

# Linagliptin treatment in subjects with type 2 diabetes with and without mild-to-moderate renal impairment

P.-H. Groop<sup>1,2,3</sup>, S. Del Prato<sup>4</sup>, M.-R. Taskinen<sup>1</sup>, D. R. Owens<sup>5</sup>, Y. Gong<sup>6</sup>, S. Crowe<sup>6</sup>, S. Patel<sup>7</sup>, M. von Eynatten<sup>6</sup> & H.-J. Woerle<sup>6</sup>

<sup>1</sup>Division of Nephrology, Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland

<sup>2</sup>Folkhälsan Institute of Genetics, Folkhälsan Research Center, Biomedicum Helsinki, Helsinki, Finland

<sup>3</sup>Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia

<sup>4</sup>Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

<sup>5</sup>Diabetes Research Group, Swansea University, Swansea, UK

<sup>6</sup>Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany

<sup>7</sup>Boehringer Ingelheim Ltd, Bracknell, UK

**Aims:** Renal disease is a frequent comorbidity of type 2 diabetes mellitus (T2DM) and an important factor complicating the choice of glucose-lowering drugs. The aim of this analysis was to evaluate the efficacy and safety of the dipeptidyl peptidase (DPP)-4 inhibitor linagliptin (5 mg/day) in mono, dual or triple oral glucose-lowering regimens in subjects with T2DM and mild or moderate renal impairment (RI).

**Methods:** In this pooled analysis of three 24-week, placebo-controlled, phase 3 trials, subjects with mild (estimated glomerular filtration rate (eGFR) 60–<90 ml/min/1.73 m<sup>2</sup>, n = 838) or moderate RI (30–<60 ml/min/1.73 m<sup>2</sup>, n = 93) were compared with subjects with normal renal function (≥90 ml/min/1.73 m<sup>2</sup>, n = 1212).

**Results:** Subjects with RI were older, had longer duration of diabetes, and increased prevalence of diabetes-related comorbidities. After 24 weeks, linagliptin achieved consistent placebo-corrected mean glycated haemoglobin (HbA1c) changes across the three renal function categories: normal (−0.63%; p < 0.0001), mild RI (−0.67%; p < 0.0001) and moderate RI (−0.53%; p < 0.01), with no inter-group difference (p = 0.74). Renal function with linagliptin remained stable across all categories. In linagliptin-treated subjects, overall adverse event (AE) rates and serious AE rates were similar to placebo. The incidence of hypoglycaemia with linagliptin and placebo was 11.1 versus 6.9%, 11.9 versus 9.0% and 15.9 versus 12.0% in the normal, mild RI and moderate RI categories, respectively.

**Conclusions:** This pooled analysis provides evidence that linagliptin is an effective, well-tolerated and convenient treatment in subjects with T2DM and mild or moderate RI.

**Keywords:** diabetic nephropathy, DPP-4 inhibitor, glycaemic control, incretin therapy, type 2 diabetes

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## Introduction

Type 2 diabetes mellitus (T2DM) is a leading cause of chronic kidney disease (CKD) [1], with an estimated 40% of subjects with T2DM having some degree of kidney disease [2–5]. A similar proportion has been reported in subjects with undiagnosed diabetes [6]. CKD contributes to significant morbidity, with the risk of cardiovascular disease (CVD), end-stage renal disease (ESRD), hypoglycaemia and death being greater in subjects with both T2DM and CKD than for either disease alone [1].

Current guidelines recommend optimising glucose control to reduce the risk or slow the progression of CKD [1,7].

Intensive glycaemic control can improve kidney outcomes [8–10]. However, the presence of reduced renal clearance or renal impairment (RI) can result in the accumulation and prolonged half-lives of certain antidiabetes drugs, which limits or complicates their use because of the increased risk of adverse events (AEs) [11]. For example, because exogenous insulin is primarily excreted by the kidneys, reduced renal function can extend the half-life of circulating insulin, thus increasing the risk of hypoglycaemia [1,12]. Importantly, clearance of some sulphonylureas (or their active metabolites) decreases as renal function declines, requiring a reduction in drug dose to avoid hypoglycaemia [1]. Therefore, certain drugs are contraindicated in subjects with RI whereas the dosages of other drugs require adjustment according to renal function and frequent monitoring to avoid AEs. Thus, there remains a need for glucose-lowering drugs that are suitable and convenient for all subjects irrespective of their renal function [2].

Dipeptidyl peptidase (DPP)-4 inhibitors have beneficial effects on glycaemic control, are generally weight neutral,

Correspondence to: Per-Henrik Groop, Division of Nephrology, Department of Medicine, Helsinki University Central Hospital, Haartmaninkatu 8, Helsinki, Finland.  
E-mail: per-henrik.groop@helsinki.fi

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and are associated with a low incidence of AEs, including hypoglycaemia [13]. Although the efficacy and safety of currently available DPP-4 inhibitors are similar [14], important pharmacological differences exist that are relevant in the presence of RI. Saxagliptin, sitagliptin and vildagliptin undergo extensive renal clearance (87, 75 and 85%, respectively) and therefore require dose adjustment in subjects with moderate or severe RI, or ESRD [15–17]. Linagliptin has a low rate of renal excretion (~5% of its overall elimination); the majority (~80%) is excreted via the enterohepatic system [18]. A phase 1 study in subjects with normal-to-severe RI (including ESRD requiring dialysis) showed that RI had minimal impact on linagliptin pharmacokinetics [19]. Similarly, an analysis of phase 3 trial data showed that RI had a minor effect on long-term exposure with linagliptin 5 mg once daily [20]. Consequently, dose adjustment of linagliptin according to different RI stages and on-treatment monitoring of renal function are not required.

