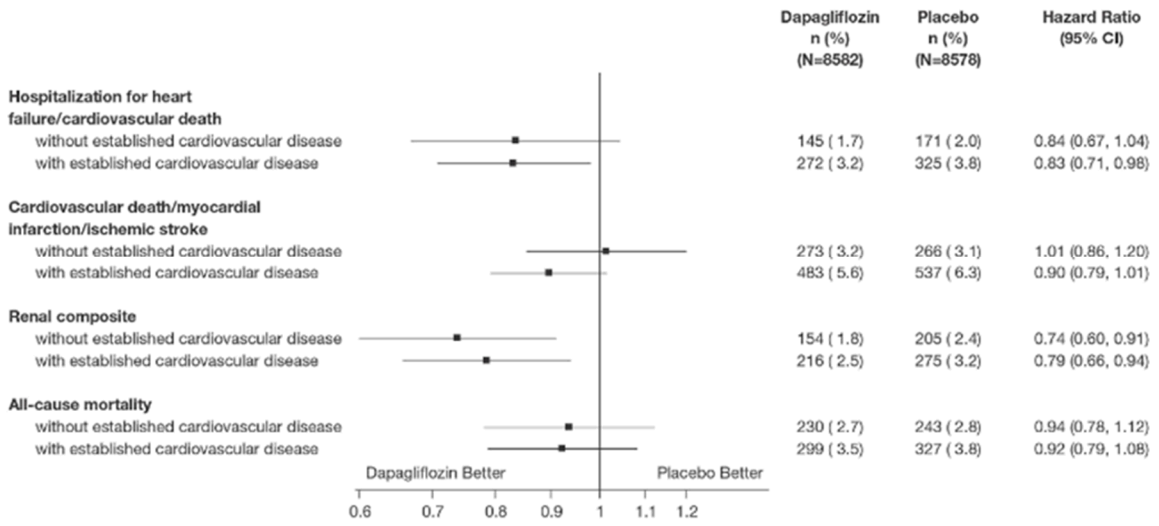
Figure 3. Treatment effects for the primary composite endpoints and their components, and the secondary endpoints and components



	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	370 (4.3)	480 (5.6)	0.76 (0.67, 0.87)	<0.001
Renal components:				
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

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

Figure 4. Treatment effects for the primary and secondary endpoints in patients with and without established CV disease



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

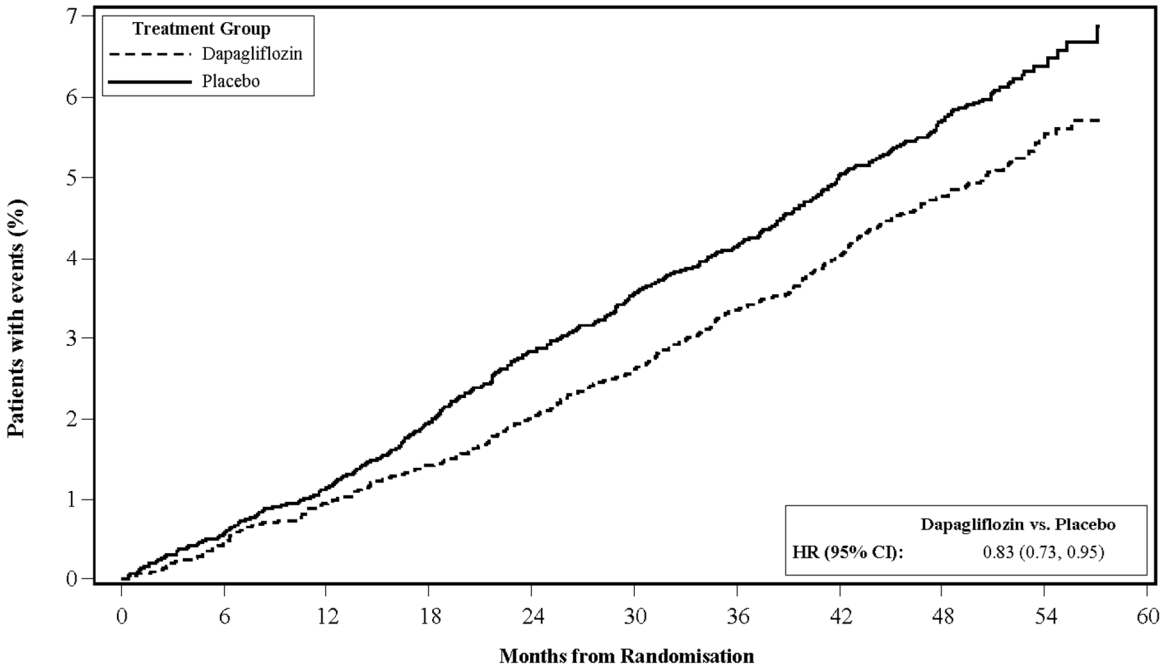
Heart failure or cardiovascular death

Dapagliflozin 10 mg was superior to placebo in preventing the primary composite endpoint of hospitalisation for heart failure or CV death (HR 0.83 [95% CI 0.73, 0.95]; p=0.005) (Figure 5).

