Trajenta® has built a unique CVOT dataset across more than 13,000 T2D patients in CARMELINA and CAROLINA*[1-6]

CARMELINA[1-3]

CAROLINA[4-6]

Recently, the long-term CV and kidney safety profile of Trajenta® has been comprehensively assessed via prespecified CARMELINA and CAROLINA subgroup analyses in

2,000+ patients aged 75 and older[3,6]

< 65 Years (6026 Patients)

65 to 74 Years (4929 Patients)

≥ 75 Years (2057 Patients)

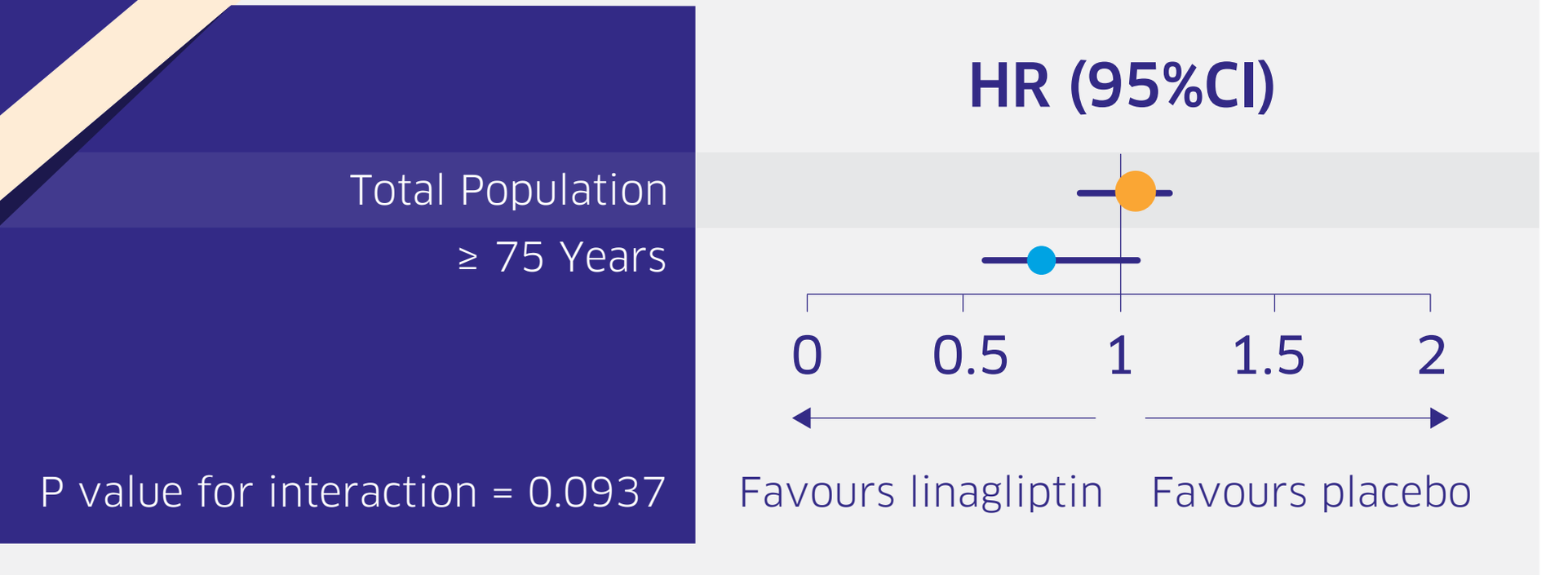
CARMELINA[1-3]

