TRAJENTA

Linagliptin 5 mg

FILM COATED TABLETS

PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Trajenta

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is linagliptin 5 mg.

For the full list of excipients, see section "DESCRIPTION" below.

3. PHARMACEUTICAL FORM

Film coated tablets.

4. INDICATIONS AND USAGE

TRAJENTA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use

TRAJENTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

TRAJENTA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using TRAJENTA *[see Warnings and Precautions (8.1)]*.

5. DOSAGE AND ADMINISTRATION

5.1. Recommended Dosage and Administration

The recommended dosage of TRAJENTA is 5 mg taken orally once daily, with or without food.

6. DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, light red, round, biconvex, bevel-edged, film-coated tablets with “D5” debossed on one side and the Boehringer Ingelheim symbol debossed on the other side.

7. CONTRAINDICATIONS

TRAJENTA is contraindicated in patients with hypersensitivity to linagliptin or any of the excipients in Trajenta listed in section 13, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred *[see Warnings and Precautions (8.3) and Adverse Reactions (9)]*.

8. WARNINGS AND PRECAUTIONS

8.1. Pancreatitis

Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with TRAJENTA. In the CARMELINA trial *[see Clinical Studies (16)]*, acute pancreatitis was reported in 9 (0.3%) patients treated with TRAJENTA and in 5 (0.1%) patients treated with placebo. Two patients treated with TRAJENTA 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 TRAJENTA. Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue TRAJENTA 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 TRAJENTA.

8.2. Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin secretagogues and insulin are known to cause hypoglycemia. The risk of hypoglycemia is increased when TRAJENTA is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin *[see Adverse Reactions (9.1)]*. The use of TRAJENTA in combination with insulin in subjects with severe renal impairment was associated with a higher rate of hypoglycemia *[see Adverse Reactions (9.1)]*. Therefore, a lower dosage of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with TRAJENTA.

8.3. Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with TRAJENTA. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred predominantly within the first 3 months after initiation of treatment with TRAJENTA, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue TRAJENTA, assess for other potential causes for the event, and institute alternative treatment for diabetes mellitus.

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 TRAJENTA.

8.4. Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking Trajenta [see Adverse Reactions (9)]. 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 the drug as a possible cause for severe joint pain and discontinue drug if appropriate.

8.5. Bullous Pemphigoid

Bullous pemphigoid was reported in 7 (0.2%) patients treated with TRAJENTA compared to none in patients treated with placebo in the CARMELINA trial *[see Clinical Studies (16)]*, 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 TRAJENTA. If bullous pemphigoid is suspected, TRAJENTA should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

8.6. 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 TRAJENTA 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 TRAJENTA.

9. ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Pancreatitis *[see Warnings and Precautions (8.1)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (8.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (8.3)]*
- Severe and Disabling Arthralgia *[see Warnings and Precautions (8.4)]*
- Bullous Pemphigoid *[see Warnings and Precautions (8.5)]*
- Heart Failure [see Warnings and Precautions (8.6)]

9.1. 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.

The safety evaluation of TRAJENTA 5 mg once daily in patients with type 2 diabetes mellitus is based on 14 placebo-controlled trials, 1 active-controlled trial, and one trial in patients with severe renal impairment. In the 14 placebo-controlled studies, a total of 3,625 patients were randomized and treated with TRAJENTA 5 mg daily and 2,176 with placebo. The mean exposure in patients treated with TRAJENTA across studies was 29.6 weeks. The maximum follow-up was 78 weeks.

TRAJENTA 5 mg once daily was studied as monotherapy in three placebo-controlled trials of 18 and 24 weeks' duration and in five additional placebo-controlled studies lasting ≤18 weeks. The use of TRAJENTA in combination with other antihyperglycemic agents was studied in six placebo-controlled trials: two with metformin (12 and 24 weeks' treatment duration); one with a sulfonylurea (18 weeks' treatment duration); one with metformin and sulfonylurea (24 weeks' treatment duration); one with pioglitazone (24 weeks' treatment duration); and one with insulin (primary endpoint at 24 weeks).

In a pooled dataset of 14 placebo-controlled clinical trials, adverse reactions that occurred in ≥2% of patients receiving TRAJENTA (n = 3,625) and more commonly than in patients given placebo (n = 2,176), are shown in Table 1.

Table 1 Adverse Reactions Reported in ≥2% of Patients Treated with TRAJENTA and Greater than Placebo in Placebo-Controlled Clinical Studies of TRAJENTA Monotherapy or Combination Therapy

Adverse Reactions	**TRAJENTA 5mg (%) n = 3,625**	**Placebo (%) n = 2,176**
Nasopharyngitis	7.0	6.1
Diarrhea	3.3	3.0
Cough	2.1	1.4

Rates for other adverse reactions for TRAJENTA 5 mg vs placebo when TRAJENTA was used in combination with specific antidiabetic agents were: urinary tract infection (3.1% vs 0%) and hypertriglyceridemia (2.4% vs 0%) when TRAJENTA was used as add-on to sulfonylurea; hyperlipidemia (2.7% vs 0.8%) and weight increased (2.3% vs 0.8%) when TRAJENTA was used as add-on to pioglitazone; and constipation (2.1% vs 1%) when TRAJENTA was used as add-on to basal insulin therapy. Other adverse reactions reported in clinical studies with treatment of TRAJENTA were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity) and myalgia.

Following 104 weeks' treatment in a controlled trial comparing TRAJENTA with glimepiride in which all patients were also receiving metformin, adverse reactions reported in ≥5% of patients treated with TRAJENTA (n = 776) and more frequently than in patients treated with a sulfonylurea (n = 775) were back pain (9.1% vs 8.4%), arthralgia (8.1% vs 6.1%), upper respiratory tract infection (8.0% vs 7.6%), headache (6.4% vs 5.2%), cough (6.1% vs 4.9%), and pain in extremity (5.3% vs 3.9%).

In the clinical trial program, pancreatitis was reported in 15.2 cases per 10,000 patient year exposure while being treated with TRAJENTA 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.

Other Adverse Reactions

Hypoglycemia

Table 2 summarizes the incidence of hypoglycemia in placebo-controlled studies of TRAJENTA. The incidence of hypoglycemia increased when TRAJENTA was administered with sulfonylurea or insulin.

Table 2 Incidence (%) of Hypoglycemia in Placebo-Controlled Clinical Studies of TRAJENTA in Patients with Type 2 Diabetes Mellitus

Add-on to Sulfonylurea (18 Weeks)	**Placebo (N=84)**	**TRAJENTA (N=161)**
Hypoglycemia with plasma glucose <54 mg/dL (%)	1.2	1.9
Severe* hypoglycemia (%)	0	0
Add-on to Metformin and Sulfonylurea (24 Weeks)	**Placebo (N=263)**	**TRAJENTA (N=792)**
Hypoglycemia with plasma glucose <54 mg/dL (%)	5.3	8.1
Severe* hypoglycemia (%)	0.8	0.6
Add-on to Basal Insulin (52 Weeks)	**Placebo (N=630)**	**TRAJENTA (N=631)**
Hypoglycemia with plasma glucose <54 mg/dL (%)	21.6	19.8
Severe* hypoglycemia (%)	1.1	1.7

*Hypoglycemia requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

In an active-controlled (glimepiride) cardiovascular safety trial with TRAJENTA (CAROLINA) with median time on treatment of 5.9 years, the incidence of severe hypoglycemia was 0.3% in the TRAJENTA group (N=3,014) and 2.2% in glimepiride group (N=3,000).

Use in Renal Impairment

TRAJENTA was compared to placebo as add-on to pre-existing antidiabetic therapy over 52 weeks in 133 patients with severe renal impairment (estimated GFR <30 mL/min). For the initial 12 weeks of the trial, background antidiabetic therapy was kept stable and included insulin, sulfonylurea, glinides, and pioglitazone. For the remainder of the trial, dosage adjustments in antidiabetic background therapy were allowed.

