Risk of hypoglycaemia in people aged ≥65 years receiving linagliptin: pooled data from 1489 individuals with type 2 diabetes mellitus

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Abstract

Aims: To investigate the risk of hypoglycaemia in people aged ≥65 years with type 2 diabetes mellitus (T2DM) treated with linagliptin, in the largest pooled analysis performed to date.

Materials and methods: 1489 patients aged ≥65 years with T2DM were pooled from 11 randomised, double-blind, parallel group, placebo-controlled trials evaluating linagliptin 5 mg alone, or in addition to various background therapies. The primary safety endpoint was the incidence of investigator-defined hypoglycaemia.

Results: There was no significant difference in the risk of hypoglycaemia between linagliptin and placebo in the all-patient population at 24 weeks (hazard ratio [HR] 1.07; 95% confidence interval [CI]: 0.84, 1.36; *P*=0.5943) – despite significant (*P*<0.0001) improvements in glycaemic control – and 1 year (HR 1.02; 95% CI: 0.81, 1.27; *P*=0.8803). Similar findings were observed for linagliptin vs placebo in subgroup analyses by background medication (e.g. SUs and/or insulin vs no such drugs), age, baseline glycated haemoglobin (HbA1c), ethnicity, and baseline estimated glomerular filtration rate. Patients with a baseline HbA1c ≥7.5% had significantly higher odds of achieving HbA1c <7.5% without hypoglycaemia in the linagliptin group compared with placebo at 24 weeks (34.1% vs 13.7%; 95% CI: 2.04, 4.12; *P*<0.0001).

Conclusions: This pooled analysis indicates that linagliptin was effective in treating older people with T2DM towards their HbA1c targets with a favourable safety and tolerability profile and low risk of hypoglycaemia. The safety profile was maintained even on background therapies with known risk of hypoglycaemia, such as insulin and sulfonylureas.

Keywords: hypoglycaemia, linagliptin, older people, pooled analysis, type 2 diabetes mellitus

What was known?

- Older patients with type 2 diabetes are at increased risk of hypoglycaemia.
- Linagliptin is a DPP-4 inhibitor, with primarily non-renal excretion, that has shown good safety and tolerability in older and vulnerable patient populations in multiple clinical trials.
- Current prescribing information for DPP-4 inhibitors (including linagliptin) advise reductions in the dose of sulphonylureas or insulin (therapies with known risk of hypoglycaemia), when used in combination with DPP-4 inhibitors.

What is new?

- Linagliptin helped more patients to achieve their glycaemic targets without any confirmed hypoglycaemic event, irrespective of background treatment with sulphonylurea and/or insulin.
- Linagliptin vs placebo did not increase the risk of hypoglycaemia in the overall population nor in any of the subgroups evaluated, which included age, ethnicity, background therapy, kidney function and baseline HbA1c.

1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major global problem in older individuals: the prevalence of T2DM increases with age and there is an elevated risk of disease-related complications, especially in patients who have had diabetes for many years. The risk of diabetes in older individuals is increasing: in the United States, the prevalence of diabetes in older people has increased by 36.0% from 1993 to 2001.[1] Furthermore, in 2017 the estimated prevalence of diabetes worldwide among people aged 65−99 years was 18.8% (122.8 million).[2] The absolute number of people with diabetes above the age of 65 years is projected to more than double by 2045 to 253.4 million.[2] In addition, impaired fasting glucose and/or glucose tolerance have a high prevalence among older individuals, and this creates a potential reservoir for further cases of overt diabetes.[3] The management of T2DM in this population is particularly complex and challenging in the context of multimorbidities. The associated polypharmacy increases the risk of both drug-drug interactions and poor adherence to multiple drug regimens.

A key issue in the management of T2DM in older individuals is that these patients are at increased risk of hypoglycaemia and of developing hypoglycaemia-related long-term complications (e.g. low quality of life, fractures, depression and dementia).[4-9] Furthermore, the benefits of intensive blood glucose-lowering strategies in older patients are more modest than those achieved in younger patients,[10] and recent data point toward potential overtreatment in the older age group.[11] While good glycaemic control continues to be a key objective of diabetes treatment for all ages, current guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes recommend a patient-centred approach, with less stringent glycaemic targets in the case of important comorbidities, longer disease duration, reduced life expectancy and increased risks associated with hypoglycaemia.[12]

One of the major challenges facing current treatment strategies is that a substantial number of older patients with T2DM struggle to achieve even their less stringent individualised glycated haemoglobin (HbA1c) targets.[12] Furthermore, many of these patients are on complex regimens that include insulin and/or a sulphonylurea (SU), drugs that increase the risk of hypoglycaemia.[13] While metformin continues to be a first-line medication in the treatment of T2DM, recent recommendations for the treatment of patients aged >65 years focus on regimens with either basal insulin, dipeptidyl peptidase-4 inhibitors (DPP4is), or a combination of these.[14]

Since 2008, the US Food and Drug Administration has requested evidence that T2DM therapies do not result in an 'unacceptable increase in cardiovascular (CV) risk'.[15] Given that the risk of CV disease also increases with age, clinical trials aimed specifically at investigating the CV risk of T2DM drugs have included significant proportions of older patients (which might have been excluded from other trials). Long-term CV outcome trials investigating the safety of DPP4is found that sitagliptin, saxagliptin and alogliptin were well tolerated, with no increase in the risk of CV death, non-fatal myocardial infarction, or non-fatal stroke (3-point major adverse CV events) in populations at high risk of CV events.[16-18] Furthermore, subanalyses of these studies in older patient populations have

raised no significant safety issues.[19,20] Two CV outcome trials (CVOTs) for linagliptin, CARMELINA® [NCT01897532] and CAROLINA® [NCT01243424], are currently ongoing with results expected from 2018.

The DPP4i linagliptin has been shown to improve glycaemic control and has a good tolerability profile, including low risk for hypoglycaemia and weight gain.[21-23] When investigated specifically in older patients (aged ≥70 years) who were receiving metformin, SUs, basal insulin, or a combination of these drugs, linagliptin was effective in lowering blood glucose compared with placebo. The incidence of adverse events (AEs) including hypoglycaemia was similar in the linagliptin and placebo patient groups.[24] A large pooled analysis of seven phase III, placebo-controlled clinical trials investigating 1331 patients ≥65 years of age has confirmed these findings.[25]

Current prescribing information for linagliptin (and other members of the DPP4i class) recommend caution when used in combination with medications known to cause hypoglycaemia (e.g. insulin and an SU).[22,26] However, a number of subgroup analyses of phase III clinical trials with linagliptin suggest that the risk of hypoglycaemia in high-risk patients is relatively low, even when combined with insulin and/or an SU.[27-30]

To further clarify the safety and efficacy of linagliptin in older patients, we performed a large pooled analysis, which specifically investigated the risk of hypoglycaemia in patients ≥65 years of age receiving linagliptin alone, or in combination with other glucose-lowering therapies.

2 MATERIALS AND METHODS

2.1 Study design

In this post hoc analysis the safety and efficacy of linagliptin was assessed in older patients (aged ≥65 years) with inadequately controlled T2DM. Data were pooled from all relevant studies: 11 randomised, double-blind, parallel group, placebo-controlled trials evaluating linagliptin 5 mg alone,

or in addition to various background therapies. Inclusion criteria across all studies specified HbA1c minimum entry levels ranging from ≥6.5% to ≥7.5% for treatment-naïve patients and from ≥7.0% to ≥7.5% for patients on background antidiabetic medication. Study designs and enrolment criteria for the included trials were similar, allowing patient-level data to be pooled for further assessment.