These pharmacological attributes of linagliptin support its use in subjects with T2DM with or without RI. A 1-year study in subjects with severe RI showed that linagliptin 5 mg provided clinically meaningful decreases in glycated haemoglobin (HbA1c) and was well-tolerated with a low risk of hypoglycaemia [21]. The aim of this pooled analysis of data from three large phase 3 trials of linagliptin [22–24] was to evaluate the consistency of the efficacy and safety of linagliptin in subjects with T2DM with mild or moderate RI.

## Materials and Methods

### Study Design

This was a pooled analysis of three 24-week, multicentre, multinational, randomised, double-blind, placebo-controlled, parallel-group clinical trials in subjects with T2DM comparing linagliptin 5 mg once daily versus placebo as monotherapy (NCT00621140) [22], add-on to metformin (NCT00601250) [24], or add-on to metformin and sulphonylurea (NCT00602472) [23]. The study designs were homogeneous, which enabled pooling of data, and have been described previously [22–24].

Eligibility criteria for each of the three studies were similar. Inclusion criteria included: age  $\geq 18$  and  $\leq 80$  years; diagnosis of T2DM; body mass index (BMI) of  $\leq 40$  kg/m<sup>2</sup>; HbA1c of  $\geq 6.5$  to  $\leq 9.0\%$  for subjects undergoing washout of previous medication and HbA1c  $\geq 7.0$  to  $\leq 10.0\%$  for subjects not undergoing washout of previous medication. The main exclusion criteria were: myocardial infarction, stroke or transient ischaemic attack within 6 months of study enrolment; impaired hepatic function at screening; treatment with rosiglitazone, pioglitazone, glucagon-like peptide-1 analogues, insulin or antiobesity drugs (e.g. sibutramine, rimonabant or orlistat) within 3 months of enrolment. In two of the three studies [23,24], patients with renal failure or RI [serum creatinine  $\geq 135$   $\mu\text{mol/l}$  ( $\geq 1.5$  mg/dl)] were also excluded.

### Efficacy and Safety Assessments

Subjects were grouped according to the degree of renal function (normal, mild RI or moderate RI). Renal function

was evaluated using the estimated glomerular filtration rate (eGFR), which was calculated using the modification of diet in renal disease (MDRD) formula [25,26]. Staging of renal function was as follows: normal, eGFR  $\geq 90$  ml/min/1.73 m<sup>2</sup>; mild RI, eGFR  $60$ – $<90$  ml/min/1.73 m<sup>2</sup>; moderate RI, eGFR  $30$ – $<60$  ml/min/1.73 m<sup>2</sup>. Renal function was also categorised based on estimated creatinine clearance (eCcr) rate using the Cockcroft–Gault (C–G) formula [27]; C–G staging was as follows (in accordance with Food and Drug Administration guidance [28]): normal,  $\geq 80$  ml/min; mild RI,  $50$ – $<80$  ml/min; moderate RI,  $30$ – $<50$  ml/min. Because the number of subjects with severe RI ( $<30$  ml/min/1.73 m<sup>2</sup>) included in the three phase 3 trials was low, they were excluded from this analysis; subjects with no renal function measurement ('missing') were also excluded.

Efficacy was assessed as change from baseline to week 24 in HbA1c and fasting plasma glucose (FPG) levels. The effect of linagliptin on HbA1c was also analysed according to predefined subgroups: age ( $<65$  or  $\geq 65$  years); BMI ( $<30$  or  $\geq 30$  kg/m<sup>2</sup>); gender (male or female); duration of T2DM ( $\leq 5$  or  $>5$  years); urine albumin-to-creatinine ratio (UACR;  $<30$  or  $\geq 30$  mg/g). Safety assessments included AEs, serious AEs (SAEs), treatment-related AEs and AEs of special interest. Investigator-reported hypoglycaemic events were defined as [29]: asymptomatic, plasma glucose concentration  $\leq 3.9$  mmol/l ( $\leq 70$  mg/dl) without symptoms; documented symptomatic, plasma glucose concentration  $\geq 3.0$  mmol/l ( $\geq 54$  mg/dl) and  $\leq 3.9$  mmol/l ( $\leq 70$  mg/dl) with symptoms; documented symptomatic, plasma glucose concentration  $<3.0$  mmol/l ( $<54$  mg/dl) with symptoms but not requiring external assistance; severe, requiring external assistance to administer resuscitative actions. Change in renal function (eGFR) over time was also assessed.

### Statistical Analysis

The change in HbA1c from baseline to 24 weeks was compared between the linagliptin and placebo groups in each renal function category using an analysis of covariance (ANCOVA). The model included continuous baseline HbA1c, treatment, time since diagnosis of diabetes, gender, baseline BMI, baseline age, washout period, race, study, RI and treatment  $\times$  RI interaction. The efficacy analyses were performed on the full analysis set (FAS), which comprised all randomised subjects with a baseline HbA1c measurement,  $\geq 1$  on-treatment HbA1c measurement and  $\geq 1$  dose of study medication. A last observation carried forward (LOCF) approach was used to replace missing data. A similar approach was used to analyse the change in FPG (FPG values were converted from mg/dl to mmol/l after statistical analysis using a factor of 0.0555) with the addition of baseline FPG. All analyses were performed at a significance level of 5%. AEs were summarised using frequency counts for all subjects treated with  $\geq 1$  dose of study drug (treated set); consistent with previous reports [22–24], no formal inferential statistical analyses were applied to the safety assessments.

