Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Trivesta-Q 10/5/1000mg Tablets

2. Qualitative and quantitative composition

Each tablet contains 10mg empagliflozin, 5 mg of Linagliptin and 1000mg metformin

3. Pharmaceutical form

A Green colored, oblong shaped film coated tablet

4. Clinical particulars

4.1 Therapeutic indications

Trivesta-Q is a combination of empagliflozin, linagliptin, and metformin hydrochloride (HCl) indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease

4.2 Posology and method of administration

Prior To Initiation Of TRIVESTA-Q

Assess renal function prior to initiation of TRIVESTA-Q and periodically thereafter

In patients with volume depletion, correct this condition prior to initiation of TRIVESTA-Q

Recommended Dosage

Individualize the starting dose of TRIVESTA-Q based on the patient's current regimen:

In patients on metformin HCl, with or without linagliptin, switch to TRIVESTA-Q containing a similar total daily dose of metformin HCl and a total daily dose of empagliflozin 10 mg and linagliptin 5 mg;

In patients on metformin HCl and any regimen containing empagliflozin, with or without linagliptin, switch to TRIVESTA-Q containing a similar total daily dose of metformin HCl, the same total daily dose of empagliflozin and linagliptin 5 mg.

Monitor effectiveness and tolerability, and adjust dosing as appropriate, not to exceed the maximum recommended daily dose of empagliflozin 25 mg, linagliptin 5 mg and metformin HCl 2000 mg.

Take TRIVESTA-Q orally, once daily with a meal in the morning.
Take TRIVESTA-Q 10 mg/5 mg/1000 mg or TRIVESTA-Q 25 mg/5 mg/1000 mg as a single tablet once daily.

Dosage Recommendations In Patients With Renal Impairment
No dose adjustment is needed in patients with an estimated glomerular filtration rate (eGFR) greater than or equal to 45 mL/min/1.73 m^2.
TRIVESTA-Q should not be initiated or continued in patients with an eGFR less than 45 mL/min/1.73 m^2.
TRIVESTA-Q is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2

Discontinuation For Iodinated Contrast Imaging Procedures
Discontinue TRIVESTA-Q at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart TRIVESTA-Q if renal function is stable.

Method of administration:
Swallow TRIVESTA-Q tablets whole. Do not split, crush, dissolve, or chew.

4.3 Contraindications
TRIVESTA-Q is contraindicated in patients with:
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end-stage renal disease, or dialysis.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis.
- Hypersensitivity to empagliflozin, linagliptin, metformin or any of the excipients in TRIVESTA-Q, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred.

4.4 Special warnings and precautions for use Lactic Acidosis
There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension, and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5

mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate:pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels, which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of TRIVESTA-Q. In TRIVESTA-Q-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue TRIVESTA-Q and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment
The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of TRIVESTA-Q with specific drugs may increase the risk of metformin- associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation. Therefore, consider more frequent monitoring of patients.

Age 65 Or Greater
The risk of metformin-associated lactic acidosis increases with the patients age because elderly patients have a greater likelihood of having

hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Radiological Studies With Contrast

Administration of intravascular iodinated contrast agents in metformintreated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop TRIVESTA-Q at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart TRIVESTA-Q if renal function is stable.

Surgery And Other Procedures

Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. TRIVESTA-Q should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States

Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue TRIVESTA-Q.

Excessive Alcohol Intake

Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving TRIVESTA-Q.

Hepatic Impairment

Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of TRIVESTA-Q in patients with clinical or laboratory evidence of hepatic disease.

Pancreatitis

Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. In the CARMELINA trial [see Clinical Studies], acute pancreatitis was reported in 9 (0.3%) patients treated with linagliptin and in 5 (0.1%) patients treated with placebo. Two patients treated with linagliptin in the CARMELINA trial had acute pancreatitis with a fatal outcome. There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients treated with linagliptin.

Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue TRIVESTA-Q and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using TRIVESTA-Q.

Heart Failure
An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of TRIVESTA-Q prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of TRIVESTA-Q.

Hypotension
Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating TRIVESTA-Q, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected.