In general, the incidence of adverse events including severe hypoglycemia was similar to those reported in other TRAJENTA trials. The observed incidence of hypoglycemia was higher (TRAJENTA, 63% compared to placebo, 49%) due to an increase in asymptomatic hypoglycemic events especially during the first 12 weeks when background glycemic therapies were kept stable. Ten TRAJENTA-treated patients (15%) and 11 placebo-treated patients (17%) reported at least one episode of confirmed symptomatic hypoglycemia (accompanying finger stick glucose ≤54 mg/dL). During the same time period, severe hypoglycemic events, defined as an event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions, were reported in 3 (4.4%) TRAJENTA-treated patients and 3 (4.6%) placebo-treated patients. Events that were considered life-threatening or required hospitalization were reported in 2 (2.9%) patients on TRAJENTA and 1 (1.5%) patient on placebo. Renal function as measured by mean eGFR and creatinine clearance did not change over 52 weeks' treatment compared to placebo.

Laboratory Test Abnormalities in Clinical Trials

Changes in laboratory findings were similar in patients treated with TRAJENTA 5 mg compared to patients treated with placebo.

Increase in Uric Acid: Changes in laboratory values that occurred more frequently in the TRAJENTA group and ≥1% more than in the placebo group were increases in uric acid (1.3% in the placebo group, 2.7% in the TRAJENTA group).

Increase in Lipase: In a placebo-controlled clinical trial with TRAJENTA in type 2 diabetes mellitus patients with micro- or macroalbuminuria, a mean increase of 30% in lipase concentrations from baseline to 24 weeks was observed in the TRAJENTA arm compared to a mean decrease of 2% in the placebo arm. Lipase levels above 3 times upper limit of normal were seen in 8.2% compared to 1.7% patients in the TRAJENTA and placebo arms, respectively.

Increase in Amylase: In a cardiovascular safety trial comparing TRAJENTA versus glimepiride in patients with type 2 diabetes mellitus, amylase levels above 3 times upper limit of normal were seen in 1.0% compared to 0.5% of patients in the TRAJENTA and glimepiride arms, respectively.

The clinical significance of elevations in lipase and amylase with TRAJENTA is unknown in the absence of potential signs and symptoms of pancreatitis *[see Warnings and Precautions (8.1)]*.

Vital Signs

No clinically meaningful changes in vital signs were observed in patients treated with TRAJENTA.

9.2. Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of **TRAJENTA**. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Gastrointestinal Disorders: Acute pancreatitis, including fatal pancreatitis *[see Indications and Usage (4)]*, mouth ulceration, stomatitis
- Immune System Disorders: Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions
- Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis, severe and disabling arthralgia
- Skin and Subcutaneous Tissue Disorders: Bullous pemphigoid, rash

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il/

10. DRUG INTERACTIONS

10.1 Inducers of P-glycoprotein or CYP3A4 Enzymes

Rifampin decreased linagliptin exposure, suggesting that the efficacy of TRAJENTA may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer *[see Clinical Pharmacology (14.3)]*.

10.2 Insulin Secretagogues or Insulin

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when linagliptin is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin. Coadministration of TRAJENTA with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower dosages of the insulin secretagogue or insulin to reduce the risk of hypoglycemia [see Warnings and Precautions (8.2)].

11. USE IN SPECIFIC POPULATIONS

11.1. Pregnancy

Risk Summary

The limited data with TRAJENTA use in pregnant women are not sufficient to inform of drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In animal reproduction studies, no adverse developmental effects were observed when linagliptin was administered to pregnant rats during the period of organogenesis at doses similar to the maximum recommended clinical dose, based on exposure *[see Data]*.

The estimated background risk of major birth defects is 6% to-10% in women with pre-gestational diabetes with a HbA1c>7 and has been reported to be as high as 20% to 25% in women with HbA1c>10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

No adverse developmental outcome was observed when linagliptin was administered to pregnant Wistar Han rats and Himalayan rabbits during the period of organogenesis at doses up to 240 mg/kg/day and 150 mg/kg/day, respectively. These doses represent approximately 943 times (rats) and 1,943 times (rabbits) the 5 mg maximum clinical dose, based on exposure. No adverse functional, behavioral, or reproductive outcome was observed in offspring following administration of linagliptin to Wistar Han rats from gestation day 6 to lactation day 21 at a dose 49 times the maximum recommended human dose, based on exposure.

Linagliptin crosses the placenta into the fetus following oral dosing in pregnant rats and rabbits.

11.2. Lactation

Risk Summary

There is no information regarding the presence of linagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. However, linagliptin is present in rat milk. Therefore, the developmental and health

benefits of breastfeeding should be considered along with the mother's clinical need for TRAJENTA and any potential adverse effects on the breastfed child from TRAJENTA or from the underlying maternal condition.

11.3. Pediatric Use

The safety and effectiveness of TRAJENTA have not been established in pediatric patients under 18 years of age.

Effectiveness of TRAJENTA was not demonstrated in a 26-week randomized, double-blind, placebo-controlled trial (NCT03429543) in 157 pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus.

11.4. Geriatric Use

In linagliptin studies, 1,085 linagliptin-treated patients were 65 years of age and older and 131 patients were 75 years of age and older. In these linagliptin studies, no overall differences in safety or effectiveness of linagliptin were observed between geriatric patients and younger adult patients.

11.5. Renal Impairment

No dosage adjustment is recommended for patients with renal impairment *[see Clinical Pharmacology (14.3)]*.
In the TRAJENTA treatment arm of the CARMELINA trial *[see Clinical Studies (16)]*, 2,200 (63%) patients had renal impairment (eGFR <60 mL/min/1.73 m^2). Approximately 20% of the population had eGFR ≥45 to <60 mL/min/1.73 m^2, 28% of the population had eGFR ≥30 to <45 mL/min/1.73 m^2 and 15% had eGFR <30 mL/min/1.73 m^2. The overall incidence of adverse reactions were generally similar between the TRAJENTA and placebo treatment arms.

11.6. Hepatic Impairment

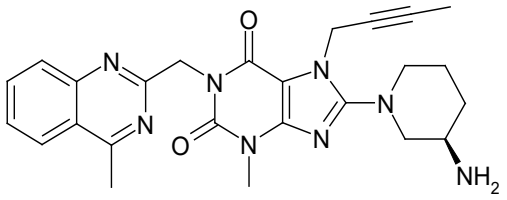
No dose adjustment is recommended for patients with hepatic impairment *[see Clinical Pharmacology (14.3)]*.

12. OVERDOSAGE

In the event of an overdose with TRAJENTA, consider contacting poison control center or a medical toxicologist for additional overdosage management recommendations. Removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely.

13. DESCRIPTION

TRAJENTA tablets for oral use contain linagliptin, an inhibitor of the DPP-4 enzyme.
The chemical name of linagliptin is 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-
The molecular formula is $C_{25}H_{28}N_8O_2$ and the molecular weight is 472.54 g/mol. The structural formula is:



Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water (0.9 mg/mL). Linagliptin is soluble in methanol (ca. 60 mg/mL), sparingly soluble in

ethanol (ca. 10 mg/mL), very slightly soluble in isopropanol (<1 mg/mL), and very slightly soluble in acetone (ca. 1 mg/mL).

Each film-coated tablet of TRAJENTA contains 5 mg of linagliptin free base and the following inactive ingredients: mannitol, pregelatinized starch, maize starch, copovidone, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, talc, macrogol, and red iron oxide.

14. CLINICAL PHARMACOLOGY

14.1. Mechanism of Action

Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta-cells in the presence of normal and elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha-cells, resulting in a reduction in hepatic glucose output.