## Results

### Subject Demographics and Clinical Characteristics at Baseline

Of 2262 subjects randomised in the three trials, data from 2143 subjects were available for the MDRD analysis: 56.6% had normal renal function (linagliptin,  $n = 870$ ; placebo,  $n = 342$ ); 39.1% had mild RI (linagliptin,  $n = 620$ ; placebo,  $n = 218$ ); 4.3% had moderate RI (linagliptin,  $n = 68$ ; placebo,  $n = 25$ ). There were no subjects with severe RI (eGFR  $< 30$  ml/min/1.73 m<sup>2</sup>); 81 subjects had no renal function measurement. Unless stated otherwise, results from the eCcr analyses were essentially similar to those from the eGFR analyses (Tables S1–S3, Supporting Information).

As expected, subjects with RI tended to be older and had a longer known disease duration ( $> 5$  years) than subjects with normal renal function (Table 1). Baseline HbA1c ranged from 8.0 to 8.2% and FPG ranged from 9.0 to 9.5 mmol/l (162.6–170.6 mg/ml). Overall, the linagliptin and placebo groups were similar in terms of demographics and clinical characteristics.

The use of glucose-lowering drugs was broadly similar across all renal function categories. The use of concomitant antihypertensive and lipid-lowering drugs tended to be higher

in subjects with RI versus subjects with normal renal function (Table 2).

The prevalences of concomitant microvascular diseases (retinopathy, nephropathy and neuropathy) in linagliptin-versus placebo-treated subjects in the normal, mild RI and moderate RI categories were 23.7 versus 19.6%, 27.1 versus 25.2% and 35.3 versus 56.0%, respectively. Corresponding prevalences of CVD were 9.4 versus 11.4%, 17.4 versus 18.3% and 22.1 versus 32.0%, respectively. Prevalences of hypertension were 54.5 versus 57.6%, 72.4 versus 70.6% and 82.4 versus 76.0%, respectively.

### Efficacy

Linagliptin was superior to placebo in reducing HbA1c in all renal function categories (Figure 1). After 24 weeks of treatment, the placebo-corrected adjusted mean [95% confidence interval (CI)] changes in HbA1c from baseline in the normal, mild RI and moderate RI categories were  $-0.63\%$  ( $-0.73, -0.53$ ;  $p < 0.0001$ ),  $-0.67\%$  ( $-0.80, -0.54$ ;  $p < 0.0001$ ) and  $-0.53\%$  ( $-0.91, -0.14$ ;  $p < 0.01$ ), respectively. There was no inter-group difference ( $p$ -value for interaction = 0.74). Linagliptin treatment resulted in a greater reduction in FPG levels compared with placebo. After 24 weeks, the placebo-corrected adjusted mean (95% CI) changes in

**Table 1.** Subject demographics and clinical characteristics at baseline (FAS).

	Normal renal function*		Mild RI*		Moderate RI*	
	Linagliptin 5 mg ( $n = 870$ )	Placebo ( $n = 342$ )	Linagliptin 5 mg ( $n = 620$ )	Placebo ( $n = 218$ )	Linagliptin 5 mg ( $n = 68$ )	Placebo ( $n = 25$ )
Male, $n$ (%)	420 (48.3)	175 (51.2)	317 (51.1)	109 (50.0)	32 (47.1)	9 (36.0)
Age years, mean $\pm$ s.d.	54.0 $\pm$ 9.6	53.6 $\pm$ 10.0	61.3 $\pm$ 8.7	59.9 $\pm$ 9.1	66.4 $\pm$ 8.0	65.6 $\pm$ 6.4
Race, $n$ (%)						
White	465 (53.4)	181 (52.9)	386 (62.3)	140 (64.2)	43 (63.2)	12 (48.0)
Black	9 (1.0)	4 (1.2)	2 (0.3)	0	0	0
Asian	396 (45.5)	157 (45.9)	232 (37.4)	78 (35.8)	25 (36.8)	13 (52.0)
BMI kg/m <sup>2</sup> , mean $\pm$ s.d.	28.9 $\pm$ 4.9	28.9 $\pm$ 4.9	29.2 $\pm$ 4.8	29.2 $\pm$ 4.7	28.6 $\pm$ 4.4	28.3 $\pm$ 4.9
GFR (MDRD) ml/min/1.73 m <sup>2</sup> , median (min, max)	107.9 (90.0, 266.4)	105.8 (90.1, 221.0)	78.5 (60.1, 90.0)	80.9 (60.5, 90.0)	56.4 (34.2, 59.5)	53.6 (30.2, 59.5)
UACR mg/g, median (min, max)†	10.6 (0.0, 10584.1)	9.7 (0.0, 4697.6)	12.4 (0.0, 3665.9)	8.8 (0.0, 1388.8)	18.6 (0.9, 1538.2)	19.4 (1.8, 4373.1)
HbA1c %, mean $\pm$ s.d.	8.1 $\pm$ 0.9	8.1 $\pm$ 0.9	8.0 $\pm$ 0.8	8.0 $\pm$ 0.8	8.2 $\pm$ 1.0	8.2 $\pm$ 0.9
FPG mmol/l (mg/dl), mean $\pm$ s.d.‡	9.1 $\pm$ 2.2 (163.8 $\pm$ 39.6)	9.3 $\pm$ 2.2 (167.0 $\pm$ 39.5)	9.1 $\pm$ 2.2 (163.2 $\pm$ 40.1)	9.0 $\pm$ 2.1 (163.0 $\pm$ 38.4)	9.5 $\pm$ 2.6 (170.6 $\pm$ 47.3)	9.0 $\pm$ 2.0 (162.6 $\pm$ 36.5)
Duration of diabetes, $n$ (%)						
Up to 1 year	109 (12.5)	44 (12.9)	74 (11.9)	37 (17.0)	4 (5.9)	3 (12.0)
$> 1$ –5 years	265 (30.5)	113 (33.0)	190 (30.6)	58 (26.6)	13 (19.1)	7 (28.0)
$> 5$ years	496 (57.0)	185 (54.1)	356 (57.4)	123 (56.4)	51 (75.0)	15 (60.0)
Exposure days, mean $\pm$ s.d.	169 $\pm$ 19.8	168 $\pm$ 22.1	169 $\pm$ 18.2	166 $\pm$ 27.1	166 $\pm$ 23.8	155 $\pm$ 41.0