This pooled analysis included clinical trials that compared linagliptin with placebo in a number of regimens:

- Monotherapy[31-33]
- Monotherapy or add-on to 1 oral antidiabetes drug[34]
- Add-on to metformin[21,35]
- Add-on to metformin and SU[22]
- Add-on to metformin and pioglitazone[36]
- Add-on to insulin with or without other glucose-lowering therapies[24,37,38]

The trials included in this analysis had a minimum duration of 24 weeks. Two trials had a study duration of 52 weeks. The studies were carried out in accordance with the Declaration of Helsinki and Good Clinical Practice principles (October 1996) as well as national Good Clinical Practice regulations, where applicable. The protocols, informed consent and patient information forms were reviewed and approved by the local institutional review boards. A synopsis of the studies included in this analysis, describing background therapies, patient numbers and study durations, is presented in Supplemental Table 1.

2.2 Endpoints

The primary efficacy endpoint in this analysis was adjusted mean change in HbA1c from baseline to 24 weeks. The primary safety endpoint was the incidence of investigator-defined hypoglycaemic AEs; prespecified as blood glucose ≤70 mg/dL (≤3.9 mmol/L) with or without symptoms, or severe hypoglycaemia requiring assistance. Secondary safety endpoints were the incidence and severity of

overall investigator-reported AEs. Additional evaluations included a composite endpoint consisting of patients achieving an HbA1c <7.5% without confirmed hypoglycaemia.

2.3 Statistical analysis

The primary efficacy analysis was performed on the full analysis set (FAS), which comprised all randomised patients treated with at least 1 dose of study drug who had a baseline and at least 1 on-treatment HbA1c measurement. Missing data were imputed using a last observation carried forward approach. The change in HbA1c from baseline to week 24 was compared between the linagliptin and placebo groups using an analysis of covariance. The model included treatment, baseline HbA1c, washout and study. Safety analyses were performed on the treated set, which comprised all patients who were treated with at least 1 dose of study drug.

Frequency and incidence rates per 100 patient-years (to account for differences in exposure) for investigator-defined hypoglycaemia were calculated and presented as both descriptive summaries and inferential analyses of the treated patient set. Kaplan-Meier analyses were used to illustrate the risk for investigator-defined hypoglycaemic events over time. Hazard ratios (HRs) and associated confidence intervals were calculated for the overall population and for subgroups of patients based on background therapy, age, baseline HbA1c, ethnicity and estimated glomerular filtration rate (eGFR) using a Cox regression model. Similarly, the model included treatment, baseline HbA1c, washout and study. Frequency and incidence rates per 100 patient-years for overall investigator-reported AEs (coded according to the Medical Dictionary for Regulatory Activities version 18.0) were calculated for the overall population.

3 RESULTS

3.1 Patient demographics and clinical characteristics at baseline

The pooled treated set comprised 1489 patients (linagliptin, n=948; placebo, n=541) and the pooled FAS population 1466 patients (linagliptin, n=936; placebo, n=530). Patient demographics and clinical

characteristics at baseline for patients receiving linagliptin and placebo are shown in Table 1. The median age for both groups was 70 years. The vast majority of the patients were white or Asian.

Two-thirds of patients were on background treatment with either insulin, SU or a combination of these. There were noticeable differences in background medication use between the linagliptin- and placebo-treated patients. Specifically, insulin use was greater among placebo patients compared with linagliptin patients (49% vs 29%, respectively), whereas SU use was lower with placebo vs linagliptin (29% vs 42%). These discrepancies resulted from variations in the background therapies between studies, combined with patient allocation ratios (linagliptin vs placebo) ranging from 3:1 to 1:1, described in Supplemental Table 1. To compensate for these differences a factor 'study' was included in the statistical methods.

3.2 Efficacy

Over 24 weeks, linagliptin produced a meaningful reduction in HbA1c with a placebo-adjusted difference of 0.60% (95% confidence interval [CI]: -0.69, -0.51; $P<0.0001$) (Supplemental Figure 1). Of note, the majority of the patients included in this study had been on strict regimens, with around 60% of them receiving ≥2 antidiabetic drugs and over two-thirds receiving either insulin, or SU, or both (Table 1).

3.3 Safety – hypoglycaemia

The time to first onset of any investigator-defined hypoglycaemic AE was similar for placebo vs linagliptin up to 24 weeks for all patients (HR: 1.07; 95% CI: 0.84, 1.36; $P=0.5943$) (Figure 1A), for patients receiving insulin and/or SU background therapy (HR: 1.07; 95% CI: 0.84, 1.38; $P=0.5762$) (Figure 1B), and for patients not receiving insulin or SU background therapy (HR: 1.01; 95% CI: 0.28, 3.60; $P=0.9894$) (Figure 1C). This finding was also seen up to 1 year for all patients (HR: 1.02; 95% CI: 0.81, 1.27; $P=0.8803$) (Figure 1D).

The frequency, incidence rate, and HR for any investigator-defined hypoglycaemic AEs up to 1 year is shown in Figure 2 and Table 2. Co-medication with SUs and/or insulin dramatically increased the risk for hypoglycaemia (with and without linagliptin treatment; Table 2). Conversely, the overall rate/100 patient-years was similar between linagliptin and placebo treatment groups for all patients (39.5 vs 43.7). Furthermore, HRs were similar between linagliptin and placebo in subgroup analyses by background medication, age, baseline HbA1c, ethnicity or baseline eGFR (Table 2). Analysis of the risk of hypoglycaemia according to quartile of HbA1c change from baseline – whether for all patients, patients treated with insulin and/or SU, or patients not treated with insulin or SU – demonstrated no significant differences between linagliptin and placebo (Supplemental Table 3). Statistical analysis was not performed for severe hypoglycaemia, due to very low number of reported incidents.

3.4 Composite endpoint

The proportion of patients with a baseline HbA1c of ≥7.5% who achieved a target HbA1c of <7.5% at 24 weeks without a confirmed hypoglycaemic event was significantly greater with linagliptin vs placebo treatment (n=1103; 34.1% vs 13.7%; odds ratio [OR]: 2.90; 95% CI: 2.04, 4.12; *P*<0.0001) (Figure 3 and Supplemental Figure 2A). This favourable effect of linagliptin was further confirmed in the subgroup of patients receiving insulin and/or SU background therapy (n=743; 28.7% vs 9.9%; OR: 3.50; 95% CI: 2.22, 5.51 *P*<0.0001: no confirmed hypoglycaemia linagliptin vs placebo) and in the subgroup of patients not receiving insulin or an SU (n=360; 43.1% vs 25.5%; OR: 2.11; 95% CI: 1.20, 3.71; *P*=0.0091: no confirmed hypoglycaemia linagliptin vs placebo). The trend was more pronounced in the case of patients with insulin/SU vs patients without insulin/SU in their treatment regimens (Figure 3 and Supplemental Figure 2B and C). The other evaluated subgroups showed similarly consistent trends.

3.5 Safety – overall AEs

Linagliptin was generally well tolerated. Rates of overall AEs, severe AEs, drug-related AEs, AEs leading to discontinuation and serious AEs per 100 patient-years with linagliptin were similar to placebo (Supplemental Table 2).

4 DISCUSSION

This paper reports a pooled analysis that focuses on the risk of hypoglycaemia in older patients with T2DM when treated with linagliptin alone or in combination with other antidiabetes drugs. As expected, linagliptin was effective in lowering HbA1c levels compared with placebo. In addition, linagliptin vs placebo did not increase the risk of hypoglycaemia in the overall population nor in any of the subgroups evaluated, which included age, ethnicity, background therapy, kidney function and baseline HbA1c.