Ketoacidosis
Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing

surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. TRIVESTA-Q is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with TRIVESTA-Q who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with TRIVESTA-Q may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, TRIVESTA-Q should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating TRIVESTA-Q, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing TRIVESTA-Q for at least 3 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing TRIVESTA-Q in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting TRIVESTA-Q.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue TRIVESTA-Q and seek medical attention immediately if signs and symptoms occur.

Acute Kidney Injury

Empagliflozin causes intravascular volume contraction and can cause renal impairment. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including empagliflozin; some reports involved patients younger than 65 years of age.

Before initiating TRIVESTA-Q, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal impairment, heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing TRIVESTA-Q in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue TRIVESTA-Q promptly and institute treatment.

Empagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating TRIVESTA-Q.Renal function should be evaluated prior to initiation of TRIVESTA-Q and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2. Use of TRIVESTA-Q is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.

Urosepsis And Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections.

Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia With Concomitant Use With Insulin And Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The use of empagliflozin or linagliptin in combination with an insulin

secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial.
Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with TRIVESTA-Q.

Necrotizing Fasciitis Of The Perineum (Fourniers Gangrene)
Reports of necrotizing fasciitis of the perineum (Fourniers gangrene), a rare but serious and life- threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with TRIVESTA-Q presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, ifnecessary, surgical debridement. Discontinue TRIVESTA-Q, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections
Empagliflozin increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop genital mycotic infections.
Monitor and treat as appropriate.

Hypersensitivity Reactions
There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin (one of the components of TRIVESTA-Q). These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with TRIVESTA-Q.

There have been postmarketing reports of serious hypersensitivity reactions (e.g., angioedema) in patients treated with empagliflozin (one of the components of TRIVESTA-Q).

If a hypersensitivity reaction occurs, discontinue TRIVESTA-Q, treat promptly per standard of care, and monitor until signs and symptoms resolve. TRIVESTA-Q is contraindicated in patients with a previous serious hypersensitivity reaction to linagliptin or empagliflozin.

Vitamin B12 Deficiency

In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 at 2 to 3 year intervals in patients on TRIVESTA-Q and manage any abnormalities.

Severe And Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP- 4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid

Bullous pemphigoid was reported in 7 (0.2%) patients treated with linagliptin compared to none in patients treated with placebo in the CARMELINA trial, and 3 of these patients were hospitalized due to bullous pemphigoid. Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving TRIVESTA-Q. If bullous pemphigoid is suspected, TRIVESTA-

Q should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Advise pregnant women, and females of reproductive potential, of the potential risk to a fetus with treatment with TRIVESTA-Q. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.

Breast-feeding

Advise women that breastfeeding is not recommended during treatment with TRIVESTA-Q.

Females And Males Of Reproductive Potential

Inform females that treatment with metformin may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy.

4.7 Effects on ability to drive and use machines

Trivesta-Q has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The following important adverse reactions are described below and elsewhere in the labeling:

- Lactic Acidosis
- Pancreatitis Heart Failure
- Hypotension
- Ketoacidosis
- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Genital Mycotic Infections
- Hypersensitivity Reactions
- Vitamin B12 Deficiency
- Severe and Disabling Arthralgia
- Bullous Pemphigoid

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Empagliflozin, Linagliptin And Metformin

The safety of concomitantly administered empagliflozin (daily dose 10 mg or 25 mg), linagliptin (daily dose 5 mg) and metformin has been evaluated in a total of 686 patients with type 2 diabetes treated for up to 52 weeks in an active-controlled clinical trial. The most common adverse reactions are shown in Table 1.

Table 1 : Adverse Reactions Reported in ≥5% of Patients Treated with Empagliflozin, Linagliptin, and Metformin in an Active-Controlled Clinical Trial of 52 Weeks

	Empagliflozin 10 mg + Linagliptin 5 mg + Metformin n=136	**Empagliflozin 25 mg + Linagliptin 5 mg + Metformin n=137**
Upper respiratory tract infection	10.3%	8.0%
Urinary tract infection[a]	9.6%	10.2%
Nasopharyngitis	8.1%	5.8%
Diarrhea	6.6%	2.2%
Constipation	5.1%	5.8%
Headache	5.1%	5.1%
Gastroenteritis	2.9%	5.8%

[a]Predefined grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis

Hypoglycemia

The incidence of hypoglycemia (defined as plasma or capillary glucose of less than 54 mg/dL) was 0.7% in patients receiving empagliflozin 10 mg/linagliptin 5 mg/metformin and 0.7% in patients receiving empagliflozin 25 mg/linagliptin 5 mg/metformin. Events of severe

hypoglycemia (requiring assistance regardless of blood glucose) did not occur in this trial.