14.2. Pharmacodynamics

Linagliptin binds to DPP-4 in a reversible manner and thus increases the concentrations of incretin hormones. Linagliptin glucose dependently increases insulin secretion and lowers glucagon secretion, thus resulting in better regulation of 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.

14.3. Pharmacokinetics

The pharmacokinetics of linagliptin has been characterized in healthy subjects and patients with type 2 diabetes mellitus. After oral administration of a single 5-mg dose to healthy subjects, peak plasma concentrations of linagliptin occurred at approximately 1.5 hours post dose (T_{max}); the mean plasma area under the curve (AUC) was 139 nmol*h/L and maximum concentration (C_{max}) was 8.9 nmol/L.

Plasma concentrations of linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of linagliptin to DPP-4. The prolonged elimination phase does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of linagliptin 5 mg, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of linagliptin 5 mg are reached by the third dose, and C_{max} and AUC increased by a factor of 1.3 at steady state compared with the first dose. The intra-subject and inter-subject coefficients of variation for linagliptin AUC were small (12.6% and 28.5%, respectively). Plasma AUC of linagliptin increased in a less than dose-proportional manner in the dose range of 1 to 10 mg. The pharmacokinetics of linagliptin is similar in healthy subjects and in patients with type 2 diabetes mellitus.

<u>Absorption</u>

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. TRAJENTA 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 1,110 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%-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.

Specific Populations

Patients with Renal Impairment

An open-label pharmacokinetic study evaluated the pharmacokinetics of linagliptin 5 mg in male and female patients with varying degrees of chronic renal impairment. The study included 6 healthy subjects with normal renal function (creatinine clearance [CrCl] ≥80 mL/min), 6 patients with mild renal impairment (CrCl 50 to <80 mL/min), 6 patients with moderate renal impairment (CrCl 30 to <50 mL/min), 10 patients with type 2 diabetes mellitus and severe renal impairment (CrCl <30 mL/min), and 11 patients with type 2 diabetes mellitus and normal renal function. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula.

Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects.

In patients with moderate renal impairment under steady-state conditions, mean exposure of linagliptin increased ($AUC_{\tau,ss}$ by 71% and C_{max} by 46%) compared with healthy subjects. This increase was not associated with a prolonged accumulation half-life, terminal half-life, or an increased accumulation factor. Renal excretion of linagliptin was below 5% of the administered dose and was not affected by decreased renal function.

Patients with type 2 diabetes mellitus and severe renal impairment showed steady-state exposure approximately 40% higher than that of patients with type 2 diabetes mellitus and normal renal function (increase in $AUC_{\tau,ss}$ by 42% and C_{max} by 35%). For both type 2 diabetes mellitus groups, renal excretion was below 7% of the administered dose.

These findings were further supported by the results of population pharmacokinetic analyses.

Patients with Hepatic Impairment
In patients with mild hepatic impairment (Child-Pugh class A), steady-state exposure (AUCτ,ss) of linagliptin was approximately 25% lower and Cmax,ss was approximately 36% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUCss of linagliptin was about 14% lower and Cmax,ss was approximately 8% lower than in healthy subjects. Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of linagliptin in terms of AUC0-24 and approximately 23% lower Cmax compared with healthy subjects. Reductions in the pharmacokinetic parameters seen in patients with hepatic impairment did not result in reductions in DPP-4 inhibition.

Effects of Age, Body Mass Index (BMI), Gender and Race

Based on the population pharmacokinetic analysis, age, BMI, gender and race do not have a clinically meaningful effect on the pharmacokinetics of linagliptin *[see Use in Specific Populations (11.4)]*

Drug Interaction Studies

In vitro Assessment of Drug Interactions

Linagliptin is a weak to moderate inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes and is not an inducer of CYP isozymes, including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 4A11.

Linagliptin is a P-glycoprotein (P-gp) substrate, and inhibits P-gp mediated transport of digoxin at high concentrations. Based on these results and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates at therapeutic concentrations.

In vivo Assessment of Drug Interactions

Strong inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations *[see Drug Interactions (10)]*. *In vivo* studies indicated evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT).

Table 3 describes the effect of coadministered drugs on systemic exposure of linagliptin.

Table 3 Effect of Coadministered Drugs on Systemic Exposure of Linagliptin

Coadministered Drug	**Dosing of Coadministered Drug***	**Dosing of Linagliptin***	**Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0**	
			AUC†	Cmax
Metformin	850 mg TID	10 mg QD	1.20	1.03
Glyburide	1.75 mg#	5 mg QD	1.02	1.01
Pioglitazone	45 mg QD	10 mg QD	1.13	1.07
Ritonavir	200 mg BID	5 mg#	2.01	2.96
Rifampin**	600 mg QD	5 mg QD	0.60	0.56

*Multiple dose (steady-state) unless otherwise noted
**For information regarding clinical recommendations *[see Drug Interactions (10.1)]*.
#Single dose
†AUC = AUC(0 to 24 hours) for single-dose treatments and AUC = AUC(TAU) for multiple dose treatments
QD = once daily
BID = twice daily
TID = three times daily

Table 4 describes the effect of linagliptin on systemic exposure of coadministered drugs.

Table 4 Effect of Linagliptin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	**Dosing of Coadministered Drug***	**Dosing of Linagliptin***	**Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0**		
				AUC†	Cmax
Metformin	850 mg TID	10 mg QD	metformin	1.01	0.89
Glyburide	1.75 mg#	5 mg QD	glyburide	0.86	0.86
Pioglitazone	45 mg QD	10 mg QD	pioglitazone metabolite M-III metabolite M-IV	0.94 0.98 1.04	0.86 0.96 1.05
Digoxin	0.25 mg QD	5 mg QD	digoxin	1.02	0.94
Simvastatin	40 mg QD	10 mg QD	simvastatin simvastatin acid	1.34 1.33	1.10 1.21
Warfarin	10 mg#	5 mg QD	R-warfarin S-warfarin INR PT	0.99 1.03 0.93** 1.03**	1.00 1.01 1.04** 1.15**
Ethinylestradiol and levonorgestrel	ethinylestradiol 0.03 mg and levonorgestrel 0.150 mg QD	5 mg QD	ethinylestradiol levonorgestrel	1.01 1.09	1.08 1.13

*Multiple dose (steady-state) unless otherwise noted
#Single dose
†AUC = AUC(INF) for single dose treatments and AUC = AUC(TAU) for multiple dose treatments
**AUC=AUC(0-168) and Cmax=Emax for pharmacodynamic end points
INR = International Normalized Ratio
PT = Prothrombin Time
QD = once daily
TID = three times daily

15. NONCLINICAL TOXICOLOGY

15.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Linagliptin did not increase the incidence of tumors in male and female rats in a 2-year study at doses of 6, 18, and 60 mg/kg. The highest dose of 60 mg/kg is approximately 418 times the clinical dose of 5 mg/day based on AUC exposure. Linagliptin did not increase the incidence of tumors in mice in a 2-year study at doses up to 80 mg/kg (males) and 25 mg/kg (females), or approximately 35- and 270-times the clinical dose based on AUC exposure. Higher doses of linagliptin in female mice (80 mg/kg) increased the incidence of lymphoma at approximately 215-times the clinical dose based on AUC exposure.
Linagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an *in vivo* micronucleus assay.
In fertility studies in rats, linagliptin had no adverse effects on early embryonic development, mating, fertility, or bearing live young up to the highest dose of 240 mg/kg (approximately 943-times the clinical dose based on AUC exposure).

16. CLINICAL STUDIES

16.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus

TRAJENTA has been studied as monotherapy and in combination with metformin, sulfonylurea, pioglitazone, and insulin. TRAJENTA has also been studied in patients with type 2 diabetes mellitus and severe chronic renal impairment.