Our results are in line with observations from previous dedicated clinical trials in older patients, which have reported that linagliptin[24,25] and other DPP4is[39-42] are effective and well-tolerated agents for glycaemic control in this patient population (i.e. lower risk of hypoglycaemia vs SU, and lower reported gastrointestinal AEs vs metformin). Moreover, DPP4is have been used successfully in older patients with T2DM towards achieving individualised glycaemic targets.[43]

Several major CV outcome trials, namely SAVOR-TIMI[16], TECOS[17] and EXAMINE[18], have investigated the CV safety of DPP4is. Although not specifically focused on older patients, these long-term studies included large numbers of subjects aged ≥65 years. In SAVOR-TIMI and TECOS, additional subgroup analyses confirmed that DPP4is demonstrate a good safety profile in older patients at high CV risk, with no increase in the risk of CV death, AEs and serious AEs in older vs younger patients.[19,20] Ongoing CVOTs for linagliptin (CARMELINA® and CAROLINA®) will provide further long-term (>4 years) data regarding the CV safety and efficacy of incretin therapies. In the context of CVOTs of incretin therapies these 2 linagliptin studies have unique designs: investigating CV outcomes against a single active comparator (CAROLINA®)[44], or analysing patients at high risk of both CV and renal events (CARMELINA®).

Here, we provide further evidence supporting the low risk of hypoglycaemia in older patients when linagliptin is given on a background of insulin and/or an SU. However, we did not find evidence to

support a previous subgroup analysis, which suggested that addition of linagliptin might decrease the incidence of hypoglycaemia relative to placebo in older patients on insulin.[27]

Treatment-induced hypoglycaemia is of particular concern in the management of T2DM in older patients and is a major cause of hospitalisation in these patients.[6,45,46] A severe hypoglycaemic episode can be immediately life-threatening, due to risk of sudden death, or injuries sustained from falls. The risk of moderate or severe hypoglycaemia in older individuals is associated with reduced satisfaction with, and adherence to, T2DM treatment,[47] which could lead to suboptimal control of hyperglycaemia and an elevated risk of diabetes-related complications. Furthermore, hypoglycaemia is associated with an increased risk of cognitive decline and dementia in older individuals,[7-9] and as T2DM and cognitive decline progress, patients experience increased difficulties in promptly identifying the symptoms of hypoglycaemia, which compounds the problem.[48,49] Given the risks associated with hypoglycaemia, including increased hip fracture incidence, poor treatment adherence, and accentuated cognitive decline, minimising the risk of hypoglycaemia is a key objective of T2DM therapeutic strategies in older patients.[12]

The American Geriatrics Society, the International Association of Gerontology and Geriatrics, the European Diabetes Working Party for Older People and the International Task Force of Experts in Diabetes all advise less stringent glycaemic targets than for younger patients.[50,51] In line with this, the most recent ADA guidelines recommend an HbA1c goal of <7.5% for older patients with few coexisting chronic illnesses, <8.0% for patients with multiple coexisting chronic conditions, and <8.5% for patients with complex conditions and reduced life expectancy.[52] Furthermore, the Japan Diabetes Society and the Japan Geriatrics Society Joint Committee on Improving Care for Elderly Patients with Diabetes both recommend glycaemic targets that are based on age, activities of daily living, cognition, and the use of drugs with high hypoglycaemic risk (e.g. SUs and insulin).[53]

In a survey assessing the incidence of hypoglycaemia in older patients with T2DM in Japan, DPP4is were the most frequently prescribed oral antidiabetes drugs and were associated with a low risk of

hypoglycaemia.[49] However, cases of severe hypoglycaemia when sitagliptin was used in combination with an SU were reported in Japan, after November 2009. A recommendation by an expert national committee to reduce the dose of SUs in this combination helped decrease the number of reported hypoglycaemia cases.[54]

In this analysis, a nearly 15-fold increase in the relative risk of hypoglycaemia was observed with SU/insulin vs no SU/insulin as background treatment in older individuals with T2DM. Nevertheless, the substantial elevation in the risk for hypoglycaemia in patients taking SUs and/or insulin was not further increased by the addition of linagliptin. Several other published analyses have also indicated that addition of linagliptin to either insulin or an SU does not increase the risk of hypoglycaemic AEs in older patients,[24,25,27] or in other vulnerable patient populations.[28-30]

As in the case of other DPP4is[55], the prescribing information for linagliptin advises that a lower dose of insulin or SU may be considered in order to reduce the risk of hypoglycaemia, when insulin or an SU is used in combination with linagliptin.[22] In the case of patients in whom hypoglycaemia is a major concern, replacing SU with alternative medications with lower risks of hypoglycaemia could be considered as well. Furthermore, careful consideration should be given when SU and/or insulin therapies are prescribed for older individuals, and as this study shows, the addition of DPP-4 inhibitors (such as linagliptin) rather than insulin uptitration could help improve the glycaemic control without exacerbating the risk of hypoglycaemia.

Furthermore, our analysis shows that linagliptin vs placebo significantly improved the probability of achieving an HbA1c target of <7.5% without hypoglycaemia after 24 weeks, and that this effect may be more pronounced in patients with insulin and/or SU background therapy. As the HR for hypoglycaemia did not change, the higher percentage of patients achieving this endpoint was due mainly to better glycaemic control with linagliptin. This finding will be reassuring to clinicians attempting to achieve recommended glycaemic targets in their older patients. The large number of patients on treatment with a wide range of therapies included in this study supports its significance.

Another strength is that the data were collected prospectively following prespecified standard operating procedures, minimizing the risk of investigator bias.

In terms of study limitations, given the nature of this post hoc pooled analysis, interpretation of the findings is somewhat restricted. Also, as only 2 of the 11 studies included in the analysis extended to 1 year, data availability at the 52-week time point were limited (however, analyses at 24 weeks, corresponding to the primary efficacy endpoint and with greater patient numbers, provided similar findings in terms of hypoglycaemic risk with linagliptin). Furthermore, the studies analysed were not primarily designed to evaluate the risk of hypoglycaemia. In addition, the non-randomised nature of the analysis resulted in an imbalance, at baseline, with regard to background medication between placebo and linagliptin subgroups. Finally, patient numbers in some of the subgroups were very small, e.g. in patients without insulin or SU background medication, and in those with moderate-to-severe renal impairment. Consequently, the results from these particular subgroups should be interpreted with caution, until future studies can provide more robust data.

In our study, the incidence of hypoglycaemia was similar between the linagliptin and placebo treatment arms, in a patient population with a mean HbA1c of 8.1%. Data from the literature suggest that the risk for hypoglycaemia may increase exponentially as HbA1c drops below 7.0% and that, in this context, the addition of DPP4is to a SU may require SU dose reduction.[54,56,57] In the present cohort, there were not sufficient events of severe hypoglycaemia to allow for a meaningful statistical analysis. Data from previous studies with DPP4is compared to SUs have indicated that the relative changes in severe episodes of hypoglycaemia are similar to those in any episodes (consisting mainly of non-severe hypoglycaemia).[58] In a pooled safety analysis of 22 clinical studies there was no increase in the proportion of patients experiencing severe hypoglycaemia requiring assistance in the linagliptin group compared with placebo (0.4% vs 0.5%).[59]

In summary, linagliptin is effective in reducing the absolute level of HbA1c and in helping older patients with T2DM to achieve the recommended HbA1c target of <7.5% without an increase in

hypoglycaemia. Importantly, linagliptin does not accentuate the risk of hypoglycaemia when used in conjunction with insulin and SUs, therapies with a known risk of hypoglycaemia. Overall, these findings indicate that linagliptin offers clinicians another therapeutic option for the management of older patients with inadequately controlled T2DM.