Exploratory analyses of the single components suggest that the difference in treatment effect was driven by hospitalisation for heart failure (HR 0.73 [95% CI 0.61, 0.88]) (Figure 3), 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 4), with and without heart failure at baseline, and was consistent across key subgroups, including age, gender, renal function (eGFR), and region.

Figure 5. Time to first occurrence of hospitalisation 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

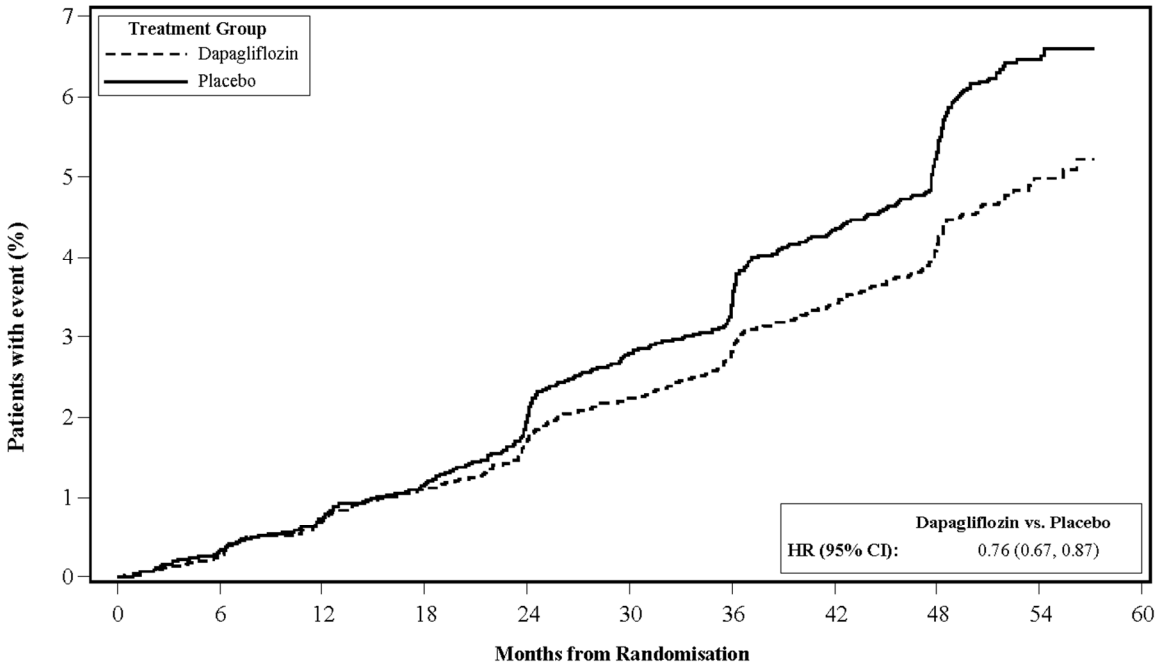
Dapagliflozin demonstrated cardiovascular safety (tested as non-inferiority versus placebo for the composite of CV death, myocardial infarction or ischemic stroke [MACE]; one-sided $p < 0.001$).

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 3 and 4).

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 6). The difference between groups was driven by reductions in events of the renal components; sustained eGFR decrease, ESRD and renal death (Figure 3), and was observed both in patients with and without CV disease (Figure 4).

Figure 6. Time to first occurrence of sustained eGFR decrease, ESRD, renal or CV death



Patients at risk

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

Patients at risk is the number of patients at risk at the beginning of the period.
Renal composite endpoint defined as sustained confirmed eGFR decrease ≥40% to eGFR <60 mL/min/1.73m^2 and/or ESRD and/or renal or CV death.
CI Confidence interval; HR Hazard ratio

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

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

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

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

Clinical safety

Saxagliptin/dapagliflozin combination

Hypoglycaemia

In the pooled safety analysis, the overall incidence of hypoglycaemia (all reported events including those with central laboratory FPG ≤ 3.9 mmol/L [70 mg/dL]) was low (2.0%) in patients treated with saxagliptin 5 mg and dapagliflozin 10 mg (combination therapy) on a background of metformin, 0.6 % in the saxagliptin plus metformin, and 2.3 % in dapagliflozin plus metformin. No episodes of major hypoglycemia (defined as a symptomatic episode with blood glucose < 3.0 mmol/L [54 mg/dL] requiring external assistance) were reported, and no subject discontinued the study treatment due to hypoglycemia.