In patients with type 2 diabetes mellitus, treatment with TRAJENTA produced clinically significant improvements in hemoglobin A1c (A1C), fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG) compared with placebo.

Monotherapy

A total of 730 patients with type 2 diabetes mellitus participated in 2 double-blind, placebo-controlled studies, one of 18 weeks' and another of 24 weeks' duration, to evaluate the efficacy and safety of TRAJENTA monotherapy. In both monotherapy studies, patients currently on an antihyperglycemic agent discontinued the agent and underwent a diet, exercise, and drug washout period of about 6 weeks that included an open-label placebo run-in during the last 2 weeks. Patients with inadequate glycemic control (A1C 7% to 10%) after the washout period were randomized; patients not currently on antihyperglycemic agents (off therapy for at least 8 weeks) with inadequate glycemic control (A1C 7% to 10%) were randomized after completing the 2-week, open-label, placebo run-in period. In the 18-week trial, only patients ineligible for metformin were recruited. In the 18-week trial, 76 patients were randomized to placebo and 151 to TRAJENTA 5 mg; in the 24-week trial, 167 patients were randomized to placebo and 336 to TRAJENTA 5 mg. Patients who failed to meet specific glycemic goals during the 18-week trial received rescue therapy with pioglitazone and/or insulin; metformin rescue therapy was used in the 24-week trial.

Treatment with TRAJENTA 5 mg daily provided statistically significant improvements in A1C, FPG, and 2-hour PPG compared with placebo (Table 5). In the 18-week trial, 12% of patients receiving TRAJENTA 5 mg and 18% who received placebo required rescue therapy. In the 24-week trial, 10.2% of patients receiving TRAJENTA 5 mg and 20.9% of patients receiving placebo required rescue therapy. The improvement in A1C compared with placebo was not affected by gender, age, race, prior antihyperglycemic therapy, baseline BMI, or a standard index of insulin resistance (HOMA-IR). As is typical for trials of agents to treat type 2 diabetes mellitus, the mean reduction in A1C with TRAJENTA appears to be related to the degree of A1C elevation at baseline. In these 18- and 24-week studies, the changes from baseline in A1C were -0.4% and -0.4%, respectively, for those given TRAJENTA , and 0.1% and 0.3%, respectively, for those given placebo. Change from baseline in body weight did not differ significantly between the groups.

Table 5 Glycemic Parameters in Placebo-Controlled Monotherapy Trials of TRAJENTA *

	18-Week Trial		**24-Week Trial**	
	TRAJENTA 5 mg	**Placebo**	**TRAJENTA 5 mg**	**Placebo**
A1C (%)				
Number of patients	n = 147	n = 73	n = 333	n = 163
Baseline (mean)	8.1	8.1	8.0	8.0
Change from baseline (adjusted mean***)	-0.4	0.1	-0.4	0.3
Difference from placebo (adjusted mean) (95% CI)	-0.6 (-0.9, -0.3)	--	-0.7 (-0.9, -0.5)	--
Patients [n (%)] achieving A1C <7%**	32 (23.5)	8 (11.8)	77 (25)	17 (12)
FPG (mg/dL)				
Number of patients	n = 138	n = 66	n = 318	n = 149
Baseline (mean)	178	176	164	166
Change from baseline (adjusted mean***)	-13	7	-9	15
Difference from placebo (adjusted mean) (95% CI)	-21 (-31, -10)	--	-23 (-30, -16)	--
2-hour PPG (mg/dL)				
Number of patients	Data not available	Data not available	n = 67	n = 24
Baseline (mean)	--	--	258	244
Change from baseline (adjusted mean***)	--	--	-34	25
Difference from placebo (adjusted mean) (95% CI)	--	--	-58 (-82, -34)	--

*Full analysis population using last observation on trial
**18-week trial: Placebo, n=68; TRAJENTA, n=136
24-week trial: Placebo, n=147; TRAJENTA, n=306

***18-week trial. HbA1c: ANCOVA model included treatment, reason for metformin intolerance and number of prior oral anti-diabetic medicine(s) (OADs) as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment, reason for metformin intolerance and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

24-week trial. HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates. PPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline postprandial glucose after two hours as covariate.

Add-on Combination Therapy with Metformin
A total of 701 patients with type 2 diabetes mellitus participated in a 24-week, randomized, double-blind, placebo-controlled trial designed to assess the efficacy of TRAJENTA in combination with metformin. Patients already on metformin (n = 491) at a dosage of at least 1,500 mg per day were randomized after completing a 2-week, open-label, placebo run-in period. Patients on metformin and another antihyperglycemic agent (n = 207) were randomized after a run-in period of approximately 6 weeks on metformin (at a dosage of at least 1,500 mg per day) in monotherapy. Patients were randomized to the

addition of either TRAJENTA 5 mg or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with glimepiride rescue.
In combination with metformin, TRAJENTA provided statistically significant improvements in A1C, FPG, and 2-hour PPG compared with placebo (Table 6). Rescue glycemic therapy was used in 7.8% of patients treated with TRAJENTA 5 mg and in 18.9% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

Table 6 Glycemic Parameters in Placebo-Controlled Trial for TRAJENTA in Combination with Metformin*

	TRAJENTA 5 mg + Metformin	**Placebo + Metformin**
A1C (%)		
Number of patients	n = 513	n = 175
Baseline (mean)	8.1	8.0
Change from baseline (adjusted mean***)	-0.5	0.15
Difference from placebo + metformin (adjusted mean) (95% CI)	-0.6 (-0.8, -0.5)	--
Patients [n (%)] achieving A1C <7%**	127 (26.2)	15 (9.2)
FPG (mg/dL)		
Number of patients	n = 495	n = 159
Baseline (mean)	169	164
Change from baseline (adjusted mean***)	-11	11
Difference from placebo + metformin (adjusted mean) (95% CI)	-21 (-27, -15)	--
2-hour PPG (mg/dL)		
Number of patients	n = 78	n = 21
Baseline (mean)	270	274
Change from baseline (adjusted mean***)	-49	18
Difference from placebo + metformin (adjusted mean) (95% CI)	-67 (-95, -40)	--

*Full analysis population using last observation on trial
**TRAJENTA 5 mg + Metformin, n=485; Placebo + Metformin, n=163
***HbA1c: ANCOVA model included treatment and number of prior oral OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates. PPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline postprandial glucose after two hours as covariate.

Initial Combination Therapy with Metformin

A total of 791 patients with type 2 diabetes mellitus and inadequate glycemic control on diet and exercise participated in the 24-week, randomized, double-blind, portion of this placebo-controlled factorial trial designed to assess the efficacy of TRAJENTA as initial therapy with metformin. Patients on an antihyperglycemic agent (52%) underwent a drug washout period of 4 weeks' duration. After the washout period and after completing a 2-week single-blind placebo run-in period, patients with inadequate glycemic control (A1C ≥7.0% to ≤10.5%) were randomized. Patients with inadequate glycemic control (A1C ≥7.5% to <11.0%) not on antihyperglycemic agents at trial entry (48%) immediately entered the 2-week, single-blind, placebo run-in period and then were randomized. Randomization was stratified by baseline A1C (<8.5% vs ≥8.5%) and use of a prior oral antidiabetic drug (none vs monotherapy). Patients were randomized in a 1:2:2:2:2:2 ratio to either placebo or one of 5 active-treatment arms. Approximately equal numbers of patients were randomized to receive initial therapy with 5 mg of TRAJENTA once daily, 500 mg or 1,000 mg of metformin twice daily, or 2.5 mg of linagliptin twice daily

in combination with 500 mg or 1,000 mg of metformin twice daily. Patients who failed to meet specific glycemic goals during the trial were treated with sulfonylurea, thiazolidinedione, or insulin rescue therapy.