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DISCLOSURES

M.N. has been member on advisory boards or has consulted with AstraZeneca (moderate), Boehringer Ingelheim (moderate), Eli Lilly & Co. (significant), Fractyl (moderate), GlaxoSmithKline (moderate), Intarcia (moderate), Menarini/Berlin Chemie (moderate), Merck, Sharp & Dohme (significant), and Novo Nordisk (significant). His institution has received grant support from AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., GlaxoSmithKline, Intarcia, Menarini/Berlin-Chemie, Merck, Sharp & Dohme, Novartis Pharma, and Novo Nordisk A/S. He has also served on the speakers' bureau of AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., GlaxoSmithKline, Menarini/Berlin Chemie (all moderate), Merck, Sharp & Dohme, and Novo Nordisk A/S (both significant). A.A. has received speaker honoraria from pharmaceutical companies Merck Sharp & Dohme, Dainippon Sumitomo Parma Co. Ltd., Kyowa Hakko Kirin Co. Ltd., AstraZeneca, Astellas Pharma Inc., Eli Lilly Japan Co. Ltd., Ono Pharmaceutical Co. Ltd., Taisho Toyama Pharmaceutical Co. Ltd., Novo Nordisk Pharma Ltd., Takeda Pharmaceutical Co. Ltd., and Boehringer Ingelheim GmbH, grant support from Daiichi-Sankyo Co. Ltd. U.H. and D.C. are employees of Boehringer Ingelheim Pharma GmbH & Co. KG. A.P. is an employee of Eli Lilly and Company. K.K. has received honoraria and research support from

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AUTHOR CONTRIBUTIONS

M.N., A.A., U.H., A.P., D.C. and K.K. were involved in the development of the clinical protocol. U.H. and A.P. were responsible for the study conduct and data collection. U.H. was involved in the statistical analysis of the data. M.N., A.A., U.H., A.P., D.C. and K.K were involved in the critical analysis of the data and writing the manuscript. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and have approved the final version. Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Paul Nistor and Charlie Bellinger of Envision Scientific Solutions, during the preparation of this manuscript.

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TABLE 1 Baseline demographics and clinical characteristics

	Linagliptin	Placebo
Patients (treated set[a]), N	948	541
Age, years, mean (SD)	71.0 (4.5)	70.8 (4.7)
Median, years (range)	70.0 (65–91)	70.0 (65–91)
Age group, n (%)		
65–69 years	408 (43.0)	257 (47.5)
70–74 years	347 (36.6)	169 (31.2)
75–79 years	165 (17.4)	82 (15.2)
≥80 years	28 (3.0)	33 (6.1)
Males, n (%)	527 (55.6)	259 (47.9)
Ethnicity, n (%)		
American Indian/Alaskan Native	3 (0.3)	2 (0.4)
Asian	219 (23.1)	97 (17.9)
Black/African American	28 (3.0)	33 (6.1)
White	698 (73.6)	409 (75.6)
Body weight, kg, mean (SD)	79.7 (17.4)	80.6 (16.5)
Body mass index, kg/m^2, mean (SD)	29.1 (5.1)	29.8 (5.0)
Renal function (eGFR by MDRD), n (%)		
Normal renal function (≥90 $mL/min/1.73^2$)	183 (19.3)	91 (16.8)
Mild impairment (60 to <90 $mL/min/1.73^2$)	533 (56.2)	290 (53.6)
Moderate impairment (30 to <60 $mL/min/1.73^2$)	184 (19.4)	122 (22.6)
Severe to end-stage impairment (<30 $mL/min/1.73^2$)	44 (4.6)	31 (5.7)
Missing	4 (0.4)	7 (1.3)
Patients (full analysis set[b]), N	936	530
HbA1c, %, mean (SD)	8.1 (0.8)	8.1 (0.8)
Fasting plasma glucose, mg/dL, mean (SD)	157.7 (42.0)	155.3 (45.7)
Time since diagnosis of diabetes, n (%)		
≤1 year	52 (5.6)	24 (4.5)
>1 to ≤5 years	162 (17.3)	59 (11.1)
>5 years	722 (77.1)	447 (84.3)
Number of prior antidiabetes drugs, n (%)		
0	72 (7.7)	35 (6.6)
1	311 (33.2)	158 (29.8)
≥2	553 (59.1)	337 (63.6)
Insulin ± other antidiabetes drugs	267 (28.5)	260 (49.1)
SU ± other antidiabetes drugs	390 (41.7)	156 (29.4)
Insulin + SU only	11 (1.2)	5 (0.9)
Insulin and/or SU	636 (67.9)	409 (77.2)
No insulin/no SU	300 (32.1)	121 (22.8)

eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; MDRD, modification of diet in renal disease; SD, standard deviation; SU, sulphonylurea.

[a]All patients who were treated with at least 1 dose of study medication.

[b]All patients who were treated with at least 1 dose of study medication, and had a baseline and at least 1 on-treatment HbA1c measurement.

TABLE 2 Frequency, incidence rate (per 100 patient-years), and HR for any investigator-defined hypoglycaemic AEs, up to 1 year

	Linagliptin				Placebo				Linagliptin vs Placebo
	n/N	%	Time at risk, patient-years	Rate/ 100 patient-years	n/N	%	Time at risk, patient-years	Rate/ 100 patient-years	HR[a] (95% CI)
All patients (treated set[b])	198/948	20.9	501.9	39.5	142/541	26.2	325.1	43.7	1.02 (0.81, 1.27)
Background medication									
Insulin and/or SU	190/576	33.0	331.6	57.3	138/389	35.5	258.0	53.5	1.02 (0.81, 1.27)
Insulin/no SU	96/247	38.9	205.8	46.7	104/257	40.5	204.1	50.9	0.94 (0.71, 1.25)
SU/no insulin	85/308	27.6	116.3	73.1	31/126	24.6	50.9	60.9	1.20 (0.79, 1.83)
No insulin/no SU	8/372	2.2	170.3	4.7	4/152	2.6	67.1	6.0	1.01 (0.28, 3.60)
Age									
<75 years	147/755	19.5	405.5	36.3	117/426	27.5	256.6	45.6	0.92 (0.72, 1.18)
≥75 years	51/193	26.4	96.4	52.9	25/115	21.7	68.5	36.5	1.37 (0.82, 2.27)
Baseline HbA1c									
<7.5%	52/238	21.8	117.1	44.4	26/128	20.3	69.7	37.3	1.38 (0.84, 2.25)
≥7.5%	146/710	20.6	384.8	37.9	116/413	28.1	255.4	45.4	0.93 (0.72, 1.19)
Ethnicity									
Asian	27/219	12.3	107.4	25.1	22/97	22.7	48.6	45.2	0.69 (0.38, 1.27)
White	163/698	23.4	381.0	42.8	111/409	27.1	257.4	43.1	1.06 (0.83, 1.36)
eGFR									
≥90 mL/min/1.73m^2	26/183	14.2	89.0	29.2	12/91	13.2	56.6	21.2	1.75 (0.86, 3.58)
60 to <90 mL/min/1.73 m^2	98/533	18.4	289.2	33.9	75/290	25.9	171.7	43.7	0.79 (0.58, 1.08)
30 to <60 mL/min/1.73 m^2	45/184	24.5	101.2	44.5	37/122	30.3	76.1	48.6	1.04 (0.65, 1.65)

AE, adverse events; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HR, hazard ratio; pt, patient; SU, sulphonylurea.

[a]The HR and CIs are based on a Cox regression with the covariate baseline HbA1c and the factors treatment, washout and study.
[b]All patients who were treated with at least 1 dose of study medication.