Empagliflozin

Adverse reactions that occurred in ≥2% of patients receiving empagliflozin and more commonly than in patients given placebo included (10 mg, 25 mg, and placebo): urinary tract infection (9.3%, 7.6%, and 7.6%), female genital mycotic infections (5.4%, 6.4%, and 1.5%), upper respiratory tract
infection (3.1%, 4.0%, and 3.8%), increased urination (3.4%, 3.2%, and 1.0%), dyslipidemia (3.9%,
2.9%, and 3.4%), arthralgia (2.4%, 2.3%, and 2.2%), male genital mycotic infections (3.1%, 1.6%,
and 0.4%), and nausea (2.3%, 1.1%, and 1.4%).

Thirst (including polydipsia) was reported in 0%, 1.7%, and 1.5% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Empagliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. Events related to volume depletion (hypotension and syncope) were reported in 3 patients (1.1%) treated with empagliflozin, linagliptin and metformin combination therapy.

Linagliptin

Adverse reactions reported in ≥2% of patients treated with linagliptin 5 mg and more commonly than in patients treated with placebo, included: nasopharyngitis (7.0% and 6.1%), diarrhea (3.3% and 3.0%), and cough (2.1% and 1.4%).

Other adverse reactions reported in clinical studies with treatment of linagliptin monotherapy were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity) and myalgia.

In the clinical trial program, pancreatitis was reported in 15.2 cases per 10,000 patient-year exposure while being treated with linagliptin, compared with 3.7 cases per 10,000 patient-year exposure while being treated with comparator (placebo and active comparator, sulfonylurea). Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

Metformin

The most common (>5%) established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache. In a 24-week clinical trial in which extended-release metformin or placebo was

added to glyburide therapy, the most common (>5% and greater than placebo) adverse reactions in the combined treatment group were hypoglycemia (13.7% vs 4.9%), diarrhea (12.5% vs 5.6%), and nausea (6.7% vs 4.2%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

In the event of an overdose with TRIVESTA-Q, contact the Poison Control Center.

Overdose of metformin HCl has occurred, including ingestion of amounts greater than 50 grams. Lactic acidosis has been reported in approximately 32% of metformin overdose cases.

Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected. Removal of empagliflozin by hemodialysis has not been studied, and removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely.

5.Pharmacological properties

5.1 Pharmacodynamic properties

Empagliflozin

Urinary Glucose Excretion

In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily. Data from single oral doses of empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.

Urinary Volume
In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

Cardiac Electrophysiology
In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

Linagliptin
Linagliptin binds to DPP-4 in a reversible manner and increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion, thus resulting in a better regulation of the glucose homeostasis. Linagliptin binds selectively to DPP-4 and selectively inhibits DPP-4, but not DPP-8 or DPP-9 activity in vitro at concentrations approximating therapeutic exposures.

Cardiac Electrophysiology
In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100-mg dose. At the 100-mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5-mg dose.

Pharmacokinetic properties

Administration of TRIVESTA-Q with food resulted in no change in overall exposure of empagliflozin or linagliptin. For metformin extended-release, high-fat meals increased systemic exposure (as measured by area-under-the-curve [AUC]) by approximately 70% relative to fasting, while Cmax is not affected. Meals prolonged Tmax by approximately 3 hours.
Empagliflozin Absorption

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady-state mean plasma AUC and Cmax were 1870 nmolÂ·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmolÂ·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose- proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

Distribution

The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [14C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Elimination

The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis.

Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life.

Metabolism

No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. In vitro studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Excretion

Following administration of an oral [14C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity

was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent

drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Linagliptin Absorption

The absolute bioavailability of linagliptin is approximately 30%. A high-fat meal reduced Cmax by 15% and increased AUC by 4%; this effect is not clinically relevant. Linagliptin may be administered with or without food.