Initial therapy with the combination of linagliptin and metformin provided significant improvements in A1C and fasting plasma glucose (FPG) compared to placebo, to metformin alone, and to linagliptin alone (Table 7).

The adjusted mean treatment difference in A1C from baseline to week 24 (LOCF) was -0.5% (95% CI -0.7, -0.3; p<0.0001) for linagliptin 2.5 mg/metformin 1,000 mg twice daily compared to metformin 1,000 twice daily; -1.1% (95% CI -1.4, -0.9; p<0.0001) for linagliptin 2.5 mg/metformin 1,000 mg twice daily compared to TRAJENTA 5 mg once daily; -0.6% (95% CI -0.8, -0.4; p<0.0001) for linagliptin 2.5 mg/metformin 500 mg twice daily compared to metformin 500 mg twice daily; and -0.8% (95% CI -1.0, -0.6; p<0.0001) for linagliptin 2.5 mg/metformin 500 mg twice daily compared to TRAJENTA 5 mg once daily.

Lipid effects were generally neutral. No meaningful change in body weight was noted in any of the 6 treatment groups.

Table 7 Glycemic Parameters at Final Visit (24-Week Trial) for Linagliptin and Metformin, Alone and in Combination in Randomized Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise**

	Placebo	**TRAJENTA 5 mg Once Daily***	**Metformin 500 mg Twice Daily**	**Linagliptin 2.5 mg Twice Daily* + Metformin 500 mg Twice Daily**	**Metformin 1,000 mg Twice Daily**	**Linagliptin 2.5 mg Twice Daily* + Metformin 1,000 mg Twice Daily**
A1C (%)						
Number of patients	n = 65	n = 135	n = 141	n = 137	n = 138	n = 140
Baseline (mean)	8.7	8.7	8.7	8.7	8.5	8.7
Change from baseline (adjusted mean****)	0.1	-0.5	-0.6	-1.2	-1.1	-1.6
Difference from placebo (adjusted mean) (95% CI)	--	-0.6 (-0.9, -0.3)	-0.8 (-1.0, -0.5)	-1.3 (-1.6, -1.1)	-1.2 (-1.5, -0.9)	-1.7 (-2.0, -1.4)
Patients [n(%)] achieving A1C <7%***	7 (10.8)	14 (10.4)	26 (18.6)	41 (30.1)	42 (30.7)	74 (53.6)
Patients (%) receiving rescue medication	29.2	11.1	13.5	7.3	8.0	4.3
FPG (mg/dL)						
Number of patients	n = 61	n = 134	n = 136	n = 135	n = 132	n = 136
Baseline (mean)	203	195	191	199	191	196
Change from baseline (adjusted mean****)	10	-9	-16	-33	-32	-49

Difference from placebo (adjusted mean) (95% CI)	--	-19 (-31, -6)	-26 (-38, -14)	-43 (-56, -31)	-42 (-55, -30)	-60 (-72, -47)

*Total daily dosage of TRAJENTA is equal to 5 mg
**Full analysis population using last observation on trial
***Metformin 500 mg twice daily, n=140; Linagliptin 2.5 mg twice daily + Metformin 500 twice daily, n=136; Metformin 1,000 mg twice daily, n=137; Linagliptin 2.5 mg twice daily + Metformin 1,000 mg twice daily, n=138
****HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

Active-Controlled Trial vs Glimepiride in Combination with Metformin

The efficacy of TRAJENTA was evaluated in a 104-week, double-blind, glimepiride-controlled, non-inferiority trial in patients with type 2 diabetes mellitus with insufficient glycemic control despite metformin therapy. Patients being treated with metformin only entered a run-in period of 2 weeks' duration, whereas patients pretreated with metformin and one additional antihyperglycemic agent entered a run-in treatment period of 6 weeks' duration with metformin monotherapy (dosage of ≥1,500 mg/day) and washout of the other agent. After an additional 2-week placebo run-in period, those with inadequate glycemic control (A1C 6.5% to 10%) were randomized 1:1 to the addition of TRAJENTA 5 mg once daily or glimepiride. Randomization was stratified by baseline HbA1c (<8.5% vs ≥8.5%), and the previous use of antidiabetic drugs (metformin alone vs metformin plus one other OAD). Patients receiving glimepiride were given an initial dosage of 1 mg/day and then electively titrated over the next 12 weeks to a maximum dosage of 4 mg/day as needed to optimize glycemic control. Thereafter, the glimepiride dosage was to be kept constant, except for down-titration to prevent hypoglycemia.
After 52 and 104 weeks, TRAJENTA and glimepiride both had reductions from baseline in A1C (52 weeks: -0.4% for TRAJENTA, -0.6% for glimepiride; 104 weeks: -0.2% for TRAJENTA, -0.4% for glimepiride) from a baseline mean of 7.7% (Table 8). The mean difference between groups in A1C change from baseline was 0.2% with 2-sided 97.5% confidence interval (0.1%, 0.3%) for the intent-to-treat population using last observation carried forward. These results were consistent with the completers analysis.

Table 8 Glycemic Parameters at 52 and 104 Weeks in Trial Comparing TRAJENTA to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin**

	Week 52		Week 104	
	TRAJENTA 5 mg + Metformin	**Glimepiride + Metformin (mean Glimepiride dosage 3 mg)**	**TRAJENTA 5 mg + Metformin**	**Glimepiride + Metformin (mean Glimepiride dosage 3 mg)**
A1C (%)				
Number of patients	n = 764	n = 755	n = 764	n = 755
Baseline (mean)	7.7	7.7	7.7	7.7
Change from baseline (adjusted mean****)	-0.4	-0.6	-0.2	-0.4
Difference from glimepiride (adjusted mean) (97.5% CI)	0.2 (0.1, 0.3)	--	0.2 (0.1, 0.3)	--
FPG (mg/dL)				
Number of patients	n = 733	n = 725	n = 733	n = 725
Baseline (mean)	164	166	164	166
Change from baseline (adjusted mean****)	-8*	-15	-2†	-9
Hypoglycemia incidence (%)***				
Number of patients	n = 776	n = 775	n = 776	n = 775
Incidence****	5.3 *	31.1	7.5 *	36.1

*p<0.0001 vs glimepiride; †p=0.0012 vs glimepiride
**Full analysis population using last observation on trial
***Hypoglycemic incidence included both asymptomatic events (not accompanied by typical symptoms and plasma glucose concentration of ≤70 mg/dL) and symptomatic events with typical symptoms of hypoglycemia and plasma glucose concentration of ≤70 mg/dL.
****HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.
Hypoglycemia incidence (%): Cochran-Mantel-Haenszel test was performed on the patient population contained in the treated set, to compare the proportion of patients with hypoglycemic events between patients treated with linagliptin and patients treated with glimepiride.

Patients treated with linagliptin had a mean baseline body weight of 86 kg and were observed to have an adjusted mean decrease in body weight of 1.1 kg at 52 weeks and 1.4 kg at 104 weeks. Patients on glimepiride had a mean baseline body weight of 87 kg and were observed to have an adjusted mean increase from baseline in body weight of 1.4 kg at 52 weeks and 1.3 kg at 104 weeks (treatment difference p<0.0001 for both timepoints).

Add-On Combination Therapy with Pioglitazone

A total of 389 patients with type 2 diabetes mellitus participated in a 24-week, randomized, double-blind, placebo-controlled trial designed to assess the efficacy of TRAJENTA in combination with pioglitazone. Therapy was stopped in patients on oral antihyperglycemic therapy for a period of 6 weeks (4 weeks followed by a 2-week, open-label, placebo run-in period). Drug-naïve patients entered directly into the 2-week placebo run-in period. After the run-in period, patients were randomized to receive either TRAJENTA 5 mg or placebo, both in addition to pioglitazone 30 mg daily. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue. Glycemic endpoints measured were A1C and FPG.