Combination therapy plus metformin had lower incidence rates of hypoglycaemia compared to insulin or SU *[see clinical efficacy and safety in section 5.1].* The overall incidence rates of hypoglycaemia for a 24-week study were 12.7% for the combination therapy plus metformin versus 33.1% for insulin plus metformin without SU. The overall incidence rates for hypoglycaemia for two 52-week studies comparing the combination therapy plus metformin to glimepiride (SU) were: for the 1st study. 4.2% for the combination therapy plus metformin versus 27.9% for glimepiride plus metformin and 2.9% for dapagliflozin plus metformin; for the 2nd study. 18.5% for the combination therapy plus metformin versus 43.1% for glimepiride plus metformin.

No episodes of major hypoglycaemia were reported in trials with the combination therapy plus metformin and no subject discontinued the study treatment due to hypoglycaemia.

Events related to decreased renal function

In the pooled safety analysis, the incidence of AEs related to decreased renal function was 2.0% of subjects in the saxagliptin and dapagliflozin plus metformin group, 1.8% subjects in the saxagliptin plus metformin group, and 0.6% subjects in the dapagliflozin + metformin group. Subjects with AEs of renal impairment had lower mean eGFR values at baseline of 61.8 mL/min/1.73m^2 compared to 93.6 mL/min/1.73m^2 in overall population. The majority of events were considered non-serious, mild or moderate in intensity, and resolved.

The change in mean eGFR from baseline at Week 24 was -1.17 mL/min/1.73 m^2 in the saxagliptin and dapagliflozin plus metformin group, -0.46 ml/min/1.73 m^2 in saxagliptin plus metformin, and 0.81 mL/min/1.73 m^2 in dapagliflozin plus metformin.

Cardiovascular Safety

In the pooled safety analysis, CV events that were adjudicated and confirmed as CV events were reported in a total of 1.0% of subjects in the saxagliptin and dapagliflozin plus metformin group, 0.6% in the saxagliptin + metformin group, and 0.9% in the dapagliflozin plus metformin group.

5.2 Pharmacokinetic properties

Saxagliptin/dapagliflozin combination
Bioequivalence has been confirmed between the Saxagliptin/Dapagliflozin (QTERN) 5 mg/10 mg tablet and the individual saxagliptin 5 mg and dapagliflozin 10 mg tablets after single dose administration in the fasted state in healthy volunteers.

Administration of Saxagliptin/Dapagliflozin (QTERN) with a high-fat meal decreases dapagliflozin C_{max} by up to 35% and prolongs T_{max} by approximately 1.5 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful. There was no food effect observed for saxagliptin. Saxagliptin/Dapagliflozin (QTERN) can be administered with or without food.

Saxagliptin
The pharmacokinetics of saxagliptin has been extensively characterized in healthy subjects and patients with type 2 diabetes. Saxagliptin was rapidly absorbed after oral administration, with maximum saxagliptin plasma concentrations (C_{max}) usually attained within two hours after administration in the fasted state. The C_{max} and AUC values increased proportionally to the increment in the saxagliptin dose. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC(INF) values for saxagliptin and its major metabolite were 78 ng·h/mL and 214 ng·h/mL, respectively. The corresponding plasma C_{max} values were 24 ng/mL and 47 ng/mL, respectively. The intra-subject coefficients of variation for saxagliptin C_{max} and AUC were less than 12%.

Following a single oral dose of 5 mg saxagliptin to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin was 2.5 hours and the mean $t_{1/2}$ value for plasma DPP4 inhibition was 27 hours. The inhibition of plasma DPP4 activity by saxagliptin for at least 24 hours after oral administration of saxagliptin is due to high potency, high affinity, and extended binding to the active site. No appreciable accumulation was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence was observed in the clearance of saxagliptin and its major metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 mg to 400 mg. Results from population-based exposure modeling suggest that the pharmacokinetics of saxagliptin and its major metabolite were similar in healthy subjects and in patients with type 2 diabetes.