In CARMELINA, Trajenta®

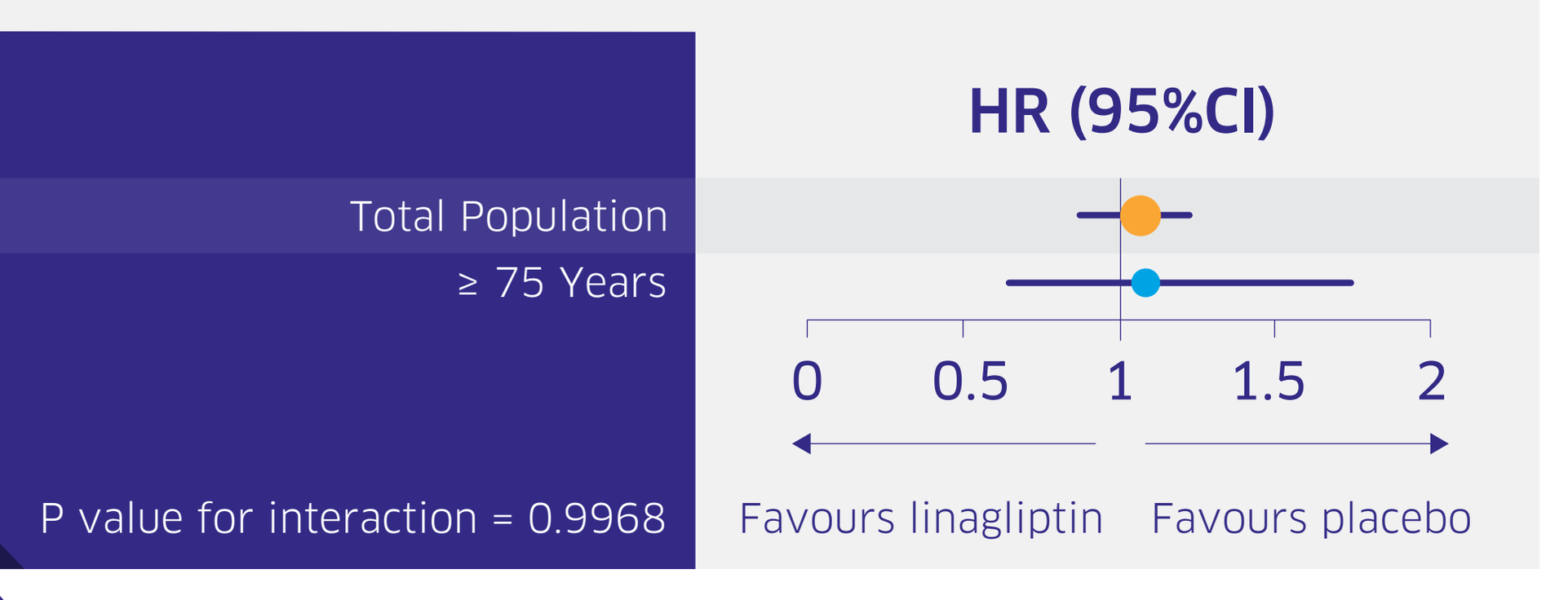
did not increase the risk

of CV or kidney events, compared to placebo, in patients aged 75 years or older†,[3].

Primary Endpoint (3P-MACE)‡



Key Secondary Endpoint (Kidney Outcome)#

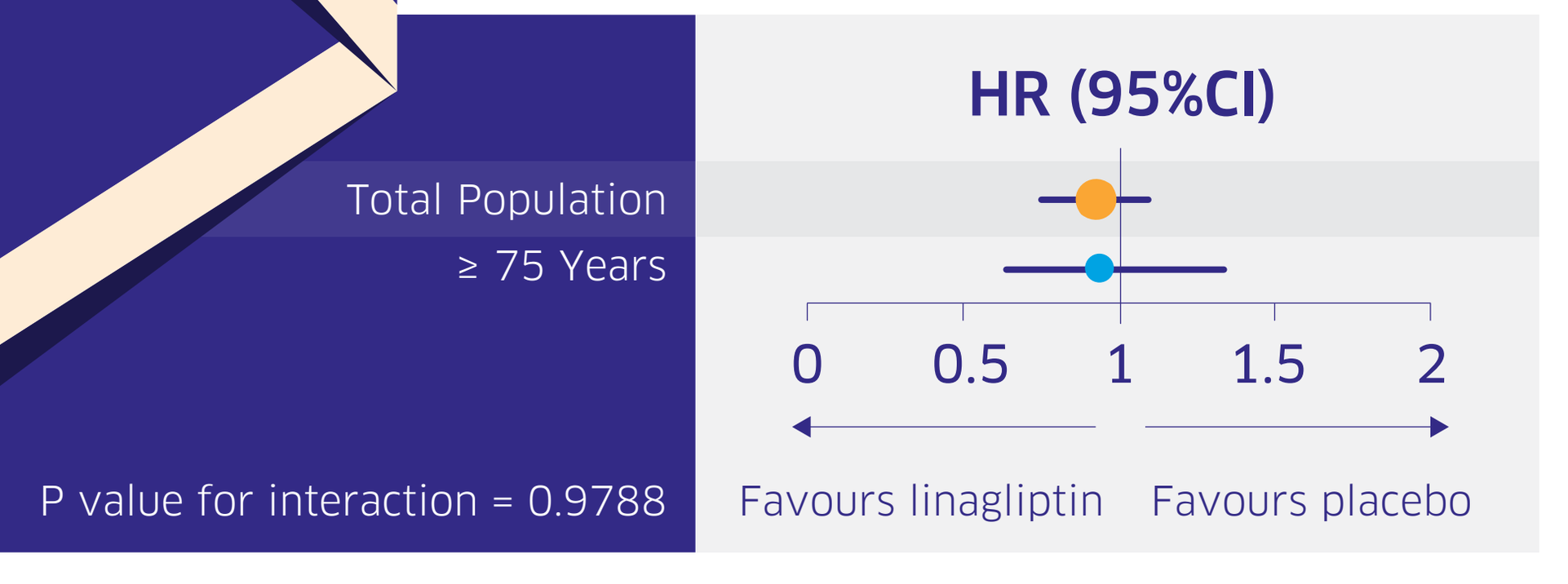


Furthermore, in patients aged 75 years or older in CARMELINA, Trajenta® was

not associated with an increased risk

of hospitalisation for heart failure§.