In initial combination with pioglitazone 30 mg, TRAJENTA 5 mg provided statistically significant improvements in A1C and FPG compared to placebo with pioglitazone (Table 9). Rescue therapy was used in 7.9% of patients treated with TRAJENTA 5 mg/pioglitazone 30 mg and 14.1% of patients treated with placebo/pioglitazone 30 mg. Patient weight increased in both groups during the trial with an adjusted mean change from baseline of 2.3 kg and 1.2 kg in the TRAJENTA 5 mg/pioglitazone 30 mg and placebo/pioglitazone 30 mg groups, respectively (p = 0.0141).

Table 9 Glycemic Parameters in Placebo-Controlled Trial for TRAJENTA in Combination Therapy with Pioglitazone*

	TRAJENTA 5 mg + Pioglitazone	**Placebo + Pioglitazone**
A1C (%)		
Number of patients	n = 252	n = 128
Baseline (mean)	8.6	8.6
Change from baseline (adjusted mean**)	-1.1	-0.6
Difference from placebo + pioglitazone (adjusted mean) (95% CI)	-0.5 (-0.7, -0.3)	--
Patients [n (%)] achieving A1C <7%	108 (42.9)	39 (30.5)
FPG (mg/dL)		
Number of patients	n = 243	n = 122
Baseline (mean)	188	186
Change from baseline (adjusted mean**)	-33	-18
Difference from placebo + pioglitazone (adjusted mean) (95% CI)	-14 (-21, -7)	--

*Full analysis population using last observation on trial
**HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

Add-On Combination with Sulfonylureas

A total of 245 patients with type 2 diabetes mellitus participated in an 18-week, randomized, double-blind, placebo-controlled trial designed to assess the efficacy of TRAJENTA in combination with sulfonylurea (SU). Patients on sulfonylurea monotherapy (n = 142) were randomized after completing a 2-week, single-blind, placebo run-in period. Patients on a sulfonylurea plus one additional oral antihyperglycemic agent (n = 103) were randomized after a wash-out period of 4 weeks and a 2-week, single-blind, placebo run-in period. Patients were randomized to the addition of TRAJENTA 5 mg or to placebo, each administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue. Glycemic endpoints measured included A1C and FPG.

In combination with a sulfonylurea, TRAJENTA provided statistically significant improvements in A1C compared with placebo following 18 weeks' treatment; the improvements in FPG observed with TRAJENTA were not statistically significant compared with placebo (Table 10). Rescue therapy was used in 7.6% of patients treated with TRAJENTA 5 mg and 15.9% of patients treated with placebo. There was no significant difference between TRAJENTA and placebo in body weight.

Table 10 Glycemic Parameters in Placebo-Controlled Trial for TRAJENTA in Combination with Sulfonylurea*

	TRAJENTA 5 mg + SU	**Placebo + SU**
A1C (%)		
Number of patients	n = 158	n = 82
Baseline (mean)	8.6	8.6
Change from baseline (adjusted mean***)	-0.5	-0.1
Difference from placebo + SU (adjusted mean) (95% CI)	-0.5 (-0.7, -0.2)	--
Patients [n (%)] achieving A1C <7%**	23 (14.7)	3 (3.7)
FPG (mg/dL)		
Number of patients	n = 155	n = 78
Baseline (mean)	180	171
Change from baseline (adjusted mean***)	-8	-2
Difference from placebo + SU (adjusted mean) (95% CI)	-6 (-17, 4)	--

SU = sulfonylurea
*Full analysis population using last observation on trial
**TRAJENTA 5 mg + SU, n=156; Placebo + SU, n=82
***HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates

Add-On Combination Therapy with Metformin and a Sulfonylurea

A total of 1,058 patients with type 2 diabetes mellitus participated in a 24-week, randomized, double-blind, placebo-controlled trial designed to assess the efficacy of TRAJENTA in combination with a sulfonylurea and metformin. The most common sulfonylureas used by patients in the trial were: glimepiride (31%), glibenclamide (26%), and gliclazide (26%, not available in the United States). Patients on a sulfonylurea and metformin were randomized to receive TRAJENTA 5 mg or placebo, each administered once daily. Patients who failed to meet specific glycemic goals during the trial were treated with pioglitazone rescue. Glycemic endpoints measured included A1C and FPG.

In combination with a sulfonylurea and metformin, TRAJENTA provided statistically significant improvements in A1C and FPG compared with placebo (Table 11). In the entire trial population (patients on TRAJENTA in combination with sulfonylurea and metformin), a mean reduction from baseline relative to placebo in A1C of -0.6% and in FPG of -13 mg/dL was seen. Rescue therapy was used in 5.4% of patients treated with TRAJENTA 5 mg and in 13% of patients treated with placebo. Change from baseline in body weight did not differ significantly between the groups.

Table 11 Glycemic Parameters in Placebo-Controlled Trial for TRAJENTA in Combination with Metformin and Sulfonylurea*

	TRAJENTA 5 mg + Metformin + SU	**Placebo + Metformin + SU**
A1C (%)		
Number of patients	n = 778	n = 262
Baseline (mean)	8.2	8.1
Change from baseline (adjusted mean***)	-0.7	-0.1
Difference from placebo (adjusted mean) (95% CI)	-0.6 (-0.7, -0.5)	--
Patients [n (%)] achieving A1C <7%**	217 (29.2)	20 (8.1)
FPG (mg/dL)		
Number of patients	n = 739	n = 248
Baseline (mean)	159	163
Change from baseline (adjusted mean***)	-5	8
Difference from placebo (adjusted mean) (95% CI)	-13 (-18, -7)	--

SU = sulfonylurea
*Full analysis population using last observation on trial
**TRAJENTA 5 mg + Metformin + SU, n=742; Placebo + Metformin + SU, n=247
***HbA1c: ANCOVA model included treatment as class-effects and baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

Add-On Combination Therapy with Insulin

A total of 1,261 patients with type 2 diabetes mellitus inadequately controlled on basal insulin alone or basal insulin in combination with oral drugs participated in a randomized, double-blind placebo-controlled trial designed to evaluate the efficacy of TRAJENTA as add-on therapy to basal insulin over 24 weeks. Randomization was stratified by baseline HbA1c (<8.5% vs ≥8.5%), renal function impairment status (based on baseline eGFR), and concomitant use of oral antidiabetic drugs (none, metformin only, pioglitazone only, metformin + pioglitazone). Patients with a baseline A1C of ≥7% and ≤10% were included in the trial including 709 patients with renal impairment (eGFR <90 mL/min), most of whom (n=575) were categorized as mild renal impairment (eGFR 60 to <90 mL/min). Patients entered a 2 week placebo run-in period on basal insulin (e.g., insulin glargine, insulin detemir, or NPH insulin) with or without metformin and/or pioglitazone background therapy. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of either 5 mg of TRAJENTA or placebo, administered once daily. Patients were maintained on a stable dosage of insulin prior to enrollment, during the run-in period, and during the first 24 weeks of treatment. Patients who failed to meet specific glycemic goals during the double-blind treatment period were rescued by increasing background insulin dosage.

TRAJENTA used in combination with insulin (with or without metformin and/or pioglitazone), provided statistically significant improvements in A1C and FPG compared to placebo (Table 12) after 24 weeks of treatment. The mean total daily insulin dosage at baseline was 42 units for patients treated with TRAJENTA and 40 units for patients treated with placebo. Background baseline diabetes mellitus therapy included use of: insulin alone (16.1%), insulin combined with metformin only (75.5%), insulin combined with metformin and pioglitazone (7.4%), and insulin combined with pioglitazone only (1%). The mean change from baseline to Week 24 in the daily dosage of insulin was +1.3 IU in the placebo group and +0.6 IU in the TRAJENTA group. The mean change in body weight from baseline to Week 24 was similar in the two treatment groups.