SUPPLEMENTAL TABLE 1 Synopsis of 11 clinical trials included in the pooled analysis

Clinical Trials.gov reg. no:	Background therapy	Randomised patients, N	Patients ≥65 years, n	Study duration, weeks	Linagliptin:Placebo ratio	Reference
NCT00621140	–	503	105	24	2:1	[31]
NCT00954447	INS ± MET ± PIO	1263	421	52	1:1	[37]
NCT00601250	MET	701	154	24	3:1	[21]
NCT00602472	MET + SU	1058	288	24	3:1	[22]
NCT00800683	Any combination[a]	133	74	52	1:1	[38]
NCT01084005	INS and/or MET and/or SU	241[b]	241	24	2:1	[24]
NCT00798161	–	214[c]	47	24	2:1	[32]
NCT01194830	≤1 OAD	226	32	24	1:1	[34]
NCT01214239	–	300	42	24	2:1	[33]
NCT00996658	MET + PIO	272	31	24	2:1	[36]
NCT01215097	MET	306	54	24	2:1	[35]

INS, insulin; MET, metformin; OAD, oral antidiabetes drug; PIO, pioglitazone; SU, sulphonylurea.
[a]Permitted therapies included: insulin, SU, glinides, PIO, α-glucosidase inhibitors.
[b]All patients ≥70 years of age.
[c]Value includes only patients from linagliptin 5 mg and placebo arms, from a larger study.

SUPPLEMENTAL TABLE 2 Summary of AEs up to 1 year (treated set[a])

	Linagliptin (N=948)				Placebo (N=541)			
	n	% (95% CI)	Time at risk, patient-years	Rate/ 100 patient-years (95% CI)	n	% (95% CI)	Time at risk, patient-years	Rate/ 100 patient-years (95% CI)
Any AE	652	68.8 (65.8, 71.6)	286.4	227.7 (210.9, 245.8)	402	74.3 (70.5, 77.8)	161.9	248.3 (225.2, 273.7)
Severe AEs	47	5.0 (3.7, 6.5)	598.3	7.9 (5.9, 10.4)	40	7.4 (5.5, 9.9)	411.3	9.7 (7.1, 13.2)
Drug-related AEs	162	17.1 (14.8, 19.6)	536.7	30.2 (25.9, 35.2)	112	20.7 (17.5, 24.3)	355.7	31.5 (26.2, 37.9)
AEs leading to discontinuation of trial medication	34	3.6 (2.6, 5.0)	611.0	5.6 (4.0, 7.8)	26	4.8 (3.3, 6.9)	421.6	6.2 (4.2, 9.0)
Serious AEs	77	8.1 (6.5, 10.0)	588.4	13.1 (10.5, 16.4)	78	14.4 (11.7, 17.6)	388.8	20.1 (16.1, 25.0)
Fatal	2	0.2 (0.1, 0.8)	612.9	0.3 (0.1 , 1.2)	4	0.7 (0.3, 1.9)	423.0	0.9 (0.4 , 2.4)
Immediately life-threatening	2	0.2 (0.1, 0.8)	612.2	0.3 (0.1, 1.2)	2	0.4 (0.1 , 1.3)	423.0	0.5 (0.1, 1.7)
Causing disability or incapacity	1	0.1 (0.0, 0.6)	612.7	0.2 (0.0, 0.9)	1	0.2 (0.0, 1.0)	423.0	0.2 (0.0 , 1.3)
Requiring hospitalisation	75	7.9 (6.4, 9.8)	588.8	12.7 (10.2, 16.0)	66	12.2 (9.7, 15.2)	391.5	16.9 (13.3, 21.4)
Prolonged hospitalization	6	0.6 (0.3, 1.4)	610.9	1.0 (0.5, 2.1)	10	1.8 (1.0, 3.4)	420.8	2.4 (1.3 , 4.4)
Other	1	0.1 (0.0, 0.6)	612.9	0.2 (0.0 , 0.9)	8	1.5 (0.8, 2.9)	420.7	1.9 (1.0, 3.8)

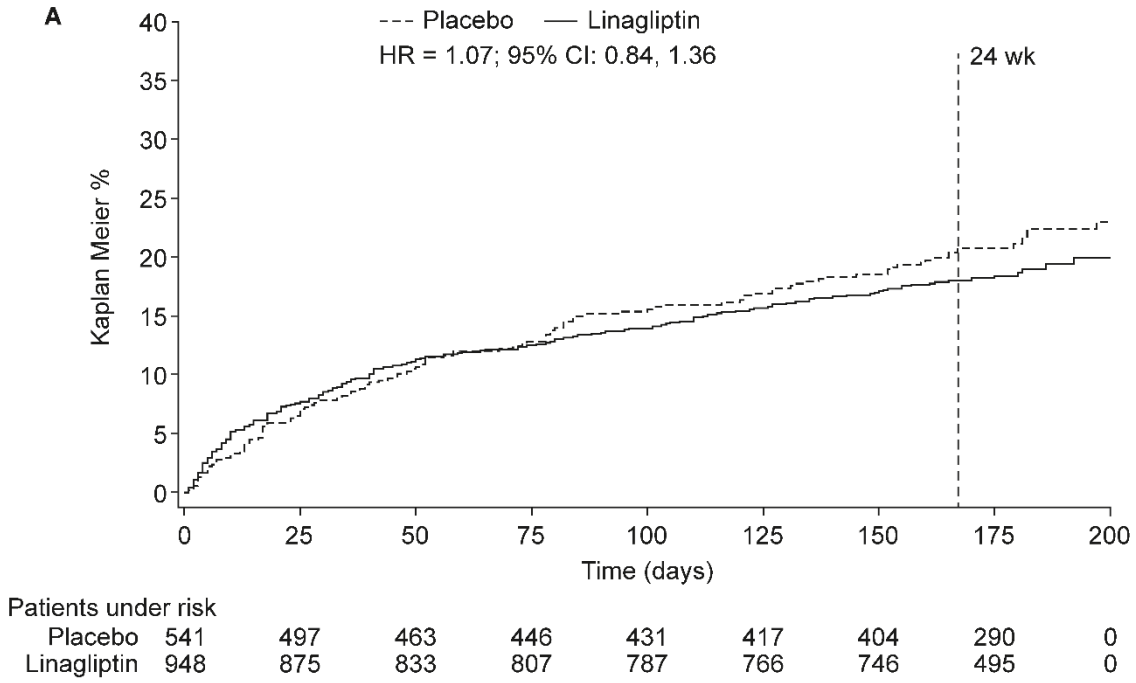
AE, adverse event; CI, confidence interval.
[a]All patients who were treated with at least 1 dose of study medication.