Exploratory Endpoint (HHF)§



New in 2020!

CAROLINA[4-6]

In CAROLINA, Trajenta®

did not increase

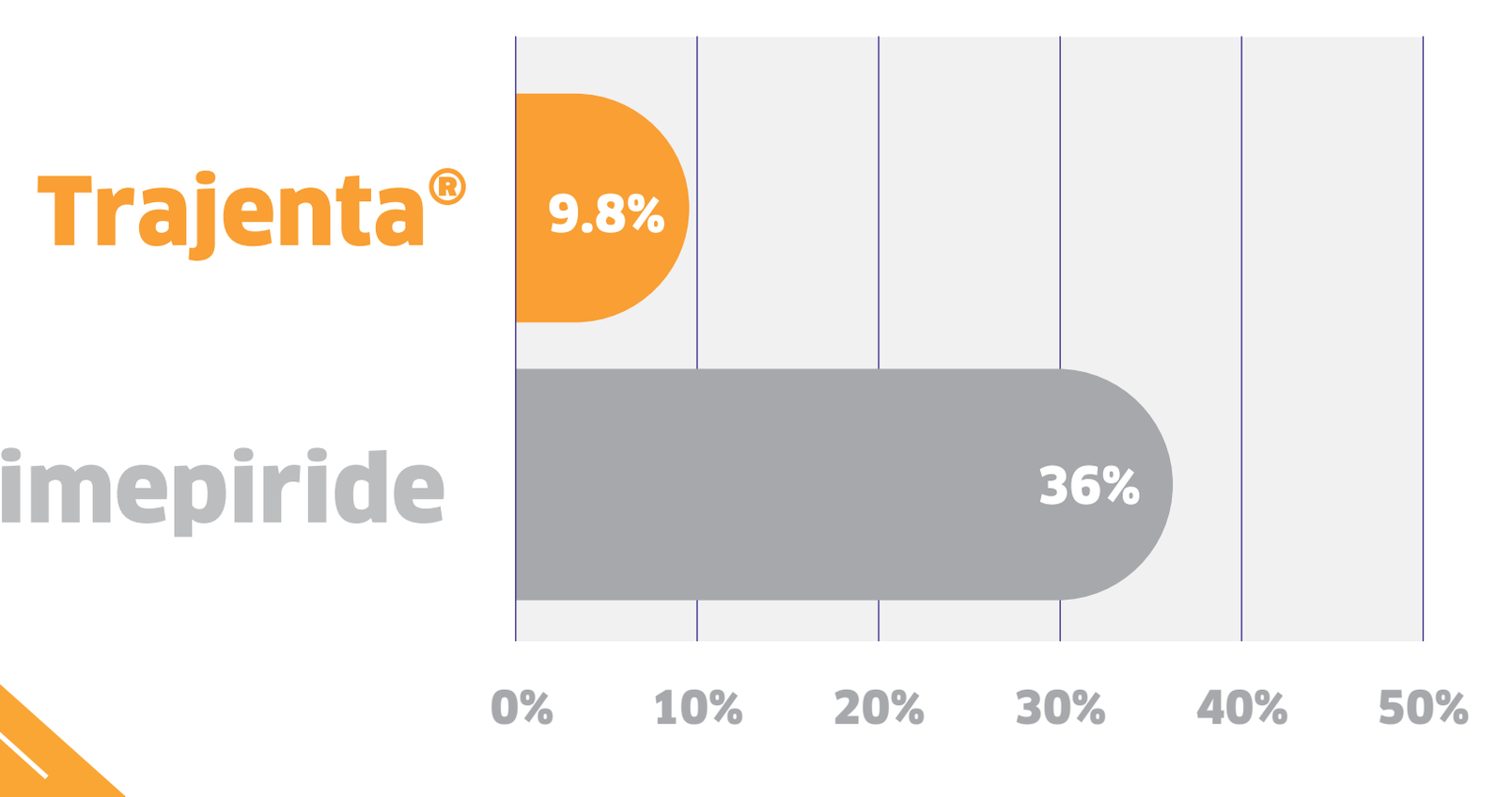
the risk of CV events, compared to glimepiride, in patients aged 75 years or older†,[6].