Absorption

Saxagliptin
The amount of saxagliptin absorbed following an oral dose is at least 75%. Food had relatively modest effects on the pharmacokinetics of saxagliptin in healthy subjects. Administration with a high-fat meal resulted in no change in saxagliptin C_{max} and a 27% increase in AUC compared with the fasted state. The time for saxagliptin to reach C_{max} (T_{max}) was increased by approximately 0.5 hours with food compared with the fasted state. These changes were not considered to be clinically meaningful.

Dapagliflozin

Dapagliflozin is rapidly and well absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (C_{max}) are usually attained within 2 hours after administration in the fasted state. The C_{max} and AUC values increase proportionally to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Food has relatively modest effects on the pharmacokinetics of dapagliflozin in healthy subjects. Administration with a high-fat meal decreases dapagliflozin C_{max} by up to 50% and prolonged T_{max} by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

Distribution

Saxagliptin
The *in vitro* protein binding of saxagliptin and its major metabolite in human serum is below measurable levels. Thus, changes in blood protein levels in various disease states (e.g., renal or hepatic impairment) are not expected to alter the disposition of saxagliptin.

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

Metabolism

Saxagliptin
The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a selective, reversible, competitive DPP4 inhibitor, half as potent as saxagliptin.

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 metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted 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 hour]) of total plasma radioactivity, similar to the 39% contribution by parent drug. Based on AUC, no other metabolite accounts for > 5% of the total plasma radioactivity. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism is a minor clearance pathway in humans.

Excretion

Saxagliptin
Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50-mg dose of ^{14}C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its major metabolite, and total radioactivity, respectively. The average renal clearance of saxagliptin

(~230 mL/min) was greater than the average estimated glomerular filtration rate (~120 mL/min), suggesting some active renal excretion. For the major metabolite, renal clearance values were comparable to estimated glomerular filtration rate. A total of 22% of the administered radioactivity was recovered in feces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed drug from the gastrointestinal tract.

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

Pharmacokinetics of the major metabolite

Saxagliptin
The C_{max} and AUC values for the major metabolite of saxagliptin increased proportionally to the increment in the saxagliptin dose. Following single oral doses of 2.5 mg to 400 mg saxagliptin in the fed or fasted states, the mean AUC values for the major metabolite ranged from 2- and 7-times higher than the parent saxagliptin exposures on a molar basis. Following a single oral dose of 5 mg saxagliptin in the fasted state, the mean terminal half-life ($t_{1/2}$) value for the major metabolite was 3.1 hours and no appreciable accumulation was observed upon repeated once-daily dosing at any dose.

Special populations

Renal impairment
Saxagliptin/dapagliflozin combination
(See section 4.4, Special warnings and special precautions for use.)

Saxagliptin
A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment compared to subjects with normal renal function.

The degree of renal impairment did not affect the C_{max} of saxagliptin or its major metabolite.

In subjects with CrCL >50 mL/min (corresponding to eGFR ≥ 45 mL/min/1.73 m^2 by MDRD eGFR equation), the AUC values of saxagliptin and its major metabolite were 1.2- and 1.7-fold higher, respectively, than AUC values in subjects with normal renal function. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not recommended.

In subjects with renal impairment with CrCL ≤50 mL/min (corresponding to eGFR <45 mL/min/1.73 m^2) or in subjects with ESRD on haemodialysis, the AUC values of saxagliptin and its major metabolite were up to 2.1- and 4.5-fold higher, respectively, than AUC values in subjects with normal renal function.

Saxagliptin is removed by haemodialysis.

Dapagliflozin

Dapagliflozin should not be used in patients with moderate or severe renal impairment (eGFR persistently < 45 mL/min/1.73m^2 or CrCl persistently < 60 mL/min). 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 were lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function, and 85, 52, 18, and 11 g of glucose/day was excreted by patients with type 2 diabetes mellitus and normal renal function or mild, moderate, or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of haemodialysis on dapagliflozin exposure is not known.

Hepatic impairment

Saxagliptin/dapagliflozin combination

(See section 4.2, Posology and administration, Patients with hepatic impairment.)

Saxagliptin

In subjects with hepatic impairment (Child-Pugh classes A, B, and C), mean C_{max} and AUC of saxagliptin were up to 8% and 77% higher, respectively, compared to healthy matched controls following administration of a single 10 mg dose of saxagliptin. The corresponding C_{max} and AUC of the major metabolite were up to 59% and 33% lower, respectively, compared to healthy matched controls. These differences are not considered to be clinically meaningful.