SUPPLEMENTAL TABLE 3 Any investigator-reported hypoglycaemia by quartiles of change in HbA1c (within treatment[a], treated set[b])

	Linagliptin			Placebo				
	n/N	% HbA1c change	Hypoglycaemia incidence rate/100 patient-years	n/N	% HbA1c change	Hypoglycaemia incidence rate/100 patient-years	HR[c]	95% CI
All patients								
Q1	37/208	<–1.1	32.80	38/123	<–0.5	52.91	0.66	0.42, 1.06
Q2	48/229	–1.1 to <–0.6	36.66	41/138	–0.5 to <0.0	47.29	0.82	0.53, 1.28
Q3	52/231	–0.6 to <–0.2	42.51	31/130	0.0 to <0.4	42.15	1.17	0.74, 1.84
Q4	59/269	≥–0.2	43.81	32/129	≥0.4	34.82	1.53	0.98, 2.40
On insulin and/or SU								
Q1	36/131	<–1.1	47.12	37/85	<–0.5	68.85	0.66	0.41, 1.06
Q2	44/147	–1.1 to <–0.6	47.42	39/103	–0.5 to <0.0	54.56	0.81	0.52, 1.28
Q3	51/148	–0.6 to <–0.2	60.59	31/91	0.0 to <0.4	55.39	1.12	0.71, 1.77
Q4	57/144	≥–0.2	73.30	31/105	≥0.4	40.51	1.60	1.02, 2.51
Not on insulin or SU								
Q1	2/88	<–1.0	4.86	1/35	<–0.6	6.01	0.01	0.00, 18.74
Q2	3/92	–1.0 to <–0.5	6.92	2/38	–0.6 to <–0.1	12.00	0.51	0.07, 3.60
Q3	1/93	–0.5 to <0.0	2.36	0/34	0.1 to <0.3	0.00	-	-
Q4	2/94	≥0.0	4.68	1/39	≥0.3	5.62	0.81	0.07, 9.61

CI, confidence interval; HbA1c, glycated haemoglobin; HR, hazard ratio; Q, quartiles of HbA1c change from baseline; SU, sulphonylurea.
[a]Quartiles were calculated for each treatment group separately.
[b]All patients who were treated with at least 1 dose of study medication.
[c]Method includes treatment, baseline HbA1c, washout and study.

FIGURE 1 Time to first onset of any investigator-defined hypoglycaemic AE (treated set). A, all patients up to 24 weeks; B, patients with insulin and/or SU background therapy up to 24 weeks; C, patients with no insulin or SU background therapy up to 24 weeks; D, all patients up to 1 year



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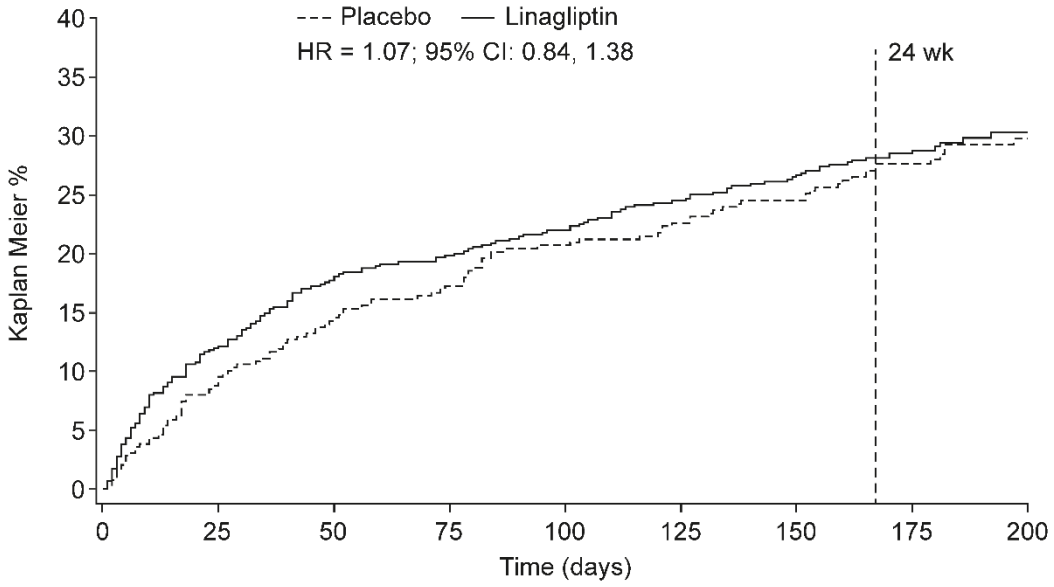

Patients under risk									
Placebo	389	351	321	309	294	282	270	217	0
Linagliptin	576	506	469	451	437	420	405	291	0

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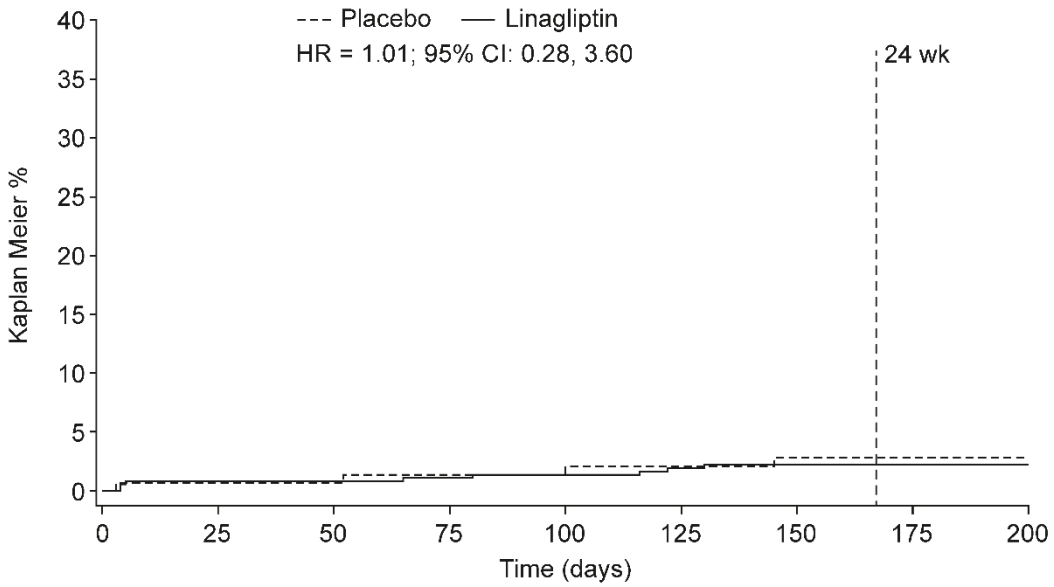
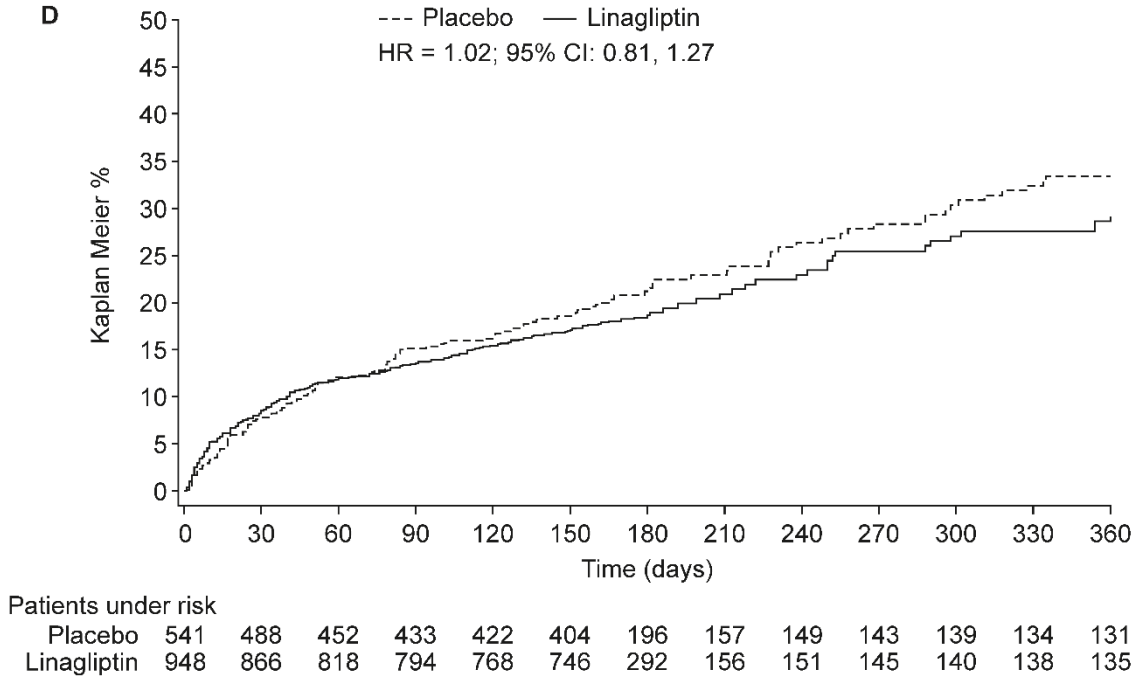
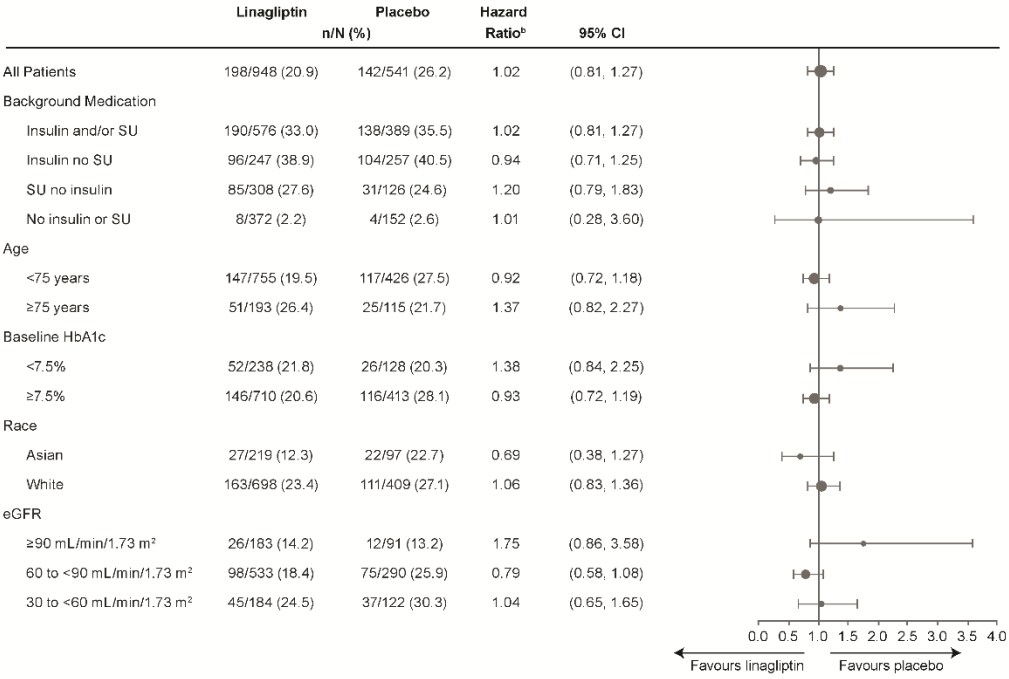