There was a

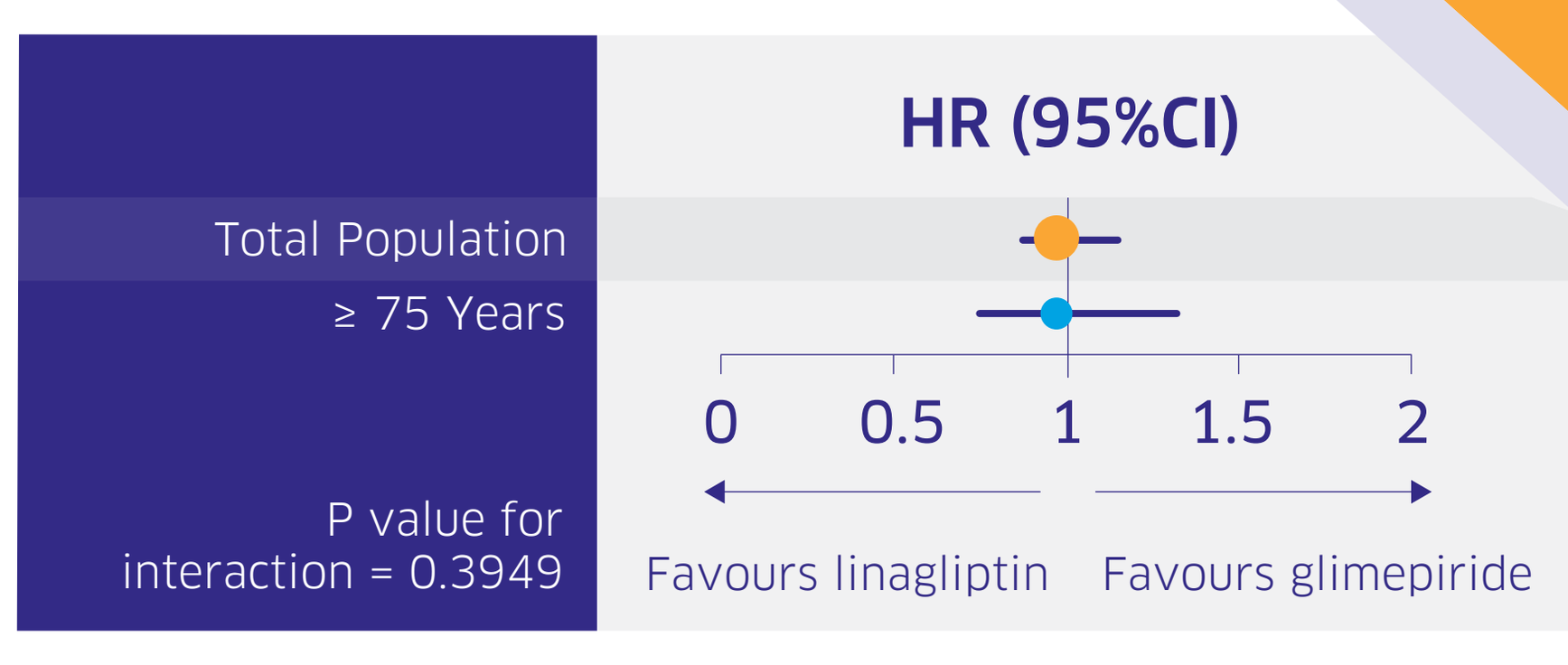
lower risk of hypoglycemia

with Trajenta®, compared to glimepiride##,[5-6]