BMI, body mass index; FAS, full analysis set; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HbA1c, glycated haemoglobin; MDRD, modification of diet in renal disease; RI, renal impairment; s.d., standard deviation; UACR, urine albumin-to-creatinine ratio.

\*Renal function according to MDRD formula: normal,  $\geq 90$  ml/min/1.73 m<sup>2</sup>; mild,  $60$ – $< 90$  ml/min/1.73 m<sup>2</sup>; moderate,  $30$ – $< 60$  ml/min/1.73 m<sup>2</sup>.

†Normal: linagliptin  $n = 824$ , placebo  $n = 329$ ; mild: linagliptin  $n = 581$ , placebo  $n = 197$ ; moderate: linagliptin  $n = 65$ , placebo  $n = 25$ .

‡Normal: linagliptin  $n = 848$ , placebo  $n = 335$ ; mild: linagliptin  $n = 602$ , placebo  $n = 209$ .

**Table 2.** Concomitant therapies at screening.

%	Normal renal function*		Mild RI*		Moderate RI*	
	Linagliptin 5 mg (n = 870)	Placebo (n = 342)	Linagliptin 5 mg (n = 620)	Placebo (n = 218)	Linagliptin 5 mg (n = 68)	Placebo (n = 25)
Subjects with $\geq 1$ specific drug	66.7	70.5	81.0	80.7	88.2	88.0
ASA	30.5	34.2	37.6	38.1	29.4	48.0
Antihypertensives	51.1	52.6	69.5	70.2	82.4	84.0
$\beta$ -blockers	14.9	16.4	23.9	26.1	30.9	20.0
ACE inhibitors	26.9	26.9	30.0	31.7	33.8	48.0
Diuretics	8.7	9.6	18.5	14.7	32.4	32.0
ARBs	10.5	10.8	16.6	13.3	19.1	16.0
Calcium antagonists	11.0	11.7	20.2	19.7	27.9	24.0
Combinations	5.9	7.3	12.9	12.4	17.6	24.0
Lipid-lowering drugs	34.5	38.3	43.7	41.7	51.5	40.0
Niacin	1.6	0.3	1.1	0.5	0	0
Fibrates	4.8	7.0	7.6	7.3	7.4	16.0
Statins	30.0	31.9	37.4	35.8	45.6	32.0
Other	2.3	2.6	2.6	0.5	1.5	4.0
Glucose-lowering drugs						
Treatment-naïve	8.3	11.4	15.6	22.9	10.3	4.0
Metformin only	28.3	27.5	29.0	30.3	25.0	24.0
SU only	1.8	3.2	3.1	2.3	1.5	8.0
Metformin + SU	59.8	56.4	50.6	43.1	60.3	64.0
Others†	1.8	1.5	1.6	1.4	2.9	0

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ASA, acetyl salicylic acid; MDRD, modification of diet in renal disease; RI, renal impairment; SU, sulphonylurea.

\*Renal function according to MDRD formula: normal,  $\geq 90$  ml/min/1.73 m<sup>2</sup>; mild, 60–<90 ml/min/1.73 m<sup>2</sup>; moderate, 30–<60 ml/min/1.73 m<sup>2</sup>.

†Including mono- and combination therapies.

FPG from baseline in the normal and mild RI categories were  $-0.9$  mmol/l ( $-1.1, -0.6$ ) [ $-16.0$  mg/dl ( $-20.7, -11.4$ );  $p < 0.0001$ ] and  $-1.2$  mmol/l ( $-1.5, -0.9$ ) [ $-22.0$  mg/dl ( $-27.8, -16.2$ );  $p < 0.0001$ ], respectively. The FPG change in the moderate RI category was not statistically significant [ $-0.3$  mmol/l ( $-1.2, 0.6$ );  $-5.5$  mg/dl ( $-22.1, 11.1$ );  $p = 0.52$ ], which may be because of the comparatively small number of subjects in this group ( $n = 92$ ). Overall, for FPG change from baseline, there was a trend toward a treatment effect modification by renal function category ( $p = 0.096$ ), partially driven by the low number of subjects in the moderate RI category.

In subjects with any renal dysfunction (i.e. mild and moderate RI categories combined), significant and comparable reductions from baseline at week 24 in HbA1c were observed within each subgroup analysed (Figure 2).