Patients under risk									
Placebo	152	146	142	137	137	135	134	73	0
Linagliptin	372	369	356	356	350	346	341	204	0



AE, adverse event; CI, confidence interval; HbA1c, glycated haemoglobin; HR, hazard ratio; SU, sulphonylurea. Model includes treatment, baseline HbA1c, washout, and study.

FIGURE 2 Investigator-defined hypoglycaemic AEs: overall and by subgroup, up to 1 year (treated set[a])

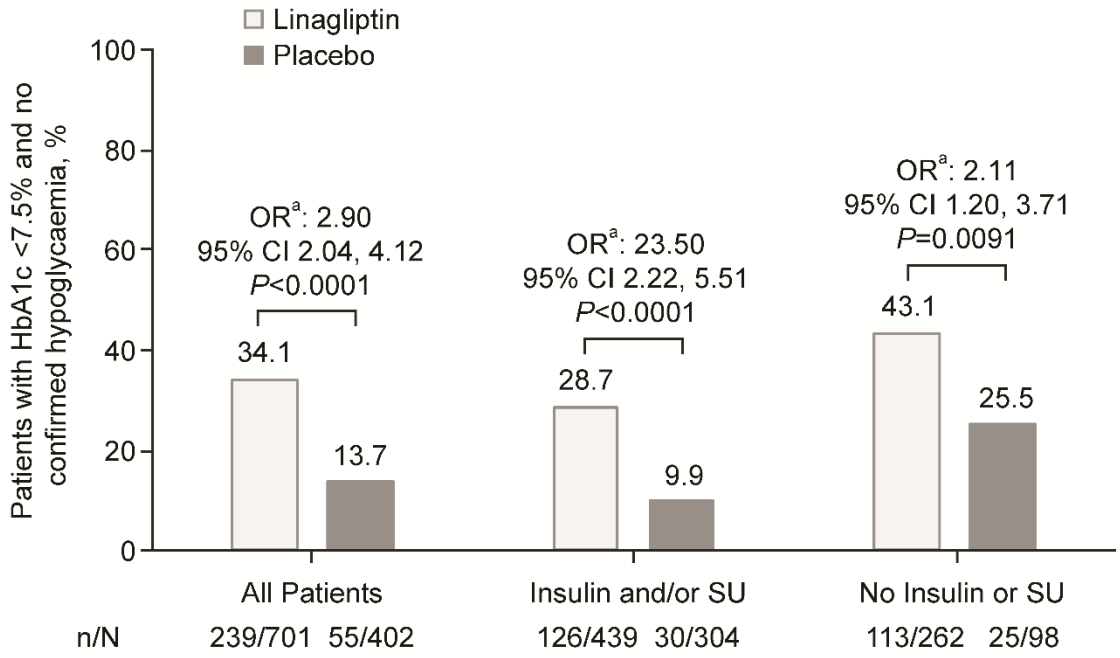


AE, adverse event; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HR, hazard ratio; SU, sulphonylurea.

[a]All patients who were treated with at least 1 dose of study medication.

[b]The HR and CIs are based on a Cox regression with the covariate baseline HbA1c and the factors treatment, washout and study.

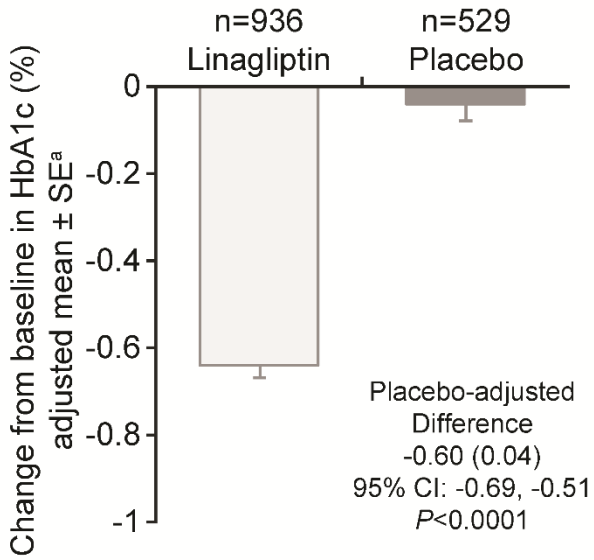
FIGURE 3 Patients with HbA1c <7.5% and no confirmed hypoglycaemia at week 24 by treatment (FAS patients with baseline HbA1c ≥7.5%)



CI, confidence interval; FAS, full analysis set: all patients who were treated with at least 1 dose of study medication, and had a baseline and at least 1 on-treatment HbA1c measurement; HbA1c, glycated haemoglobin; OR, odds ratio; SU, sulphonylurea.