Table 12 Glycemic Parameters in Placebo-Controlled Trial for TRAJENTA in Combination with Insulin*

	TRAJENTA 5 mg + Insulin	**Placebo + Insulin**
A1C (%)		
Number of patients	n = 618	n = 617
Baseline (mean)	8.3	8.3
Change from baseline (adjusted mean***)	-0.6	0.1
Difference from placebo (adjusted mean) (95% CI)	-0.7 (-0.7, -0.6)	--
Patients [n (%)] achieving A1C <7%**	116 (19.5)	48 (8.1)
FPG (mg/dL)		
Number of patients	n = 613	n = 608
Baseline (mean)	147	151
Change from baseline (adjusted mean***)	-8	3
Difference from placebo (adjusted mean) (95% CI)	-11 (-16, -6)	--

*Full analysis population using last observation carried forward (LOCF) method on trial
**TRAJENTA+Insulin, n=595; Placebo+Insulin, n=593
***HbA1c: ANCOVA model included treatment, categorical renal function impairment status and concomitant OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment, categorical renal function impairment status and concomitant OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

The difference between treatment with linagliptin and placebo in terms of adjusted mean change from baseline in HbA1c after 24 weeks was comparable for patients with no renal impairment (eGFR ≥90 mL/min, n=539), with mild renal impairment (eGFR 60 to <90 mL/min, n= 565), or with moderate renal impairment (eGFR 30 to <60 mL/min, n=124).

Renal Impairment
A total of 133 patients with type 2 diabetes mellitus participated in a 52 week, double-blind, randomized, placebo-controlled trial designed to evaluate the efficacy and safety of TRAJENTA in patients with both type 2 diabetes mellitus and severe chronic renal impairment. Participants with an estimated (based on the four variables modified diet in renal disease [MDRD] equation) GFR value of <30 mL/min were eligible to participate in the trial. Randomization was stratified by baseline HbA1c (≤8% and >8%) and background antidiabetic therapy (insulin or any combination with insulin, SU or glinides as monotherapy and pioglitazone or any other antidiabetics excluding any other DPP-4 inhibitors). For the initial 12 weeks of the trial, background antidiabetic therapy was kept stable and included insulin, sulfonylurea, glinides, and pioglitazone. For the remainder of the trial, dosage adjustments in antidiabetic background therapy were allowed. At baseline in this trial, 62.5% of patients were receiving insulin alone as background diabetes mellitus therapy, and 12.5% were receiving sulfonylurea alone.
After 12 weeks of treatment, TRAJENTA 5 mg provided statistically significant improvement in A1C compared to placebo, with an adjusted mean change of -0.6% compared to placebo (95% confidence interval -0.9, -0.3) based on the analysis using last observation carried forward (LOCF). With adjustments in antidiabetic background therapy after the initial 12 weeks, efficacy was maintained for 52 weeks, with an adjusted mean change from baseline in A1C of -0.7% compared to placebo (95% confidence interval -1.0, -0.4) based on analysis using LOCF.

16.2 Cardiovascular Safety Trials in Patients with Type 2 Diabetes Mellitus

CARMELINA

The cardiovascular risk of TRAJENTA was evaluated in CARMELINA, a multi-national, multi-center, placebo-controlled, double-blind, parallel group trial comparing TRAJENTA (N=3,494) to placebo (N=3,485) 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 TRAJENTA and placebo when these were added to standard of care treatments for diabetes mellitus 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 mellitus, 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% White, 9% Asian, 6% Black or African American, and 36% were of Hispanic or Latino ethnicity. 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/1.73m^2. The mean eGFR was 55 mL/min/1.73m^2 and 27% of patients had mild renal impairment (eGFR 60 to 90 mL/min/1.73m^2), 47% of patients had moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2) and 15% of patients had severe renal impairment (eGFR <30 mL/min/1.73 m^2). 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, non-fatal myocardial infarction or non-fatal stroke. The trial was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE.

The results of CARMELINA, including the contribution of each component to the primary composite endpoint, are shown in Table 13. The estimated hazard ratio for MACE associated with TRAJENTA 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. The Kaplan-Meier curve depicting time to first occurrence of MACE is shown in Figure 1.

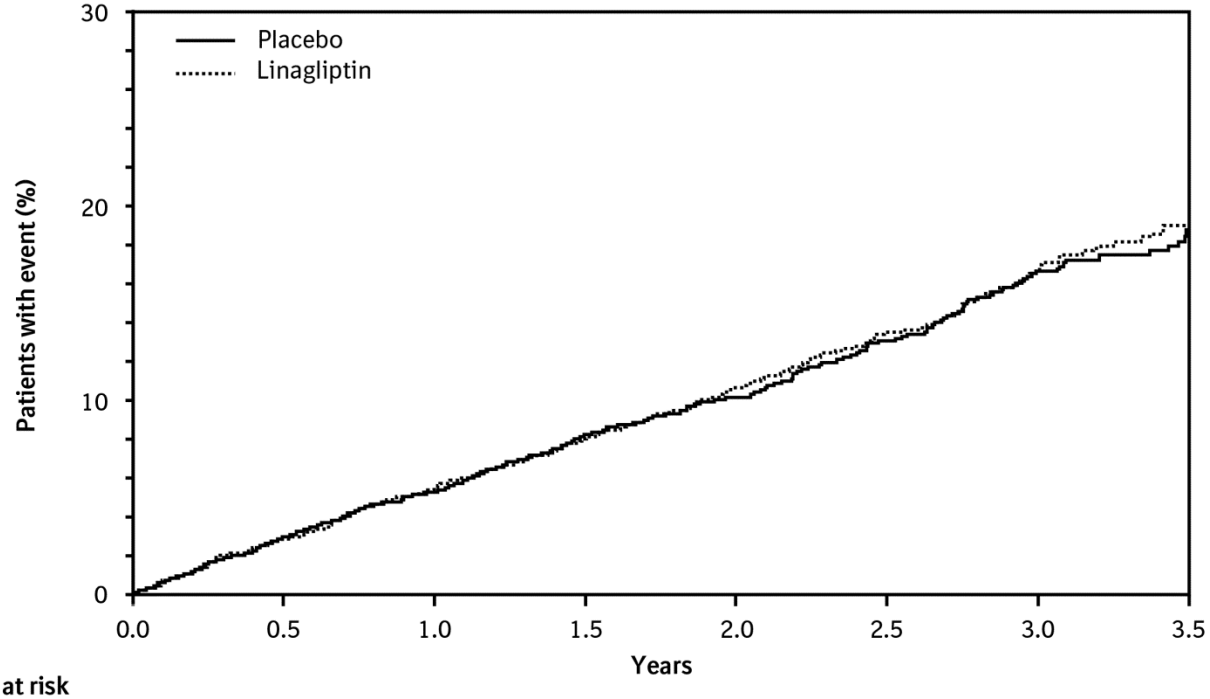
Table 13 Major Adverse Cardiovascular Events (MACE) by Treatment Group in the CARMELINA Trial

	TRAJENTA 5 mg n = 3,494		**Placebo n = 3,485**		**Hazard Ratio**
	Number of Subjects (%)	**Incidence Rate per 1,000 PY***	**Number of Subjects (%)**	**Incidence Rate per 1,000 PY***	**(95% CI)**
Composite of first event of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke (MACE)	434 (12.4)	57.7	420 (12.1)	56.3	1.02 (0.89, 1.17)
CV death**	255 (7.3)	32.6	264 (7.6)	34.0	0.96 (0.81, 1.14)
Non-fatal MI**	156 (4.5)	20.6	135 (3.9)	18.0	1.15 (0.91, 1.45)
Non-fatal stroke**	65 (1.9)	8.5	73 (2.1)	9.6	0.88 (0.63, 1.23)

*PY=patient years

**A patient may have experienced more than one component; therefore, the sum of the components is larger than the number of patients who experienced the composite outcome.