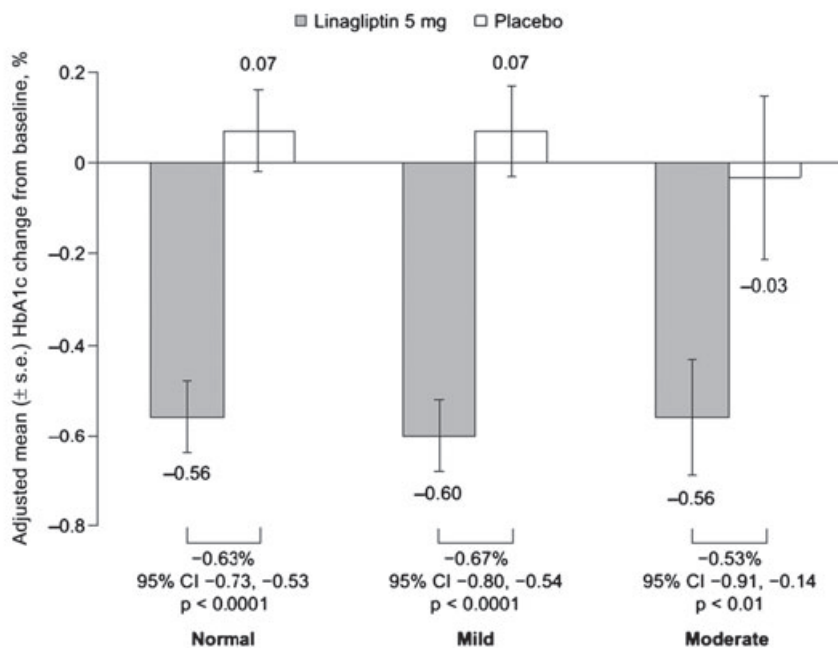
## Safety

Linagliptin treatment was generally well-tolerated across the three renal function categories (Table 3). In both treatment groups, a slight trend for higher rates of any AEs, SAEs and drug-related AEs was seen in subjects with RI. The incidence of AEs with linagliptin was comparable to placebo in each renal function category. In the moderate RI category, there were no reported drug-related AEs with placebo compared with an incidence rate of 14.5% ( $n = 10$ ) with linagliptin. Notably, hypoglycaemia was reported by 7 of 10 linagliptin-treated subjects with drug-related AEs in this category. Overall, there was no clustering of any specific type of unexpected AE

(Table 3). In an analysis of AEs by system organ class (SOC), the incidences of cardiac disorders for linagliptin and placebo were: normal renal function, 1.9 and 1.4%; mild RI, 3.7 and 0.5%; moderate RI, 1.4 and 4.0%. The incidences of AEs relating to renal and urinary disorders were similar for linagliptin and placebo in subjects with normal renal function (2.5 and 4.0%), mild RI (3.8 and 3.2%) and moderate RI (4.3 and 4.0%). There were no drug-related AEs of renal failure. Renal function (eGFR) remained stable over 24 weeks following linagliptin or placebo treatment (Figure 3). Although only one subject (0.2%) developed hyperkalaemia (from the mild RI category and who received linagliptin), no other clinically significant laboratory findings emerged. According to the eCcr categorisation, there was a trend for higher rates of any AEs, SAEs and drug-related AEs in subjects with RI compared with subjects without RI, but overall rates were similar between linagliptin and placebo (Table S3).

The incidence of severe hypoglycaemia was low, with no meaningful differences between treatment groups. The incidence of any investigator-reported hypoglycaemia with linagliptin was higher in subjects with RI: 11.1, 11.9 and 15.9% in the normal, mild and moderate renal function categories, respectively; with placebo, these rates were 6.9, 9.0 and 12.0%, respectively (Table 3). The incidence of hypoglycaemia was  $< 1\%$  in subjects receiving linagliptin as monotherapy [22] or as an add-on to metformin therapy [24]. Subjects receiving linagliptin as add-on to metformin plus sulphonylurea [23] had the highest incidence of hypoglycaemia (linagliptin, 23.7%; placebo, 16.0%).

<b>Mean (<math>\pm</math> s.e.) baseline HbA1c, %</b>	8.15 (0.03)	8.11 (0.05)	8.02 (0.03)	8.00 (0.06)	8.21 (0.12)	8.16 (0.19)
<b>Patients analysed (n)</b>	870	342	620	218	68	25