Distribution

The mean apparent volume of distribution at steady-state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1110 L, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75% to 89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Elimination

Linagliptin has a terminal half-life of about 200 hours at steady-state, though the accumulation half-life is about 11 hours. Renal clearance at steady-state was approximately 70 mL/min.

Metabolism

Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

Excretion

Following administration of an oral [14C]-linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing.

Metformin HCl Absorption

Following a single oral dose of 1000 mg (2 x 500 mg tablets) metformin HCl extended-release after a meal, the time to reach maximum plasma metformin concentration (Tmax) is achieved at approximately 7 to 8 hours. In both single-and multiple-dose studies in healthy subjects, once daily 1000 mg (2 x 500 mg tablets) dosing provides equivalent

systemic exposure, as measured by AUC, and up to 35% higher Cmax of metformin relative to the immediate-release given as 500 mg twice daily.
Single oral doses of metformin HCl extended-release from 500 mg to 2500 mg resulted in less than proportional increase in both AUC and Cmax. Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from metformin extended-release tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin Tmax by approximately 3 hours but Cmax, was not affected.

Distribution
The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin HCl tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

Elimination
Metformin has a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Metabolism
Intravenous single-dose studies in normal subjects demonstrate that metformin does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion
Following oral administration, approximately 90% of the absorbed drug is excreted via the renal route within the first 24 hours. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination.

5.2 Preclinical safety data

Empagliflozin And Linagliptin Add-On Combination Therapy With Metformin For Glycemic Control

A total of 686 patients with type 2 diabetes participated in a double-blind, active-controlled study to evaluate the efficacy and safety of empagliflozin 10 mg or 25 mg in combination with linagliptin 5 mg, compared to the individual components.

Patients with type 2 diabetes inadequately controlled on at least 1500 mg of metformin per day entered a single-blind placebo run-in period for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7 and 10.5% were randomized 1:1:1:1:1 to one of 5 active-treatment arms of empagliflozin 10 mg or 25 mg, linagliptin 5 mg, or linagliptin 5 mg in combination with 10 mg or 25 mg empagliflozin as a fixed dose combination tablet.
At Week 24, empagliflozin 10 mg or 25 mg used in combination with linagliptin 5 mg provided statistically significant improvement in HbA1c (p-value <0.0001) and FPG (p-value <0.001)

compared to the individual components in patients who had been inadequately controlled on metformin (see Table 7, Figure 3). Treatment with empagliflozin 10 mg or 25 mg used in combination with linagliptin 5 mg also resulted in a statistically significant reduction in body weight compared to linagliptin 5 mg (p-value <0.0001). There was no statistically significant difference compared to empagliflozin alone.

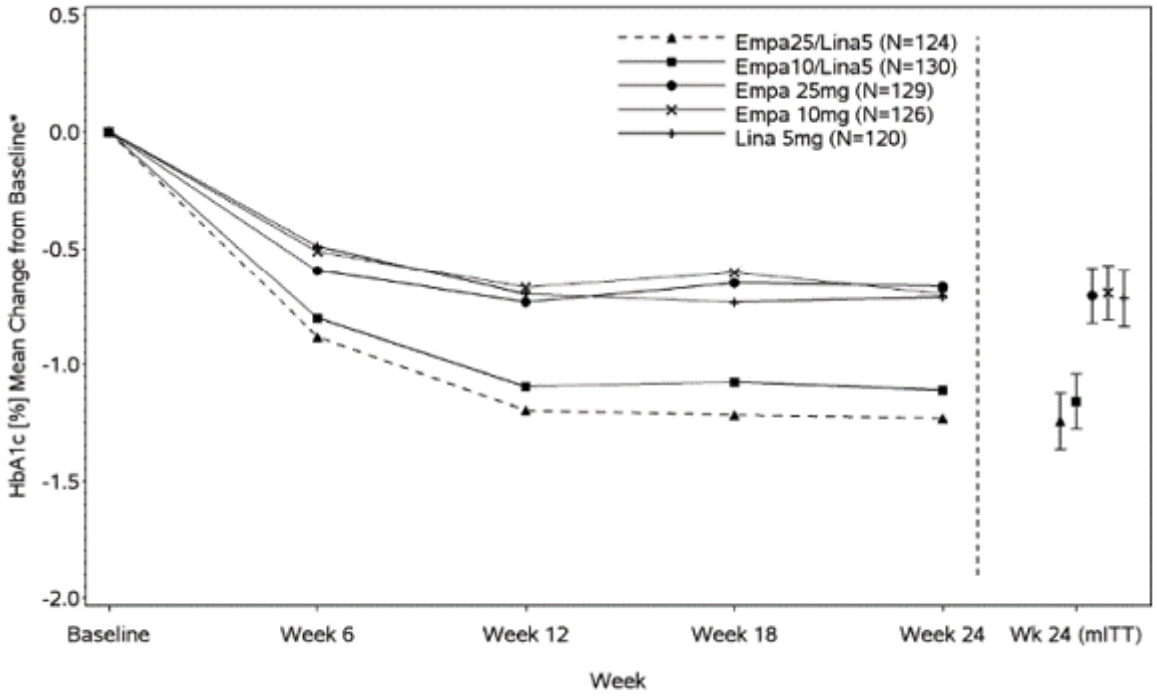
Table 7 : Glycemic Parameters at 24 Weeks in a Study Comparing Empagliflozin in Combination with Linagliptin to the Individual Components as Add-on Therapy in Patients Inadequately Controlled on Metformin