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. 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.

Body mass index

Saxagliptin

No dosage adjustment is recommended based on body mass index. BMI was not identified as a significant covariate on the apparent clearance of saxagliptin or its major metabolite in an exposure modeling analysis.

Dapagliflozin
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.

Geriatric

Saxagliptin
Elderly subjects (65 to 80 years) had 23% and 59% higher geometric mean C_{max} and geometric mean AUC values, respectively, for parent saxagliptin than young subjects (18–40 years). Differences in major metabolite pharmacokinetics between elderly and young subjects generally reflected the differences observed in parent saxagliptin pharmacokinetics. The difference between the pharmacokinetics of saxagliptin and the major metabolite in young and elderly subjects is likely to be due to multiple factors including declining renal function and metabolic capacity with increasing age. Age was not identified as a significant covariate on the apparent clearance of saxagliptin and its major metabolite in an exposure modeling analysis.

Dapagliflozin
The effect of age (young: ≥ 18 to < 40 years [n=105] and elderly: ≥ 65 years [n=224]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients ≥ 40 to < 65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10.4% lower than in the reference group (90% CI; 87.9, 92.2%) and 25% higher in elderly patients compared to the reference group (90% CI; 123, 129%). These differences in systemic exposure were considered to not be clinically meaningful.

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

Gender
Saxagliptin/dapagliflozin combination
Saxagliptin/Dapagliflozin (QTERN) may be used regardless of gender.

Saxagliptin
There were no differences observed in saxagliptin pharmacokinetics between males and females. Compared to males, females had approximately 25% higher exposure values for the major metabolite than males, but this difference is unlikely to be of clinical relevance. Gender was not

identified as a significant covariate on the apparent clearance of saxagliptin and its major metabolite in an exposure modeling analysis.

Dapagliflozin
Gender was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. The mean dapagliflozin AUCss in females (n=619) was estimated to be 22% higher than in males (n=634) (90% CI; 117,124).

Race
Saxagliptin/dapagliflozin combination
Saxagliptin/Dapagliflozin (QTERN) may be used regardless of race.

Saxagliptin
An exposure modeling analysis compared the pharmacokinetics of saxagliptin and its major metabolite in 309 white subjects with 105 non-white subjects (consisting of 6 racial groups). No significant difference in the pharmacokinetics of saxagliptin and its major metabolite were detected between these two populations.

Dapagliflozin
Race (White, Black, or Asian) was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. Differences in systemic exposures between these races were small. Compared to Whites (n=1147), Asian subjects (n=47) had no difference in estimated mean dapagliflozin systemic exposures (90% CI range; 3.7% lower, 1% higher). Compared to Whites, Black subjects (n=43) had 4.9% lower estimated mean dapagliflozin systemic exposures (90% CI range; 7.7% lower, 3.7% lower).

5.3 Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility

Non-clinical studies of either saxagliptin or dapagliflozin revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity or carcinogenicity.

Saxagliptin

Two-year carcinogenicity studies were conducted in mice and rats at oral doses of 50, 250, and 600 mg/kg/day and 25, 75, 150, and 300 mg/kg/day, respectively. Saxagliptin did not induce tumours in either mice or rats at the highest doses evaluated. The highest doses evaluated in mice were equivalent to approximately 900 (males) and 1210 (females) times the human exposure at the recommended human dose of 5 mg/day (RHD). In rats, exposures were approximately 370 (males) and 2300 (females) times the RHD.

The mutagenic and clastogenic potential of saxagliptin was tested at high concentrations and exposures in a battery of genetic toxicity studies including an *in vitro* Ames bacterial assay, an *in vitro* cytogenetics assay in primary human lymphocytes, an *in vivo* oral micronucleus assay in rats, an *in vivo* oral DNA repair study in rats, and an oral *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes. Saxagliptin was not mutagenic or clastogenic based on the combined outcomes of these studies. The major metabolite was not mutagenic in an *in vitro* Ames bacterial assay.

In a rat fertility study, males were treated with oral gavage doses of 100, 200, and 400 mg/kg/day for two weeks prior to mating, during mating, and up to scheduled termination (approximately

four weeks total) and females were treated with oral gavage doses of 125, 300, and 750 mg/kg/day for two weeks prior to mating through gestation day 7. No adverse effects on fertility were observed at 200 mg/kg/day (males) or 125 mg/kg/day (females) resulting in respective exposures (AUC) of approximately 630 (males) and 805 (females) times human exposure at the RHD. At higher, maternally toxic doses (300 and 750 mg/kg/day), increased fetal resorptions were observed (approximately 2150 and 6375 times the RHD). Additional effects on estrous cycling, fertility, ovulation, and implantation were observed at 750 mg/kg (approximately 6375 times the RHD).