Percent of patients aged 75 and older experiencing a hypoglycaemic event##

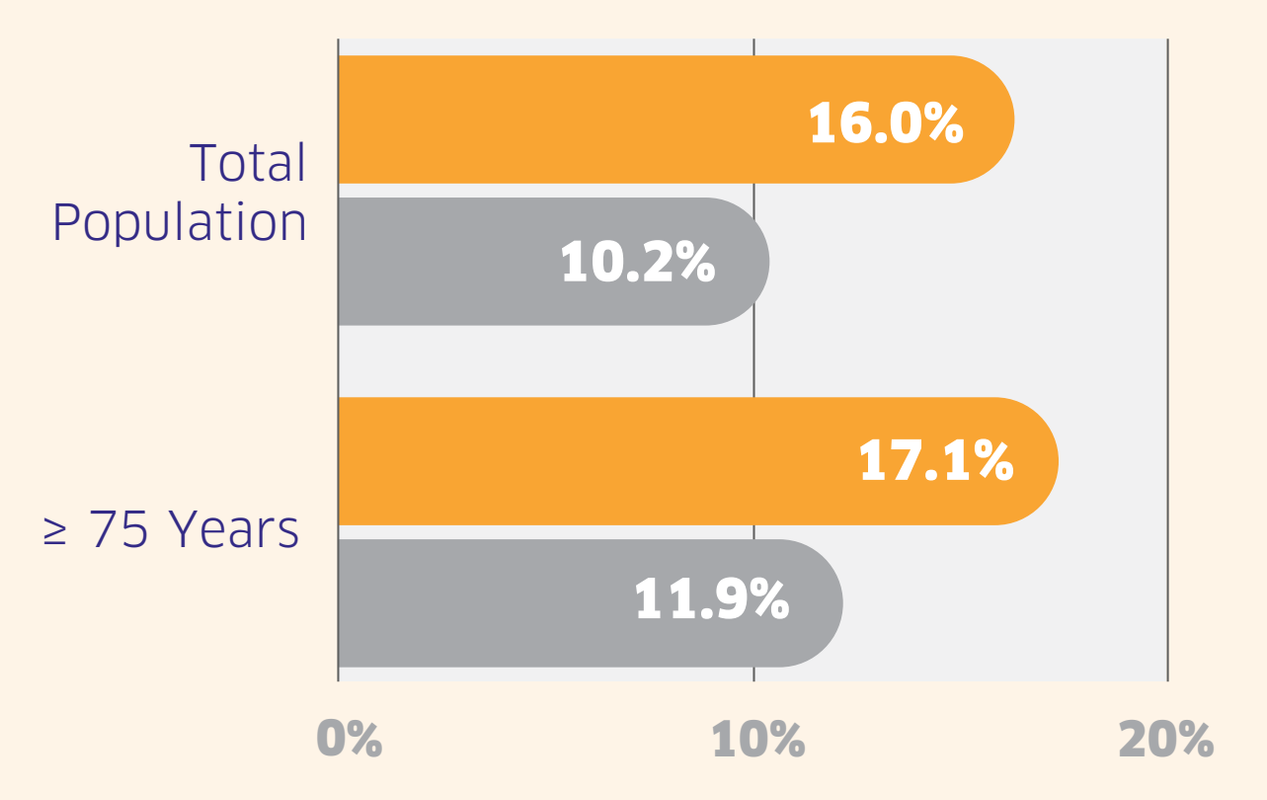


Primary Endpoint (3P-MACE)††



Percent of patients meeting the Composite Endpoint‡‡

(P value for interaction = 0.23)



Importantly,

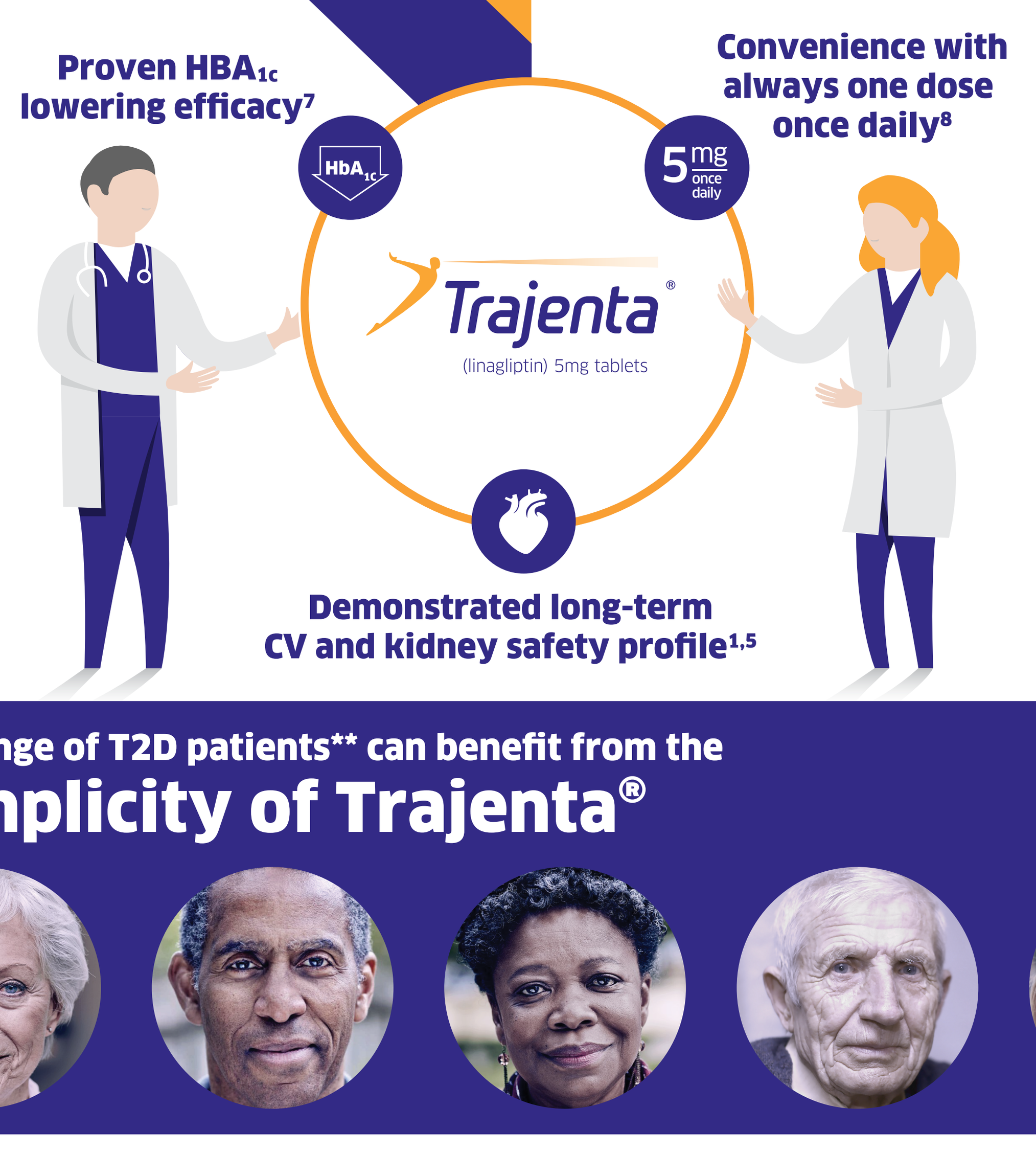
more patients

taking Trajenta® achieved target HbA_{1c} without hypoglycaemia, weight gain and rescue medication‡‡.