	Empagliflozin 10 mg/ Linagliptin 5 mg	**Empagliflozin 25 mg/ Linagliptin 5 mg**	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Linagliptin 5 mg**
HbA1c (%)					
Number of patients	n=135	n=133	n=137	n=139	n=128
Baseline (mean)	8.0	7.9	8.0	8.0	8.0
Change from baseline (adjusted mean)	-1.1	-1.2	-0.7	-0.6	-0.7
Comparison vs empagliflozin 25 mg or 10 mg (adjusted mean) (95% CI)[a]	-0.4 (-0.6, 0.2)[d]	-0.6 (-0.7,-0.4)[d]	--	--	--

Comparison vs linagliptin 5 mg (adjusted mean) (95% CI)[a]	-0.4 (-0.6, 0.2)[d]	-0.5(-0.7, -0.3)[d]	--	--	--
Patients [n (%)] achieving HbA1c <7%[b]	74 (58)	76 (62)	35 (28)	43 (33)	43 (36)
FPG (mg/dL)					
Number of patients	n=133	n=131	n=136	n=137	n=125
Baseline (mean)	157	155	162	160	156
Change from baseline (adjusted mean)	-33	-36	-21	-21	-13
Comparison vs empagliflozin 25 mg or 10 mg (adjusted mean) (95% CI)[a]	-12 (-18, -5)[d]	-15 (-22, -9)[d]	--	--	--
Comparison vs linagliptin 5 mg (adjusted mean) (95% CI)[a]	-20 (-27, -13)[d]	-23 (-29, -16)[d]	--	--	--
Body Weight					
Number of patients	n=135	n=134	7 3 15	n=140	n=128
Baseline (mean) in kg	87	85	86	88	85
% change from baseline (adjusted mean)	-3.1	-3.4	-3.0	-3.5	-0.7
Comparison vs empagliflozin 25 mg or 10 mg (adjusted mean) (95% CI)[c]	0.0 (-0.9, 0.8)	0.1 (-0.8, 0.9)	--	--	--
Comparison vs linagliptin 5 mg (adjusted mean) (95% CI)[c]	-2.4 (-3.3, -1.5)[d]	-2.7 (-3.6, -1.8)[d]		--	--

[a]Full analysis population (observed case) using MMRM. MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c.
[b]Patients with HbA1c above 7% at baseline: empagliflozin 25 mg/linagliptin 5 mg, n=123; empagliflozin 10 mg/linagliptin 5 mg, n=128; empagliflozin 25 mg, n=132; empagliflozin 10 mg, n=125; linagliptin 5 mg, n=119. Non-completers were considered failures (NCF).
[c]Full analysis population using last observation carried forward. ANCOVA model included treatment, renal function, region, baseline weight, and baseline HbA1c.
[d]p<0.001 for FPG; p<0.0001 for HbA1c and body weight

Figure 3 : Adjusted Mean HbA1c Change at Each Time Point (Completers) and at Week 24 (mITT population)



*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline.