Dapagliflozin

Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in 2-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 microg/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. This data strongly suggests 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.

Teratogenicity and impairment of early development

Saxagliptin

Saxagliptin was not teratogenic at any dose evaluated in rats or rabbits. At high doses in rats, saxagliptin caused a minor and reversible developmental delay in ossification of the fetal pelvis at ≥240 mg/kg/day (≥ 1560 times the human exposure AUC at the RHD). Maternal toxicity and reduced fetal body weights were observed at 900 mg/kg/day (8290 times the RHD). In rabbits, the effects of saxagliptin were limited to minor skeletal variations observed only at maternally toxic doses (200 mg/kg/day, exposures 1420 times the RHD).

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (≥250 mg/kg/day, exposures ≥1690 times the RHD). No functional or behavioural toxicity was observed in offspring of rats administered saxagliptin at any dose.

Dapagliflozin

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

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥ 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 prenatal 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-fetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested (20, 60, or 180 mg/kg/day); 180 mg/kg/day is associated with a systemic exposure multiple of approximately 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-fetal lethality, increased incidences of fetal malformations and skeletal variations, and reduced fetal body weights. Malformations included a low incidence of great vessel malformations, fused ribs and vertebral centras, and duplicated manubria and sternal centra. Variations were primarily reduced ossifications.

Animal toxicology

Saxagliptin

Saxagliptin produced skin changes (scabs and/or ulceration) in extremities (tail, digits, scrotum, and/or nose) and microscopic multiorgan mononuclear cell infiltration and inflammation in cynomolgus monkeys at doses ≥ 2 mg/kg/day for one to three months (≥ 7 times the human exposure at the RHD). In a three-month study, at 3 mg/kg/day (≥ 20 times exposure at the RHD) skin healing during the dosing period was observed with complete recovery of both skin and microscopic changes following a drug-free recovery period. The mononuclear cell infiltrates or inflammation are considered to be an exacerbation of background changes commonly observed in monkeys. The no-effect level for skin and microscopic changes is 0.3 mg/kg/day (one females to three males times the RHD). Similar skin lesions have not been observed in mice, rats, or dogs at exposures up to 1210, 2300, or 55 times the human exposure at the RHD, respectively. Clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.

Saxagliptin produced bloody/mucoid feces in dogs (at exposures ≥ 19 times the RHD) with a no-effect level 4 times the RHD.

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 non-clinical 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.

Saxagliptin/dapagliflozin combination
In a 3-month repeat-dose study of the combination of saxagliptin and dapagliflozin in rats, there were no toxicologic or toxicokinetic interactions with a NOAEL at AUC exposures equating to 7 times the maximum recommended human dose (MRHD) for both compounds.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each film-coated tablet of the Saxagliptin/Dapagliflozin (QTERN) contains 5 mg saxagliptin as saxagliptin hydrochloride and dapagliflozin propanediol monohydrate equivalent to 10 mg dapagliflozin. The following inactive ingredients include: microcrystalline cellulose, croscarmellose sodium, anhydrous lactose, magnesium stearate, silicon dioxide, polyvinyl alcohol, macrogol 3350, titanium dioxide, talc, yellow iron oxide, red iron oxide, shellac, indigo carmine aluminium lake.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Please refer to the outer carton.

6.4 Special precautions for storage

Store at temperatures not exceeding 30°C.

6.5 Instructions for use, handling and disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

6.6 Availability

Saxagliptin/Dapagliflozin (QTERN) 5 mg/ 10 mg Film-Coated Tablet – Alu/Alu Blister Pack x 10’s in Box of 30’s

7. REGISTRATION NUMBER

DR-XY46439

8. DATE OF FIRST AUTHORIZATION

11 December 2018

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, please report to the Food and Drug Administration (FDA) at www.fda.gov.ph and to AstraZeneca at patientsafety.ph@astrazeneca.com. The patient should seek medical attention immediately at the first sign of any adverse drug reaction.

Date of Revision of Text: August 2021
Based on CDS dated December 2019 with ANGEL Reference: Doc ID-003164856 v.7.0 and FDA Advisory 2019-169 dated 02 July 2019
Philippine-specific Text ANGEL Reference: Doc ID-003330956 v.9.0

Imported by the Marketing Authorization Holder
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