Figure 1 Kaplan-Meier: Time to First Occurrence of MACE in the CARMELINA Trial



Patients at risk								
Placebo (n)	3485	3353	3243	2625	1931	1285	758	251
Linagliptin (n)	3494	3373	3254	2634	1972	1306	778	269

CAROLINA

The cardiovascular risk of TRAJENTA was evaluated in CAROLINA, a multi-center, multi-national, randomized, double-blind, parallel group trial comparing TRAJENTA (N=3,023) to glimepiride (N=3,010) in adult patients with type 2 diabetes mellitus and a history of established cardiovascular disease and/or multiple cardiovascular risk factors. The trial compared the risk of major adverse cardiovascular events (MACE) between TRAJENTA and glimepiride when these were added to standard of care treatments for diabetes mellitus and other cardiovascular risk factors. The trial was event driven, the median duration of follow-up was 6.23 years and vital status was obtained for 99.3% of patients.

Patients were eligible to enter the trial if they were adults with type 2 diabetes mellitus with insufficient glycemic control (defined as HbA1c of 6.5% to 8.5% or 6.5% to 7.5% depending on whether treatment-naïve, on monotherapy or on combination therapy), and were defined to be at high cardiovascular risk with previous vascular disease, evidence of vascular related end-organ damage, age ≥70 years, and/or two cardiovascular risk factors (duration of diabetes mellitus >10 years, systolic blood pressure >140 mmHg, current smoker, LDL cholesterol ≥135 mg/dL).

At baseline the mean age was 64 years and the population was 60% male, 73% White, 18% Asian, 5% Black or African American, and 17% were of Hispanic or Latino ethnicity. The mean HbA1c was 7.15% and mean duration of type 2 diabetes mellitus was 7.6 years. The trial population included 34% patients ≥70 years of age and 19% patients with renal impairment defined as eGFR <60 mL/min/1.73 m^2. The mean eGFR was 77 mL/min/1.73m^2. Patients were taking at least one antidiabetic drug (91%) and the most common were metformin (83%) and sulfonylurea (28%). Patients were also taking antihypertensives (89%), lipid lowering drugs (70%) with 65% on statin, and aspirin (47%).

The primary endpoint, MACE, was the time to first occurrence of one of three composite outcomes which included cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The trial was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the upper bound of the 95% CI for the hazard ratio of MACE.

The results of CAROLINA, including the contribution of each component to the primary composite endpoint, are shown in Table 14. The Kaplan-Meier curve depicting time to first occurrence of MACE is shown in Figure 2.

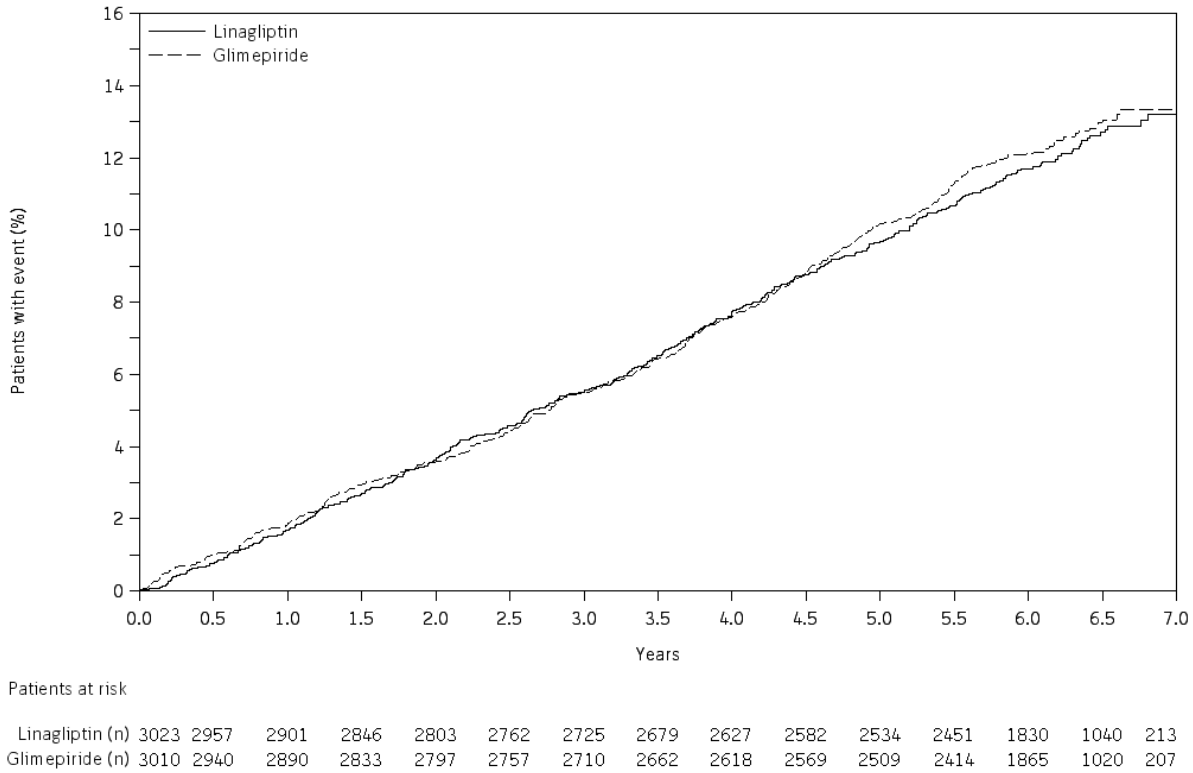
Table 14 Major Adverse Cardiovascular Events (MACE) by Treatment Group in the CAROLINA Trial

	TRAJENTA 5 mg n=3,023		**Glimepiride (1 mg to 4 mg) n=3,010**		**Hazard Ratio**
	Number of Subjects (%)	**Incidence Rate per 1,000 PY***	**Number of Subjects (%)**	**Incidence Rate per 1,000 PY***	**(95% CI)**
Composite of first event of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke (MACE)	356 (11.8)	20.7	362 (12.0)	21.2	0.98 (0.84, 1.14)
CV death**	169 (5.6)	9.2	168 (5.6)	9.2	1.00 (0.81, 1.24)
Non-fatal MI**	145 (4.8)	8.3	142 (4.7)	8.2	1.01 (0.80, 1.28)
Non-fatal stroke**	91 (3.0)	5.2	104 (3.5)	6.0	0.87 (0.66, 1.15)

*PY=patient years

**A patient may have experienced more than one component; therefore, the sum of the components is larger than the number of patients who experienced the composite outcome

Figure 2 Time to First Occurrence of 3P-MACE in CAROLINA



17. HOW SUPPLIED/STORAGE AND HANDLING

TRAJENTA tablets are available as light red, round, biconvex, bevel-edged, film-coated tablets containing 5 mg of linagliptin. TRAJENTA tablets are debossed with “D5” on one side and the Boehringer Ingelheim symbol on the other side.

They are supplied as blister packs of 7, 30 and 90 film-coated tablets.

Not all the pack sizes may be marketed.

Shelf life

The expiry date of the product is indicated on the packaging materials.

Storage

Store below 25°C.

18. MANUFACTURER

Boehringer Ingelheim International GmbH
Binger Strasse 173, 55216 Ingelheim am Rhein, Germany

19. REGISTRATION HOLDER

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