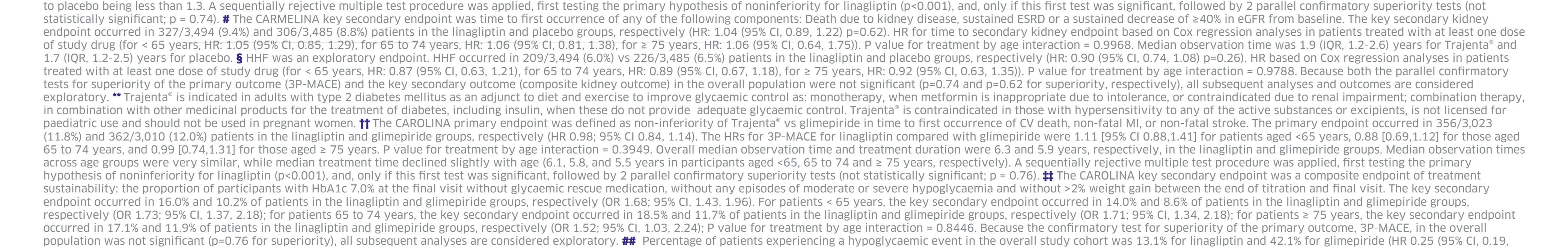
Composite Endpoint‡‡

The proportion of participants with HbA_{1c} ≤7.0% at the final visit without glycemic rescue medication, without any episodes of moderate or severe hypoglycemia and without >2% weight gain between the end of titration and final visit.

Trajenta® is the only globally-available DPP4i that combines proven efficacy, a demonstrated CV and kidney safety profile, and the unique convenience of always one dose, once daily.