[a]Model includes treatment, baseline HbA1c, washout, and study.

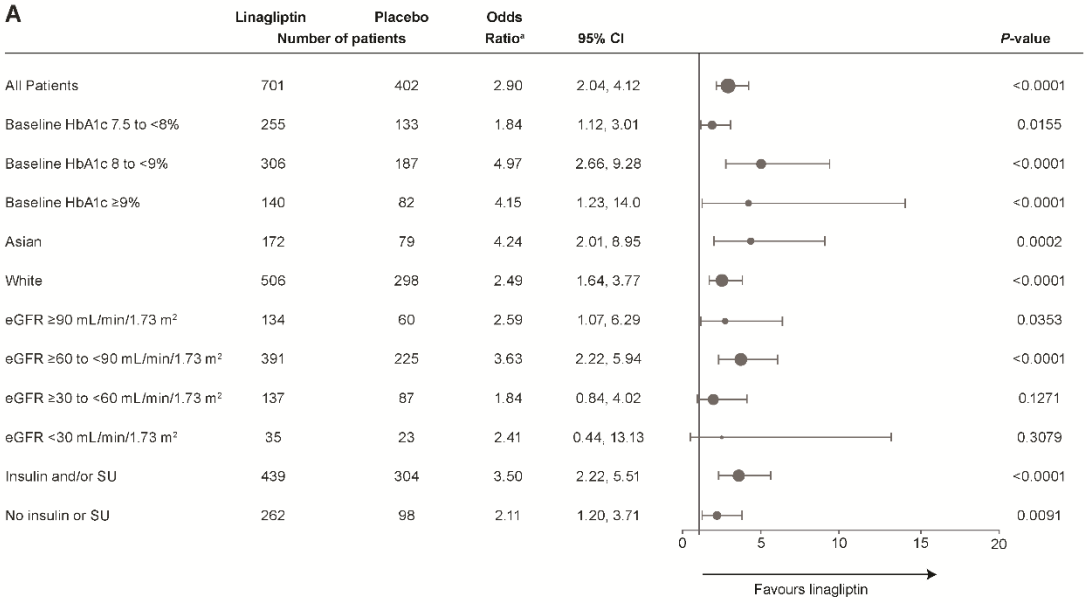
SUPPLEMENTAL FIGURE 1 Change in HbA1c from baseline to week 24 (FAS, LOCF)

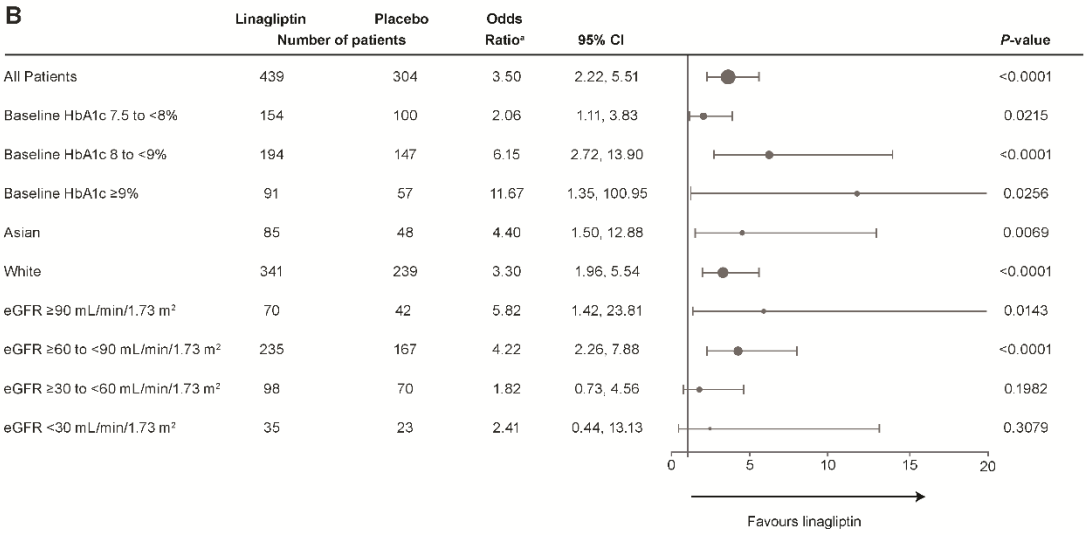


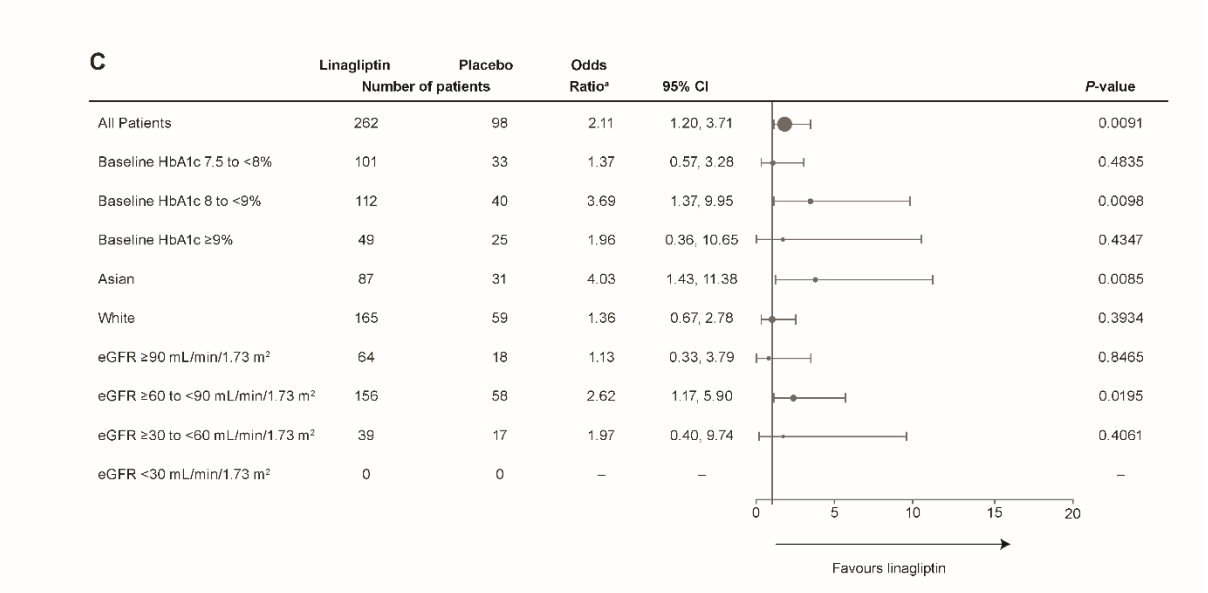
FAS, full analysis set: all patients who were treated with at least 1 dose of study medication, and had a baseline and at least 1 on-treatment HbA1c measurement; LOCF, last observation carried forward.

[a]Model includes treatment, baseline HbA1c, washout, and study.

SUPPLEMENTAL FIGURE 2 Subgroup analyses for patients with HbA1c <7.5% and no confirmed hypoglycaemia at week 24 (FAS). A, patients with baseline HbA1c ≥7.5%; B, patients with baseline HbA1c ≥7.5% and with insulin and/or SU background therapy; C, patients with baseline HbA1c ≥7.5% and with no insulin or SU background therapy







CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set: all patients who were treated with at least 1 dose of study medication, and had a baseline and at least 1 on-treatment HbA1c measurement; HbA1c, glycated haemoglobin; SU, sulphonylurea.

[a]Model includes treatment, study, washout and baseline HbA1c.