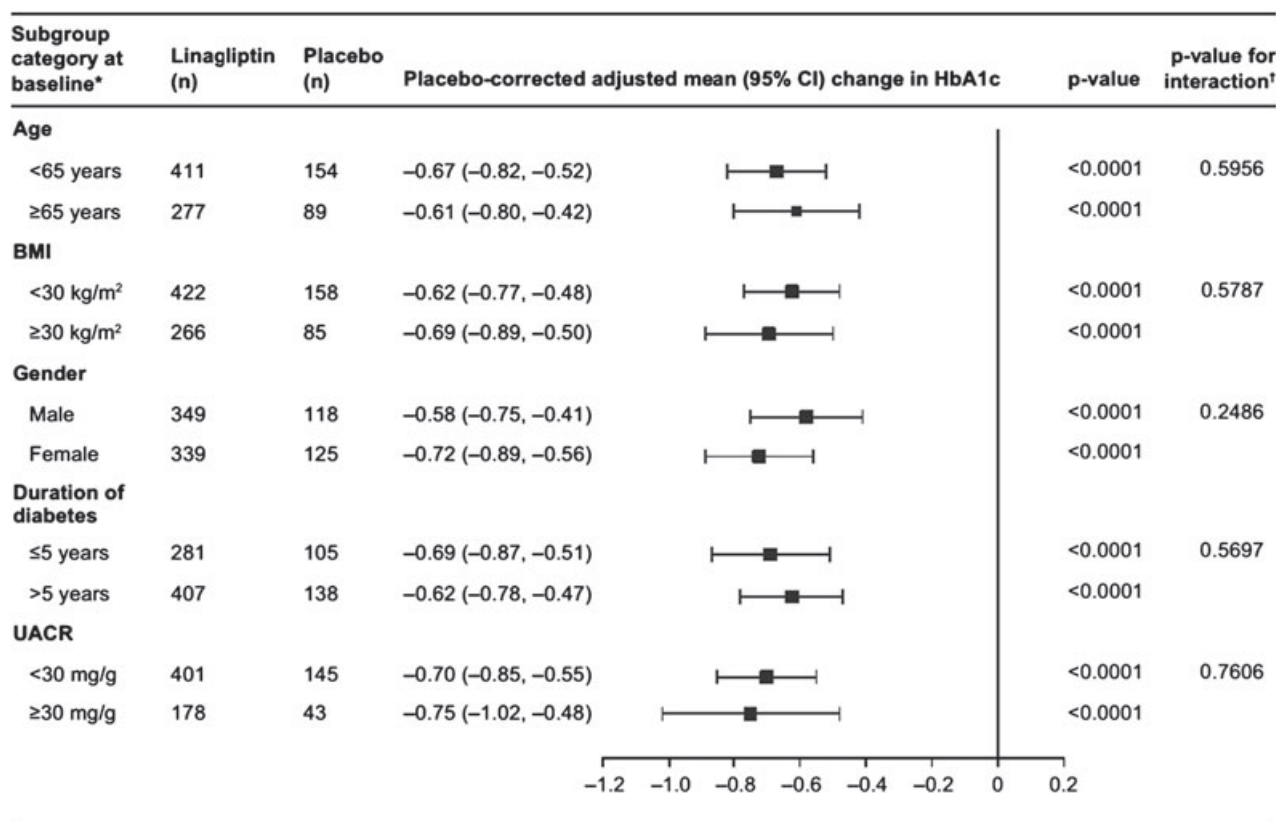
**Figure 1.** Adjusted mean change from baseline in HbA1c following treatment with linagliptin 5 mg or placebo after 24 weeks (FAS – LOCF). Model includes continuous baseline HbA1c, baseline body mass index (category), washout period, treatment, study, age group, gender, time since diagnosis of diabetes, race, renal function (MDRD) and treatment  $\times$  renal function (MDRD). CI, confidence interval; FAS, full analysis set; HbA1c, glycated haemoglobin; LOCF, last observation carried forward; MDRD, modification of diet in renal disease; s.e., standard error.

## Discussion

Linagliptin is an oral, once-daily glucose-lowering therapy that does not require dose adjustment in renally impaired subjects with T2DM [18]. In subjects with T2DM and severe RI, linagliptin 5 mg was well-tolerated with an acceptable safety profile and, added to existing background therapy, achieved a placebo-corrected reduction in HbA1c of 0.72% after 52 weeks [21]. Findings from the current analysis add to this evidence, now reporting the efficacy and safety of linagliptin in subjects with mild or moderate RI (no subjects with severe RI or ESRD were included). On the basis of data from phase 3 clinical trials of linagliptin in either mono, dual or triple glucose-lowering regimens, significant reductions in HbA1c were observed in each RI category which were comparable to the reduction seen in the normal renal function category. Taken together, these data indicate that the degree of RI has no clinically meaningful impact on the efficacy of linagliptin. Elderly subjects often have RI as well as other age-related comorbidities, and therefore selecting the appropriate glucose-lowering therapy in this population can be challenging [30]. In the combined analysis of subjects with mild and moderate RI (Figure 2), the effect of linagliptin treatment on reducing HbA1c levels in elderly subjects ( $\geq 65$  years) and subjects with a longer known duration of diabetes ( $> 5$  years) was comparable to younger subjects and subjects with early onset disease. This finding is consistent with the results from a randomised placebo-controlled phase 3

clinical trial of linagliptin in elderly patients ( $\geq 70$  years) with T2DM [31].

In our analysis, the safety and tolerability profile of linagliptin was comparable to placebo across all renal function categories studied, and is consistent with a previous pooled analysis of eight clinical trials of linagliptin [32]. In the moderate RI category, the incidence of drug-related AEs was higher with linagliptin than with placebo, a finding which may have been driven by the high proportion of linagliptin subjects (7 of 10 subjects) who reported hypoglycaemia as a drug-related AE. Slightly higher rates of investigator-reported hypoglycaemia were observed in subjects with moderate RI compared with subjects with normal renal function; however, it is well-known that subjects with RI have an increased risk for hypoglycaemia [12,33]. Across all renal function categories, a higher incidence of hypoglycaemia was observed in subjects receiving linagliptin compared with placebo. This finding may have been driven by the large proportion of subjects in the analysis who had sulphonylurea background therapy (50–60% across the linagliptin groups); combining sulphonylurea and incretin therapies may elevate the risk of hypoglycaemia even though the latter compounds have a low risk for hypoglycaemia as monotherapies [34,35]. Although subjects with T2DM and CKD are at high risk of CVD [1], including subjects with mild or moderate RI [36], the proportion of subjects with cardiac disorders (SOC) was low and similar across all treatment groups in this analysis.