A broad range of T2D patients** can benefit from the Simplicity of Trajenta®



Footnotes

* CARMELINA included 6,979 patients with albuminuria & previous macrovascular disease, and/or impaired kidney function with or without CV comorbidities. CAROLINA® included 6,033 patients with one or more of the following: a) previous vascular disease, b) evidence of vascular- related end-organ damage, c) age: ≥ 70 years and d) ≥ 2 CV risk factors (smoking, hypertension, T2D duration ≥ 10 years, dyslipidemia). † When added to standard of care. ‡ The CARMELINA primary endpoint was time to first occurrence of any of the following components: CV death, death, non-fatal MI, non-fatal stroke. The primary endpoint occurred in 434/3,494 (12.4%) and 420/3,485 (12.1%) patients in the linagliptin and placebo groups, respectively (HR 1.02; 95% CI 0.89, 1.17). HR for time to 3P-MACE based on Cox regression analyses in patients treated with at least 1 dose of study drug (for < 65 years, HR: 1.11 (95% CI, 0.89, 1.40), for 65 to 74 years, HR: 1.09 (95% CI, 0.89, 1.33), for ≥ 75 years, HR: 0.76 (95% CI, 0.57, 1.02)). P value for treatment by age interaction = 0.0937. Median observation time was 2.2 (IQR, 1.5-2.9) years for Trajenta® and 2.2 (IQR, 1.5-2.8) years for placebo. The primary aim was to establish noninferiority of linagliptin compared with placebo for time to 3P-MACE, defined by the upper limit of the 2-sided 95% CI for the HR of linagliptin relative to placebo being less than 1.3. A sequentially rejective multiple test procedure was applied, first testing the primary hypothesis of noninferiority for linagliptin (p<0.001), and, only if this first test was significant, followed by 2 parallel confirmatory superiority tests (not statistically significant; p = 0.74). # The CARMELINA key secondary endpoint was time to first occurrence of any of the following components: Death due to kidney disease, sustained ESRD or a sustained decrease of ≥40% in eGFR from baseline. The key secondary kidney endpoint occurred in 327/3,494 (9.4%) and 306/3,485 (8.8%) patients in the linagliptin and placebo groups, respectively (HR: 1.04 (95% CI, 0.89, 1.22) p=0.62). HR for time to secondary kidney endpoint based on Cox regression analyses in patients treated with at least one dose of study drug (for < 65 years, HR: 1.05 (95% CI, 0.85, 1.29), for 65 to 74 years, HR: 1.06 (95% CI, 0.81, 1.38), for ≥ 75 years, HR: 1.06 (95% CI, 0.64, 1.75)). P value for treatment by age interaction = 0.9968. Median observation time was 1.9 (IQR, 1.2-2.6) years for Trajenta® and 1.7 (IQR, 1.2-2.5) years for placebo. § HHF was an exploratory endpoint. HHF occurred in 209/3,494 (6.0%) vs 226/3,485 (6.5%) patients in the linagliptin and placebo groups, respectively (HR: 0.90 (95% CI, 0.74, 1.08) p=0.26). HR based on Cox regression analyses in patients treated with at least one dose of study drug (for < 65 years, HR: 0.87 (95% CI, 0.63, 1.21), for 65 to 74 years, HR: 0.89 (95% CI, 0.67, 1.18), for ≥ 75 years, HR: 0.92 (95% CI, 0.63, 1.35)). P value for treatment by age interaction = 0.9788. Because both the parallel confirmatory tests for superiority of the primary outcome (3P-MACE) and the key secondary outcome (composite kidney outcome) in the overall population were not significant (p=0.74 and p=0.62 for superiority, respectively), all subsequent analyses and outcomes are considered exploratory. ** Trajenta® is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control as: monotherapy, when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment; combination therapy, in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control. Trajenta® is contraindicated in those with hypersensitivity to any of the active substances or excipients, is not licensed for paediatric use and should not be used in pregnant women. †† The CAROLINA primary endpoint was defined as non-inferiority of Trajenta® vs glimepiride in time to first occurrence of CV death, non-fatal MI, or non-fatal stroke. The primary endpoint occurred in 356/3,023 (11.8%) and 362/3,010 (12.0%) patients in the linagliptin and glimepiride groups, respectively (HR 0.98; 95% CI 0.84, 1.14). The HRs for 3P-MACE for linagliptin compared with glimepiride were 1.11 [95% CI 0.88,1.41] for patients aged <65 years, 0.88 [0.69,1.12] for those aged 65 to 74 years, and 0.99 [0.74,1.31] for those aged ≥ 75 years. P value for treatment by age interaction = 0.3949. Overall median observation time and treatment duration were 6.3 and 5.9 years, respectively, in the linagliptin and glimepiride groups. Median observation times across age groups were very similar, while median treatment time declined slightly with age (6.1, 5.8, and 5.5 years in participants aged <65, 65 to 74 and ≥ 75 years, respectively). A sequentially rejective multiple test procedure was applied, first testing the primary hypothesis of noninferiority for linagliptin (p<0.001), and, only if this first test was significant, followed by 2 parallel confirmatory superiority tests (not statistically significant; p = 0.76). ‡‡ The CAROLINA key secondary endpoint was a composite endpoint of treatment sustainability: the proportion of participants with HbA1c 7.0% at the final visit without glycaemic rescue medication, without any episodes of moderate or severe hypoglycaemia and without >2% weight gain between the end of titration and final visit. The key secondary endpoint occurred in 16.0% and 10.2% of patients in the linagliptin and glimepiride groups, respectively (OR 1.68; 95% CI, 1.43, 1.96). For patients < 65 years, the key secondary endpoint occurred in 14.0% and 8.6% of patients in the linagliptin and glimepiride groups, respectively (OR 1.73; 95% CI, 1.37, 2.18); for patients 65 to 74 years, the key secondary endpoint occurred in 18.5% and 11.7% of patients in the linagliptin and glimepiride groups, respectively (OR 1.71; 95% CI, 1.34, 2.18); for patients ≥ 75 years, the key secondary endpoint occurred in 17.1% and 11.9% of patients in the linagliptin and glimepiride groups, respectively (OR 1.52; 95% CI, 1.03, 2.24); P value for treatment by age interaction = 0.8446. Because the confirmatory test for superiority of the primary outcome, 3P-MACE, in the overall population was not significant (p=0.76 for superiority), all subsequent analyses are considered exploratory. ## Percentage of patients experiencing a hypoglycaemic event in the overall study cohort was 13.1% for linagliptin and 42.1% for glimepiride (HR 0.25 (95% CI, 0.19, 0.33) non-inferiority p<0.0001). Percentage of patients experiencing a hypoglycaemic event in patients aged 75 and older was 9.8% for linagliptin and 36% for glimepiride. The risk for moderate or severe hypoglycaemia in the overall study cohort was substantially lower with linagliptin than glimepiride (HR=0.18 [95% CI 0.15,0.21]) with no evidence of heterogeneity across age groups (P=0.23 for treatment-by-age-group interaction); Moderate: Investigator-reported episode of symptomatic hypoglycaemia with plasma glucose ≤70 mg/dL; Severe: Requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Kaplan-Meier estimate; HR and 95% CI derived from Cox regression with factor treatment; 2-sided p-value. Because the confirmatory test for superiority of the primary outcome, 3P-MACE, in the overall population was not significant (p=0.76 for superiority), all subsequent analyses are considered exploratory.