Empagliflozin Cardiovascular Outcome Study In Patients With Type 2 Diabetes Mellitus And Atherosclerotic Cardiovascular Disease

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. The effect of empagliflozin on cardiovascular risk in adult patients with type 2 diabetes and established, stable, atherosclerotic cardiovascular disease is presented below.

The EMPA-REG OUTCOME study, a multicenter, multi-national, randomized, double-blind parallel group trial compared the risk of experiencing a major adverse cardiovascular event (MACE) between empagliflozin and placebo when these were added to and used

concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease.

Coadministered antidiabetic medications were to be kept stable for the first 12 weeks of the trial. Thereafter, antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

A total of 7020 patients were treated (empagliflozin 10 mg = 2345; empagliflozin 25 mg = 2342; placebo = 2333) and followed for a median of 3.1 years. Approximately 72% of the study population was Caucasian, 22% was Asian, and 5% was Black. The mean age was 63 years and approximately 72% were male.

All patients in the study had inadequately controlled type 2 diabetes mellitus at baseline (HbA1c greater than or equal to 7%). The mean HbA1c at baseline was 8.1% and 57% of participants had diabetes for more than 10 years. Approximately 31%, 22% and 20% reported a past historyof neuropathy, retinopathy and nephropathy to investigators respectively and the mean eGFR was 74 mL/min/1.73 m^2. At baseline, patients were treated with one (~30%) or more (~70%) antidiabetic medications including metformin (74%), insulin (48%), sulfonylurea (43%) and dipeptidyl peptidase-4 inhibitor (11%).

All patients had established atherosclerotic cardiovascular disease at baseline including one (82%) or more (18%) of the following: a documented history of coronary artery disease (76%), stroke (23%) or peripheral artery disease (21%). At baseline, the mean systolic blood pressure was 136 mmHg, the mean diastolic blood pressure was 76 mmHg, the mean LDL was 86 mg/dL, the mean HDL was 44 mg/dL, and the mean urinary albumin to creatinine ratio (UACR) was 175 mg/g. At baseline, approximately 81% of patients were treated with renin angiotensin system inhibitors, 65% with beta-blockers, 43% with diuretics, 77% with statins, and 86% with antiplatelet agents (mostly aspirin).

The primary endpoint in EMPA-REG OUTCOME was the time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event was defined as occurrence of either a cardiovascular death or a nonfatal myocardial infarction (MI) or a nonfatal stroke. The statistical analysis plan had pre-specified that the 10 and 25 mg doses would be combined. A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE and superiority on MACE if non-inferiority was demonstrated.

Type-1 error was controlled across multiples tests using a hierarchical testing strategy.

Empagliflozin significantly reduced the risk of first occurrence of primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (HR: 0.86; 95% CI 0.74, 0.99). The treatment effect was due to a significant reduction in the risk of cardiovascular death in subjects randomized to empagliflozin (HR: 0.62; 95% CI 0.49, 0.77), with no change in the risk of non-fatal myocardial infarction or non-fatal stroke (see Table 8 and Figure 4 and 5).