**Figure 2.** Subgroup analysis of placebo-corrected adjusted mean change in HbA1c from baseline after 24 weeks in subjects with mild and moderate RI (FAS – LOCF). \*Subjects with mild or moderate RI (MDRD categorisation) at baseline were pooled in this analysis. †p-value for interaction between treatment and subgroup category. Model includes continuous baseline HbA1c, washout period, treatment, study, variable of interest and treatment × variable of interest. BMI, body mass index; CI, confidence interval; FAS, full analysis set; HbA1c, glycated haemoglobin; LOCF, last observation carried forward; MDRD, modification of diet in renal disease; RI, renal impairment; UACR, urine albumin-to-creatinine ratio.

Linagliptin did not appear to cause electrolyte disturbances and no cases of drug-related renal failure were reported. Renal function remained stable throughout the evaluation period in all treatment groups of different RI stages. A similar finding was seen in subjects with severe RI treated with linagliptin for 1 year [21]. Interestingly, in a pooled analysis of four phase 3 clinical trials of linagliptin 5 mg, albuminuria, another biomarker of renal disease [37], was significantly reduced by 32% with linagliptin versus 6% with placebo ( $p < 0.05$ ) [38]. It is envisaged that more information concerning the renal effects of linagliptin will be learned from two recently initiated large clinical studies [CARMELINA™ (NCT01897532) and MARLINA-T2D™ (NCT01792518)] which are investigating the effect of linagliptin versus placebo on cardiovascular and/or renal endpoints and changes in prevalent albuminuria, respectively. Patients with evidence of renal complications are allowed to enrol in both studies.

The findings from this analysis have important clinical implications. Many commonly used glucose-lowering therapies are contraindicated in subjects with RI, depending on their degree of RI, such as acarbose (if eCcr <25 ml/min) and some sulphonylureas [e.g. glibenclamide (glyburide) if ≥3 CKD stages (eGFR <60 ml/min)] [1]. Owing to reports of metformin-associated lactic acidosis, the use of metformin

is also contraindicated in some prescribing guidelines [7], although this contraindication remains controversial and is often disregarded in clinical practice [39,40]. Other glucose-lowering therapies may be used at a reduced dose but require periodic renal function monitoring prior to and during treatment to avoid inappropriate dosing; for example, insulin, repaglinide and gliclazide require dose reduction in subjects with severe RI [11]. Thiazolidinediones may be given without dose adjustment and with no additional risk of hypoglycaemia, although side-effects such as fluid retention, weight gain and an increased risk of cardiovascular events and fractures may be exacerbated in subjects with RI [41]. DPP-4 inhibitors are associated with a low risk of hypoglycaemia and a low incidence of AEs [13]. Saxagliptin, sitagliptin and vildagliptin require a reduction in the standard clinical dose in subjects with moderate or severe RI, or ESRD [15–17]. Reduced doses of these DPP-4 inhibitors improved glycaemic control in these subjects [42–45], although comparisons of their clinical effectiveness with their respective standard dosing regimens are not available. In addition, because renal function will probably change over time, renal function monitoring is recommended prior to initiating treatment with saxagliptin, sitagliptin or vildagliptin and periodically thereafter [15–17]. Linagliptin does not require dose adjustment in subjects with any degree

**Table 3.** Overall AEs, hypoglycaemic episodes and common AEs ( $\geq 5\%$  in any linagliptin group) – treated set\*

%	Normal renal function†		Mild RI†		Moderate RI†	
	Linagliptin 5 mg (n = 886)	Placebo (n = 346)	Linagliptin 5 mg (n = 630)	Placebo (n = 221)	Linagliptin 5 mg (n = 69)	Placebo (n = 25)
Any AE	58.2	58.7	59.0	57.0	66.7	60.0
Serious AEs	2.4	4.0	3.8	2.7	5.8	4.0
Drug-related AEs	10.2	8.4	13.5	11.3	14.5	0
Any investigator-reported hypoglycaemia‡	11.1	6.9	11.9	9.0	15.9	12.0
Severe hypoglycaemia requiring assistance§	0.1	0.6	0.3	0	2.9	0
Common AEs						
Cough	2.1	1.4	1.9	0.9	5.8	0
Dizziness	2.4	1.4	2.4	1.4	7.2	20.0
Hyperglycaemia	6.4	15.3	5.4	14.0	8.7	4.0
Nasopharyngitis	4.9	4.6	5.1	4.1	5.8	8.0
Upper respiratory tract infection	4.6	6.1	3.7	5.0	4.3	12.0

AEs, adverse events; RI, renal impairment.

\*MedDRA version 12.1 used for reporting.

†Renal function according to modification of diet in renal disease formula: normal,  $\geq 90$  ml/min/1.73 m<sup>2</sup>; mild, 60–<90 ml/min/1.73 m<sup>2</sup>; moderate, 30–<60 ml/min/1.73 m<sup>2</sup>.

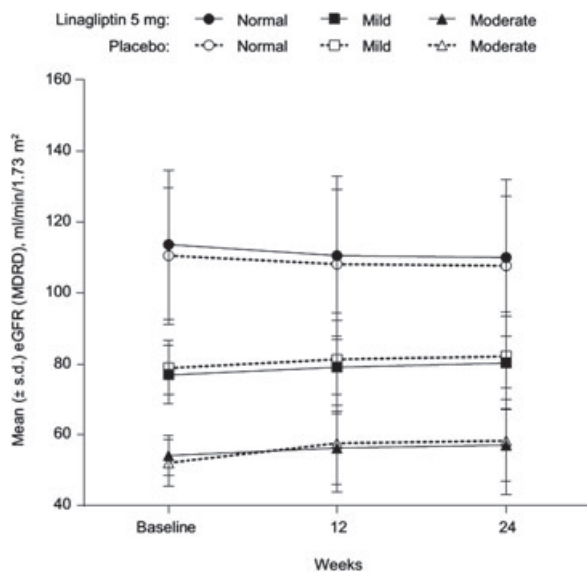
‡Hypoglycaemic episodes were classified by the investigator according to the following definitions:

Asymptomatic hypoglycaemia: event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration of  $\leq 3.9$  mmol/l ( $\leq 70$  mg/dl).