Abbreviations

CI: Confidence intervals; **CV:** Cardiovascular; **eGFR:** Estimated glomerular filtration rate; **ESRD:** End stage renal disease; **HHF:** Hospitalisation for heart failure; **HR:** Hazard ratio; **IQR:** interquartile range; **MI**: myocardial infarction; **OR:** Odds ratio

References

1. Rosenstock J, et al. JAMA 2019; 321: 69-79. **2.** Rosenstock J, et al. Cardiovasc Diabetol 2018; 17:39. **3.** Cooper M, et al. Diabetes Obes Metab. 2020; 1–12. **4.** Marx N, et al. Diab Vasc Res. 2015; 12: 164-74. **5.** Rosenstock J, et al. JAMA. 2019; doi:10.1001/jama.2019.13772. **6.** Espeland MA, et al. Diab Obes Met 2020. doi: 10.1111/dom.14254. **7.** Del Prato S, et al. J Diab Compl. 2013; 27:274-9. **8.** Trajenta® Summary of Product Characteristics. October 2019.

Short version of the EU Summary of Product Characteristics (SPC)
Medicinal Product: Trajenta® 5mg film-coated tablets

Each tablet contains 5 mg of linagliptin. For the full list of excipients, consult section 6.1. of the full SPC. **Therapeutic indications:** Trajenta is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control as: a) monotherapy: when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment. b) combination therapy: in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control. **Posology and method of administration: Posology:** The dose of linagliptin is 5 mg once daily. When linagliptin is added to metformin, the dose of metformin should be maintained, and linagliptin administered concomitantly. When linagliptin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin, may be considered to reduce the risk of hypoglycaemia. **Renal impairment:** For patients with renal impairment, no dose adjustment for linagliptin is required. **Hepatic impairment:** Pharmacokinetic studies suggest that no dose adjustment is required for patients with hepatic impairment but clinical experience in such patients is lacking. **Elderly:** No dose adjustment is necessary based on age. **Paediatric population:** The safety and efficacy of linagliptin in children and adolescents has not yet been established. No data are available. **Method of administration:** The tablets can be taken with or without a meal at any time of the day. If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. **Contraindications**: Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions for use:** Linagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. **Hypoglycaemia:** Linagliptin alone showed a comparable incidence of hypoglycaemia to placebo. In clinical trials of linagliptin as part of combination therapy with medicinal products not known to cause hypoglycaemia (metformin), rates of hypoglycaemia reported with linagliptin were similar to rates in patients taking placebo. When linagliptin was added to a sulphonylurea (on a background of metformin), the incidence of hypoglycaemia was increased over that of placebo. Sulphonylureas and insulin are known to cause hypoglycaemia. Therefore, caution is advised when linagliptin is used in combination with a sulphonylurea and/or insulin. A dose reduction of the sulphonylurea or insulin may be considered. **Acute pancreatitis:** Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Acute pancreatitis has been observed in patients taking linagliptin. In a cardiovascular and renal safety study (CARMELINA) with median observation period of 2.2 years, adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Trajenta should be discontinued; if acute pancreatitis is confirmed. Trajenta should not be restarted. Caution should be exercised in patients with a history of pancreatitis. **Bullous pemphigoid**: Bullous pemphigoid has been observed in patients taking linagliptin. In the CARMELINA study, bullous pemphigoid was reported in 0.2% of patients on treatment with linagliptin and in no patient on placebo. If bullous pemphigoid is suspected, Trajenta should be discontinued. **Interaction with other medicinal products and other forms of interaction:** Linagliptin is considered unlikely to cause interactions with other P-gp substrates. Clinical data suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low. For more detailed information on interactions with linagliptin, please consult the full version of the SPC. **Pregnancy and lactation: Pregnancy:** The use of linagliptin has not been studied in pregnant women. As a precautionary measure, it is preferable to avoid the use of linagliptin during pregnancy. **Breast-feeding:** A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from linagliptin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **Effects on ability to drive and use machines:** Linagliptin has no or negligible influence on the ability to drive and use machines. However, patients should be alerted to the risk of hypoglycaemia especially when combined with sulphonylurea and/or insulin. **Undesirable effects: Linagliptin 5 mg daily as monotherapy or as add-on therapy** (in clinical studies, post-marketing experience, or cardiovascular outcome trials): very common (≥ 1/10) - hypoglycaemia (observed in combination with metformin plus sulphonylurea); common (≥ 1/100 to <1/10) - lipase increased; uncommon (≥ 1/1,000 to < 1/100) - nasopharyngitis, hypersensitivity (e.g. bronchial hyperreactivity), cough, constipation (observed in combination with insulin), rash, amylase increased; rare (≥ 1/10,000 to < 1/1,000) - pancreatitis, angioedema, urticaria, bullous pemphigoid. **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 the national reporting systems. **Revision date:** October 2019