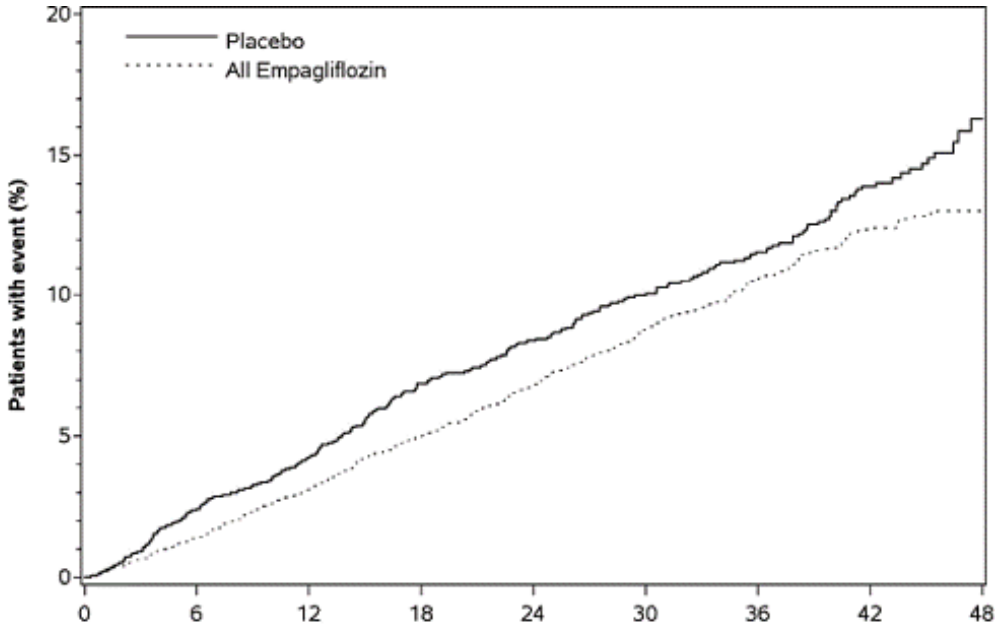
Results for the 10 mg and 25 mg empagliflozin doses were consistent with results for the combined dose groups.

Table 8 : Treatment Effect for the Primary Composite Endpoint, and its Components[a]

	Placebo N=2333	**Empagliflozin N=4687**	**Hazard ratio vs placebo (95% CI)**
Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence)[b]	282 (12.1%)	490 (10.5%)	0.86 (0.74, 0.99)
Non-fatal myocardial infarction[c]	121 (5.2%)	213 (4.5%)	0.87 (0.70, 1.09)
Non-fatal stroke[c]	60 (2.6%)	150 (3.2%)	1.24 (0.92, 1.67)
Cardiovascular death[c]	137 (5.9%)	172 (3.7%)	0.62 (0.49, 0.77)

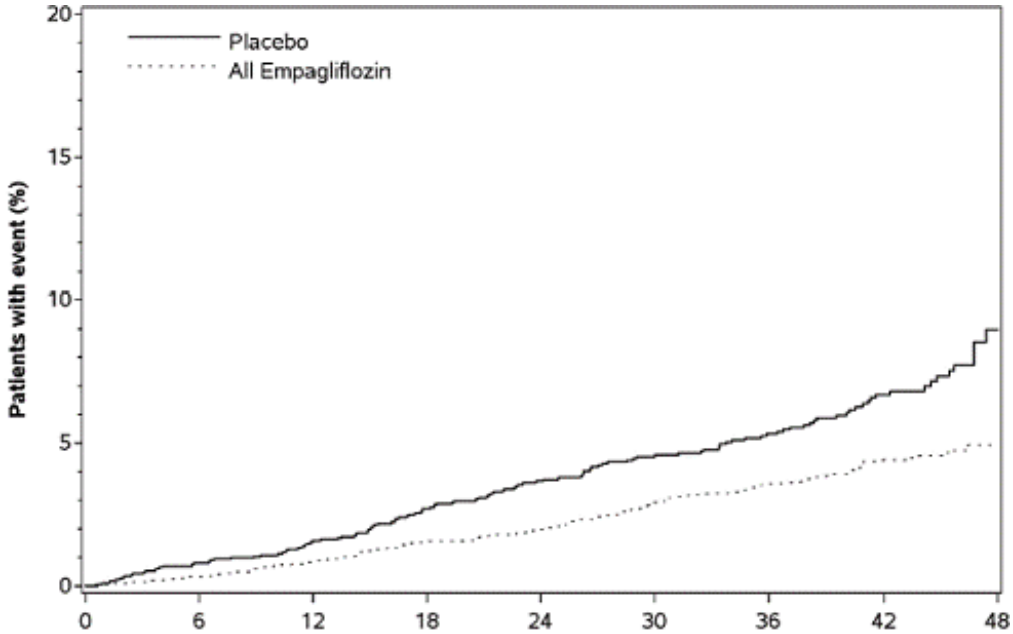
[a]Treated set (patients who had received at least one dose of study drug)
[b]p-value for superiority (2-sided) 0.04
[c] Total number of events

Figure 4 : Estimated Cumulative Incidence of First MACE



Subjects at risk									
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166
All Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370

Figure 5 : Estimated Cumulative Incidence of Cardiovascular Death



Subjects at risk									
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177
All Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414

The efficacy of empagliflozin on cardiovascular death was generally consistent across major demographic and disease subgroups.