Documented symptomatic hypoglycaemia with a measured plasma glucose concentration of  $\geq 3.0$  mmol/l ( $\geq 54$  mg/dl) and  $\leq 3.9$  mmol/l ( $\leq 70$  mg/dl), accompanied by typical symptoms of hypoglycaemia.

Documented symptomatic hypoglycaemia with a measured plasma glucose concentration of  $< 3.0$  mmol/l ( $< 54$  mg/dl), accompanied by typical symptoms of hypoglycaemia but no need for external assistance.

§Severe hypoglycaemic episode: event requiring assistance of another person to administer carbohydrate, glucagon or other resuscitative actions.



**Figure 3.** Mean change in renal function (eGFR) over time in subjects treated with linagliptin 5 mg or placebo (FAS). Renal function according to MDRD formula; normal,  $\geq 90$  ml/min/1.73 m<sup>2</sup>; mild, 60–<90 ml/min/1.73 m<sup>2</sup>; moderate, 30–<60 ml/min/1.73 m<sup>2</sup>. eGFR, estimated glomerular filtration rate; FAS, full analysis set; MDRD, modification of diet in renal disease; s.d., standard deviation.

of RI [18–20], a recommendation supported by the findings of this analysis and a previous study in subjects with severe RI [21].

As with all pooled analyses, there are certain inherent limitations. Owing to the retrospective nature of this

analysis, the findings should be regarded as exploratory. The comparatively low number of subjects with moderate RI restricts the interpretation of the results observed in this category. In addition, insulin is a commonly used therapy in this subject population and it would have been interesting to investigate the efficacy and safety of linagliptin when added to background insulin therapy; however, subjects receiving insulin were excluded from the three phase 3 trials included. In this regard, a recent analysis of subjects with mild, moderate or severe RI and who were inadequately controlled on insulin therapy showed that linagliptin was well-tolerated and improved glycaemic control without excessive risk of hypoglycaemia [46].

In summary, this pooled analysis showed that the presence of mild or moderate RI has no clinically meaningful impact on the efficacy and safety of linagliptin in subjects with T2DM. Because subjects with RI have additional safety and tolerability concerns, such as increased risk of hypoglycaemia and CVD, treatment choices are limited. Given the convenience of a single daily dose, no requirement for dose adjustment, and no additional drug-induced safety monitoring of kidney function, our analysis indicates that linagliptin is an effective and well-tolerated treatment option in subjects with mild or moderate RI.

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## Conflict of Interest

S. D. P., M.-R. T., D. R. O., Y. G., M. v. E., S. P. and H.-J. W. contributed to the study design. P.-H. G., S. D. P., M.-R. T., D. R. O., Y. G., M. v. E., S. C., S. P. and H.-J. W. participated in the analysis and interpretation of data. All authors were involved in drafting the article and provided intellectual content of critical importance. All authors have seen and approved the final version. P.-H. G. (MD) has served on advisory boards for and has received speakers' fees from Boehringer Ingelheim. S. D. P. (MD) has received honoraria for attending meetings, consultancy fees, speaker fees and/or travel grants from Boehringer Ingelheim. M.-R. T. (MD) has received honoraria for attending meetings, consultancy fees, speaker fees and/or travel grants from Boehringer Ingelheim. D. R. O. (MD) has received consultancy fees, speaker fees and/or travel grants from Boehringer Ingelheim. Y. G. (MD), M. v. E. (MD), S. C. (MSc), S. P. (MB CHB) and H.-J. W. (MD) are all employees of Boehringer Ingelheim.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Adjusted mean change from baseline in glycated haemoglobin (HbA1c) following treatment with linagliptin 5 mg or placebo after 24 weeks [full analysis set – last observation carried forward (FAS – LOCF)]. Model includes continuous baseline HbA1c, baseline body mass index (BMI) (category), washout period, treatment, study, age group, gender, time since diagnosis of diabetes, race, renal function (C–G) and treatment  $\times$  renal function (C–G).

**Figure S2.** Subgroup analysis of placebo-corrected adjusted mean change in glycated haemoglobin (HbA1c) from baseline after 24 weeks in subjects with mild and moderate declining renal function [full analysis set – last observation carried forward (FAS – LOCF)]. \*Subjects with mild or moderate declining renal function (C–G categorisation) at baseline were pooled in this analysis. †p-value for interaction between treatment and subgroup category. Model includes continuous baseline HbA1c, washout period, treatment, study, variable of interest and treatment  $\times$  variable of interest.

**Figure S3.** Mean change in renal function estimated glomerular filtration rate (eGFR) over time in subjects treated with linagliptin 5 mg or placebo [full analysis set (FAS)]. Renal function according to C–G formula; normal,  $\geq 80$  ml/min; mild,  $50 < 80$  ml/min; moderate,  $30 < 50$  ml/min.

**Table S1.** Subject demographics and clinical characteristics at baseline full analysis set (FAS)\*.

**Table S2.** Concomitant therapies at screening.

**Table S3.** Overall adverse events (AEs), hypoglycaemic episodes and common AEs ( $\geq 5\%$  in any linagliptin group) – treated set\*.

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