Vital status was obtained for 99.2% of subjects in the trial. A total of 463 deaths were recorded during the EMPA-REG OUTCOME trial. Most of these deaths were categorized as cardiovascular deaths. The non-cardiovascular deaths were only a small proportion of deaths, and were balanced between the treatment groups (2.1% in patients treated with empagliflozin, and 2.4% of patients treated with placebo).

Linagliptin Cardiovascular Safety Trial

The cardiovascular risk of linagliptin was evaluated in CARMELINA (NCT0189753), a multi- national, multi-center, placebo-controlled, double-blind, parallel group trial comparing linagliptin (N=3494) to placebo (N=3485) in adult patients with type 2 diabetes mellitus and a history of established macrovascular and/or renal disease. The trial compared the risk of major adverse cardiovascular events (MACE) between linagliptin and placebo when these were added to standard of care treatments for diabetes and other cardiovascular risk factors. The trial was event driven, the median duration of follow-up was 2.2 years and vital status was obtained for 99.7% of patients.

Patients were eligible to enter the trial if they were adults with type 2 diabetes, with HbA1c of 6.5% to 10%, and had either albuminuria and previous macrovascular disease (39% of enrolled population), or evidence of impaired renal function by eGFR and Urinary Albumin Creatinine Ratio (UACR) criteria (42% of enrolled population), or both (18% of enrolled population).

At baseline the mean age was 66 years and the population was 63% male, 80% Caucasian, 9% Asian, and 6% Black. Mean HbA1c was 8.0% and mean duration of type 2 diabetes mellitus was 15 years. The trial population included 17% patients ≥75 years of age and 62% patients with renal impairment defined as eGFR <60 mL/min/1.73 m². The mean eGFR was 55 mL/min/1.73 m² and 27% of patients had mild renal impairment (eGFR 60 to 90 mL/min/1.73 m²), 47% of patients had moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m²) and 15% of patients had severe renal impairment (eGFR <30 mL/min/1.73 m²). Patients were taking at least one antidiabetic drug (97%), and the most common were insulin and analogues (57%), metformin (54%) and sulfonylurea (32%). Patients were also taking antihypertensives (96%), lipid lowering drugs (76%) with 72% on statin, and aspirin (62%).

The primary endpoint, MACE, was the time to first occurrence of one of three composite outcomes which included cardiovascular death, nonfatal myocardial infarction or nonfatal stroke. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE. The incidence rate of MACE in both treatment arms: 56.3 MACE per 1000 patient-years on placebo vs. 57.7 MACE per 1000 patient-years on linagliptin. The estimated hazard ratio for MACE associated with linagliptin relative to placebo was 1.02 with a 95% confidence interval of (0.89, 1.17). The upper bound of this confidence interval, 1.17, excluded the risk margin of 1.3.

6. Pharmaceutical particulars

6.1 List of excipients

Methocel K100M
Polyox N60K
Magnesium stearate
Hydroxypropyl methyl cellulose ES
Isopropyl alcohol
PEG 8000
L-arginine
Methanol
R/O Water
Tabcoat Green

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30˚C. Keep in a dry place.

6.5 Nature and contents of the container

Unit Carton containing 4 blister strips of 7 tablets each with printed Alu Alu on one side and Alu Foil on the other side.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

Company) Name: Wilshire Laboratories (Pvt) Ltd
Address: 124/1-Industrial Estate. Kot Lakh pat, Lahore,
Country: Pakistan
Telephone: +92-42-35121668-9, 35116579-35116685
Telefax: +92-42-35151721

Manufacturing site address:
WILSHIRE LABORATORIES (PVT) LTD, 124/1-Industrial Estate. Kot Lakhpat, Lahore, Pakistan

Local Technical Representative:
Cintana Healthcare, Nyangumi Road, Kilimani, P.O. BOX 4521400100, Nairobi, Kenya.

8. Marketing authorization number(s)
CTD10694

9. Date of first authorization/renewal of the authorization
8/03/2024

10. Date of revision of the text
November 2024

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable