Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
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Title of trial:	A phase III, randomised, double-blind, placebo-controlled parallel group safety and efficacy study of linagliptin (5 mg administered orally once daily) over 12 weeks followed by a 40 week double-blind extension period (placebo patients switched to glimepiride) in drug naive or previously treated type 2 diabetic patients with moderate to severe renal impairment and insufficient glycaemic control
Coordinating Investigator:	[redacted]
Trial sites:	Multinational, multicentre trial: 52 trial sites in 9 countries (Australia, Canada, Finland, Israel, Japan, New Zealand, Slovakia, Sweden, and United States)
Publication (reference):	Data from this trial have not been published.
Clinical phase:	III
Objectives:	To investigate the efficacy, safety, and tolerability of linagliptin 5 mg compared to placebo given over 12 weeks in drug naive or previously treated patients with type 2 diabetes mellitus with moderate to severe renal impairment and insufficient glycaemic control. In addition, safety was investigated in this patient population with longer term (40 week) treatment in comparison to sulfonylurea drug (glimepiride). This trial has been reported in two parts: Part 1 (interim analysis) included the primary analysis from data up to and including Visit 6 (after completion of the 12 week placebo-controlled part of the study). This is reported in an interim report [U12-1219-01], issued 02 Apr 2012. Part 2 (final analysis) includes the data from the first 12 weeks, plus the additional 40 weeks of efficacy and safety data (up to Week 52), when patients who had been treated with placebo for the first 12 weeks were switched to glimepiride.
Methodology:	Randomised, double-blind, placebo-controlled (12 weeks, Treatment Period 1), followed by a double-blind, parallel group comparison, extension period (40 weeks, Treatment Period 2).

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No. of patients:			
planned:	Entered: 240		
actual:	Enrolled: 463 Randomised: 235		
	Linagliptin 5 mg Randomised: 113	treated: 113	analysed (for primary endpoint): 113
	Placebo/Glimepiride Randomised: 122	treated: 122	analysed (for primary endpoint): 120
Diagnosis and main criteria for inclusion:	Patients ≥18 years with type 2 diabetes mellitus, a glycosylated haemoglobin (HbA_{1c}) ≥7.0% and ≤10.0% and moderate to severe chronic renal insufficiency (glomerular filtration rate [GFR] <60 mL/min/1.73m^2), and body mass index (BMI) ≤45 kg/m^2		
Test product:	Linagliptin, tablet (Treatment Periods 1 and 2)		
dose:	5 mg once daily		
mode of admin.:	Oral		
batch nos.:	4000044 and 4000045		

Reference therapy:	Placebo to match linagliptin, tablet (Treatment Period 1)	Glimepiride, overencapsulated tablet (Treatment Period 2)	Placebo to match glimepiride, overencapsulated tablet (Treatment Period 2)
dose:	Not applicable	Starting dose of 1 mg, titration to a maximum dose of 4 mg by investigator	Not applicable
mode of admin.:	Oral	Oral	Oral
batch nos.:	4000047	B091003943 (1 mg), B091003942 (2 mg), B091003940 (3 mg), and B091003945 (4 mg)	B091003319

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Duration of treatment:	A 2 week placebo run-in period was followed by a randomised, double-blind treatment period of 12 weeks treatment with either linagliptin 5 mg or placebo. Patients previously on placebo were then switched to glimepiride and patients previously on linagliptin continued with linagliptin for a further 40 weeks of double-blind treatment.
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary endpoint was the change from baseline in HbA_{1c} after 12 weeks of treatment. Important secondary endpoints were the occurrence of a treat-to-target efficacy response (i.e. HbA_{1c} of <6.5% and <7.0% after 12 and 52 weeks of treatment), relative efficacy response (HbA_{1c} lowering by at least 0.5% after 12 and 52 weeks of treatment), and change from baseline in HbA_{1c} by visit over time, and change from baseline in fasting plasma glucose (FPG) by visit over time and after 12 weeks of treatment.
Safety:	Incidence and intensity of adverse events (AEs), withdrawals due to AEs, physical examination, vital signs, 12-lead electrocardiogram (ECG), change from baseline in clinical laboratory parameters.
Statistical methods:	Primary endpoint: The hypothesis that linagliptin 5 mg is superior to placebo was tested using an analysis of covariance (ANCOVA) with treatment, class of renal function impairment (moderate versus severe), prior use of antidiabetes drugs, and baseline HbA_{1c} as linear covariate. Secondary and other endpoints: Descriptive statistics, and logistic regression. Safety endpoints: Descriptive statistics.

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SUMMARY – CONCLUSIONS:

Efficacy results:

Change in the patient population since publication of the interim report

There were 6 patients (5 patients treated with linagliptin and 1 patient treated with placebo/glimepiride) who were treated at a site at which serious non-compliance was identified after the data for these patients had been included in the interim report. The data for these patients were subsequently excluded from the final analysis reported here. Exclusion of the data from these patients did not change the efficacy or safety conclusions of the interim report.

Disposition and compliance

All of the 235 patients who were randomised received trial medication (122 patients placebo/glimepiride; 113 patients linagliptin). Of these, 50 patients (21.3%) prematurely discontinued trial medication before Week 52 (26.2% placebo/glimepiride; 15.9% linagliptin). Approximately 95% of patients on linagliptin were compliant up to Week 46. Compliance at Week 52/End of Treatment was affected by data from patients who discontinued treatment prematurely.

Demographics

The demographic characteristics of the study population were balanced between the treatment groups. More than 60% of the patients were male, and the proportion of males in each treatment group was similar (64.8% placebo/glimepiride; 61.9% linagliptin). Most patients were White (70.2%), 18.3% of patients were Asian, 8.9% of patients were Black or African American, and 2.6% were Native Hawaiian or other Pacific Islander. Mean age overall was 66.6 years.

According to estimated glomerular filtration rate (eGFR) calculated by the modification of diet in renal disease (MDRD) formula at baseline, the majority of patients (61.7%) had moderate renal impairment (eGFR 30 to <60 mL/min/1.73m^2: 59.8% placebo/glimepiride; 63.7% linagliptin) and 34.0% of patients had severe renal impairment (eGFR <30 mL/min/1.73m^2: 36.9% placebo/glimepiride; 31.0% linagliptin).

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Efficacy results: (continued)

The majority of patients were taking insulin at enrolment (88.3% placebo/glimepiride; 83.2% linagliptin). Insulin was the only background antidiabetes agent in 80.8% of patients on placebo/glimepiride and 71.7% of patients on linagliptin. Only 3.3% of patients on placebo and 4.4% of patients on linagliptin were taking oral antidiabetes agents without insulin as background therapy.

Primary endpoint

The primary endpoint was the change from baseline in HbA_{1c} after 12 weeks of treatment. The primary efficacy analysis was based on the full analysis set (FAS), which included all treated patients with a baseline and at least one on-treatment HbA_{1c} measurement available. The adjusted mean change from baseline to Week 12 in HbA_{1c} was -0.11% in patients receiving placebo (n=120), and -0.53% in patients taking linagliptin (n=113). The estimated treatment difference between linagliptin and placebo of the adjusted mean change from baseline in HbA_{1c} at Week 12, was -0.42% (95% confidence interval [CI]: -0.60, -0.24; $p<0.0001$), demonstrating superiority of linagliptin over placebo in the reduction of HbA_{1c}. Renal impairment category was not a significant factor in the primary analysis ($p = 0.4659$).

Secondary endpoints

Statistically significant ($p<0.0001$) differences between the adjusted mean changes from baseline in HbA_{1c} (linagliptin - placebo) were observed across each visit at Weeks 4, 8 and 12. After Week 12, when patients previously treated with placebo were switched to glimepiride, adjusted mean HbA_{1c} decreased in the placebo/glimepiride group to a nadir of -0.74% at Week 24. In the linagliptin group, HbA_{1c} continued to fall and was -0.73% at Week 24. After Week 28, the change from baseline in adjusted mean HbA_{1c} in the placebo/glimepiride group rose and was -0.50% at Week 52, whereas the corresponding value in the linagliptin group was lower, at -0.64%.

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Efficacy results: (continued)

The mean changes from baseline to Week 52 in HbA_{1c} were less in the placebo/glimepiride group than in the linagliptin group for patients with moderate renal impairment (-0.31% placebo/glimepiride; -0.55% linagliptin), but not in patients with severe renal impairment (-0.53% placebo/glimepiride; -0.55% linagliptin).

The differences between the linagliptin and placebo treatments in adjusted mean change from baseline in FPG was significant in favour of linagliptin at Week 4 and Week 8 but not at Week 12: i.e. -17.51 mg/dL ($p = 0.0055$) at Week 4; -16.97 mg/dL ($p = 0.0044$) at Week 8; and -9.29 mg/dL ($p = 0.1602$) at Week 12. At Week 16, after patients on placebo had switched to glimepiride, the differences between the treatments in adjusted mean change from baseline in FPG was significant in favour of glimepiride: 15.26 mg/dL ($p = 0.0240$). Thereafter the differences between the treatments were not statistically significant ($p>0.05$).

Higher proportions of patients in the linagliptin group achieved target HbA_{1c} values <7.0%, <6.5% and a reduction from baseline of at least 0.5% to Week 52 than patients in the placebo/glimepiride group (12.5%, 6.7%, and 23.3%, respectively, placebo/glimepiride; 23.9%, 9.7%, and 34.5%, respectively, linagliptin). A higher proportion of patients on linagliptin with baseline $HbA_{1c} \geq 7.0\%$ achieved the target treatment outcome of HbA_{1c} <7.0% at Week 52 (11.8% of patients placebo/glimepiride; 22.1% of patients linagliptin; $p = 0.0327$). Among patients with baseline $HbA_{1c} \geq 6.5\%$, more patients in the linagliptin group achieved the target HbA_{1c} <6.5% after 52 weeks than patients in the placebo/glimepiride group (6.7% placebo/glimepiride; 9.9% linagliptin), which was not statistically significant ($p = 0.3805$).

Other endpoints

More patients in the linagliptin group achieved a target HbA_{1c} response without episodes of hypoglycaemia or weight gain than patients in the placebo/glimepiride group at each timepoint. The proportion of patients achieving this target at Week 12 was 3.3% of patients in the placebo group and 11.5% of patients in the linagliptin group. At Week 52, the proportion of patients achieving the target was 0.8% in the placebo/glimepiride group and 8.8% in the linagliptin group.

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Efficacy results: (continued)

There were small decreases in insulin doses between baseline and Week 12 in both groups. Adjusted mean (SE) insulin doses at baseline were 74.31 (6.48) IU in the placebo/glimepiride group and 75.32 (5.06) IU in the linagliptin group. The adjusted mean (SE) changes from baseline to Week 12 in insulin doses were -0.56 (1.18) IU in the placebo/glimepiride group, and -2.63 (1.18) IU in the linagliptin group. The estimated difference in the adjusted mean change from baseline to Week 12 in insulin dose between linagliptin and placebo was -2.07 IU (95% CI: -4.24, 0.10; p = 0.0613). Adjusted mean insulin doses decreased in both groups throughout Treatment Period 2. At Week 52, mean insulin dose was decreased from baseline by -6.81 IU in the placebo/glimepiride group and by -7.99 in the linagliptin group. The estimated difference in the adjusted mean change from baseline to Week 52 in insulin dose between linagliptin and placebo/glimepiride was -1.18 IU (95% CI: -8.03, 5.68; p = 0.7352).

Mean eGFR fluctuated over the 1-year period of the study, with a tendency to a small decrease over time, and comparable changes in both treatment groups. Mean urine albumin to creatinine ratio tended to decrease slightly over time in both treatment groups, and was lower in the linagliptin group than in the placebo/glimepiride group at every timepoint.

Pharmacokinetic/pharmacodynamic results

The overall geometric mean trough plasma concentration of linagliptin at Weeks 12, 24 and 52 were 7.77, 7.62, and 5.94 nmol/L, respectively. Geometric mean plasma trough linagliptin levels were similar in patients with different degrees of renal dysfunction, ranging at the various sampling timepoints: from 7.36 to 7.91 nmol/L in patients with mild renal impairment, from 6.14 to 7.45 nmol/L in patients with moderate renal impairment, from 5.90 to 8.50 nmol/L in patients with severe renal impairment and from 2.39 to 9.46 nmol/L in patients with end stage renal disease. Concomitant administration of P-gp and/or CYP 3A4 inhibitors resulted in a slight increase in trough concentrations, with values ranging for the various weeks of sampling between 5.61 and 7.59 nmol/L for patients without any P-gp or CYP 3A4 inhibitors compared to 7.93 to 11.08 nmol/L for patients with concomitant use of P-gp or CYP 3A4 inhibitors.

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Safety results:

Exposure

All 235 randomised patients received at least one dose of trial medication and were included in the Treated Set: 122 patients received placebo, 114 patients received glimepiride, and 113 patients received linagliptin. Mean exposure to study medication was 308.1 days for patients randomised to placebo/glimepiride, 242.8 days for patients receiving glimepride (mean dose 2.2 mg daily), and 336.5 days for patients randomised to linagliptin. Cumulative patient exposure in the linagliptin group was 104.1 patient years.

After the up-titration period, the mean dose of glimepiride overall was 2.2 mg daily for the remainder of the trial.

Adverse events

Overall, there were 120 patients (98.4%) with AEs in the placebo/glimepiride group and 108 patients (95.6%) with AEs in the linagliptin group. During Treatment Period 2, the incidence of AEs was 96.5% of patients receiving glimepiride and 90.7% of patients receiving linagliptin.

The majority of the AEs were of mild or moderate intensity. The most frequently reported AEs in both treatment periods were hypoglycaemia (70.5% placebo/glimepiride; 61.1% linagliptin), followed by hyperglycaemia (17.2% placebo/glimepiride; 17.7% linagliptin); and nasopharyngitis (14.8% placebo/glimepiride; 18.6% linagliptin). Hypoglycaemia, hyperglycaemia and nasopharyngitis were also the most common AEs during Treatment Period 2.

AEs in both treatment periods that were assessed by the investigators as being drug-related were reported in 49.2% of patients in the placebo/glimepiride group and 45.1% of patients in the linagliptin group. Severe AEs that were also treatment-related were reported for 7 patients: hypoglycaemia in 3/114 patients (2.6%) receiving glimepride and 2/113 patients (1.8%) receiving linagliptin; and cardiac failure congestive and anaemia were each reported in 1 patient receiving linagliptin.

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Safety results: (continued)

AEs led to discontinuation of study medication in 13.9% of patients in the placebo/glimepiride group and 8.0% of patients in the linagliptin group. The most common reasons for discontinuation of study drug were hypoglycaemia (2.5% placebo/glimepiride; 0.0% linagliptin), cardiac failure congestive (1.6% placebo/glimepiride; 0.9% linagliptin), and renal failure acute (0.8% placebo/glimepiride; 1.8% linagliptin). The most common reasons for discontinuation of glimepiride were hypoglycaemia (1.8%), and cardiac failure congestive (1.8%).

The proportion of patients with at least one investigator-defined hypoglycaemic episode throughout the trial was numerically lower in the linagliptin group (72 patients, 63.7%) than in the placebo/glimepiride group (87 patients, 71.3%). The incidence of hypoglycaemia was similar in both groups during Treatment Period 1; the difference between the groups was mostly observed during Treatment Period 2.

Overall, investigator-defined hypoglycaemia with plasma glucose <54 mg/dL was reported in 26.2% of patients in the placebo/glimepiride group, and 23.0% of patients in the linagliptin group. The proportions of patients with severe hypoglycaemia requiring assistance were 6.6% placebo/glimepiride, and 8.8% linagliptin. Every patient with an episode of severe hypoglycaemia was concomitantly taking insulin. The difference between the groups in the proportion of patients with hypoglycaemic events during the trial was not statistically significant ($p = 0.2438$, Cochran-Mantel-Haenszel test). Logistic regression of the occurrence of hypoglycaemia indicated that renal impairment status was not associated with a significant difference in the odds of having a hypoglycaemic event (odds ratio 0.922, $p = 0.9184$ for mild versus moderate renal impairment and 1.395, $p = 0.3379$ for severe or end stage versus moderate renal impairment). Prior use of antidiabetes therapy was a significant factor for hypoglycaemia ($p<0.0001$) but age was not.

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Safety results: (continued)

Patients who switched from placebo to glimepiride were more likely to have episodes of hypoglycaemia than patients taking linagliptin for more than 12 weeks. Seventy-nine patients (69.3%) taking glimepiride and 62 patients (57.9%) taking linagliptin had at least one investigator-defined hypoglycaemic episode during Treatment Period 2. Plasma glucose, where measured, was <54 mg/dL during the worst episode in 38.0% of patients with hypoglycaemia taking glimepiride and 51.6% of patients with hypoglycaemia taking linagliptin. Plasma glucose levels of ≥54 and ≤70 mg/dL were measured during the worst episode in 51.9% of patients with hypoglycaemia taking glimepiride and 40.3% of patients with hypoglycaemia taking linagliptin.

There were 8 patients (6.6%) in the placebo/glimepiride group and 3 patients (2.7%) in the linagliptin group with confirmed cardiovascular death, myocardial infarction (MI), stroke or hospitalisation due to unstable angina as adjudicated by the Clinical Event Committee (CEC). Of the 8 patients in the placebo/glimepiride group with CEC confirmed events, 1 case of non-fatal MI occurred during Part 1 in a patient taking placebo; the other events occurred during Part 2 in patients taking glimepiride and included 2 patients with non-fatal MI, 3 patients who were hospitalised due to unstable angina, 2 patients with non-fatal stroke, and 1 patient who had a transient ischaemic attack. In the linagliptin group, 2 patients were hospitalised due to unstable angina, and 1 patient had a fatal stroke. CEC confirmed unstable angina was reported in 10.7% of patients in the placebo/glimepiride group and 12.4% of patients in the linagliptin group.

Two patients died during the trial: 1 patient died of sepsis during treatment with glimepiride, and 1 patient died of a cerebrovascular accident during treatment with linagliptin (CEC adjudicated event). Neither of these cases was considered drug-related.

There were 29.5% of patients in the placebo/glimepiride group and 24.8% of patients in the linagliptin group with SAEs during the treatment period. Five patients experienced SAEs that were considered to be drug-related: hypoglycaemia in 1 patient receiving glimepiride, and 2 patients receiving linagliptin; and anaemia and cardiac failure congestive, each in 1 patient receiving linagliptin.

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Safety results: (continued)

Pre-specified renal AEs were identified in 8.2% of patients in the placebo/glimepiride group and 4.4% of patients in the linagliptin group; hepatic AEs were identified in 6.6% of patients in the placebo/glimepiride group and 0.9% of patients in the linagliptin group; and hypersensitivity reactions were identified in 0.8% of patients in the placebo/glimepiride group and 1.8% of patients in the linagliptin group. There were no cases of cutaneous AEs or pancreatitis.

'Other significant AEs' (as defined by ICH E3) were reported by 6.6% of patients in the placebo/glimepiride group and 2.7% of patients in the linagliptin group. Significant AEs with onset during treatment with placebo were hypoglycaemia (2 patients), and muscle spasms (1 patient). Significant AEs with onset during treatment with glimepiride were hypoglycaemia (2 patients), rash, chills, and epidermal growth factor receptor decreased (each in 1 patient). Significant AEs in the linagliptin group were hypoglycaemia, asthenia, and blood calcium increased (each in 1 patient).

Laboratory evaluation and vital signs

Laboratory analyses (haematology, clinical chemistry, and urinalysis) did not reveal any clinically significant findings compared to baseline. In particular, there were no significant changes from baseline to last value on treatment with linagliptin in potassium, creatinine, and urinary microalbumin creatinine ratio. In particular, mean eGFR over time was comparable between the groups, and urinary microalbumin creatinine ratio tended to decrease slightly over time in both groups, but was lower in the linagliptin group at every timepoint. Possibly clinically significant abnormalities were reported for fewer than 30% of patients with data in either treatment group. There were no cases of Hy's law in this study. No differences in changes in renal function were observed between treatments.

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Safety results: (continued)	Overall, no clinically significant differences between the treatment groups were observed in blood pressure and pulse rate from baseline to end of treatment. The mean change from baseline to Week 52 in body weight was +0.98 kg in the placebo/glimepiride group and -0.46 kg in the linagliptin group (estimated treatment difference 1.68 kg, 95% CI: 0.57, 2.79; p = 0.0031). The adjusted mean change from baseline to Week 12 in body weight was +0.38 kg in patients taking placebo and -0.34 kg in patients taking linagliptin. The estimated difference between the treatments was 0.72 kg (95% CI: 0.08, 1.37, p = 0.0282). *Use of Rescue Medication* Twenty-four patients (20.0%) in the placebo/glimepiride group and 30 patients (26.5%) in the linagliptin group took rescue therapy. The odds ratio of requiring rescue therapy (linagliptin : placebo/glimepiride) was 1.524 (p = 0.1874).
Conclusions:	A statistically significant and clinically relevant reduction in the change from baseline in HbA_{1c} after 12 weeks of treatment was observed for linagliptin compared with placebo. After patients on placebo were switched to glimepiride, there was an initial decrease in HbA_{1c} to values that were similar to those in the linagliptin group. However, glycaemic control was more persistent in the linagliptin group and, at Week 52, the adjusted mean change from baseline was lower in the linagliptin group (-0.64%) than in the placebo/glimepiride group (-0.50%). The reported safety results were comparable between linagliptin and placebo/glimepiride, and between linagliptin and glimepiride, with no distinct safety concerns observed. No differences in renal function were observed between treatment groups. There was no increased risk for hypoglycaemia for patients taking linagliptin whereas patients switched to glimepiride were more likely to have episodes of hypoglycaemia than patients treated with glimepiride during Treatment Period 2.

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Report date: 04 MAR 2012	**Trial No. / U No.:** 1218.64 / U13-1283-01	**Dates of trial:** 17 MAR 2010 – 18 JUN 2012	**Date of revision:** Not applicable

Conclusions (continued):	There was a significant difference between the groups in the change from baseline in body weight at Week 52, with an overall increase in the placebo/glimepiride group and an overall decrease in the linagliptin group. Linagliptin trough plasma levels were similar across visits and renal staging groups, underlying that the non-renal excretion of linagliptin does not lead to the need for any dose alteration in patients with moderate or severe renal impairment. In this study in vulnerable patients with T2DM and moderate to severe renal impairment and receiving antidiabetes background therapy, linagliptin 5 mg once daily was effective in reducing HbA_{1c} after 12 weeks of treatment. The reduction in HbA_{1c} was sustained over the full 52-week study period, being numerically better than glimepiride in the extension phase between 12 to 52 weeks. Linagliptin was weight neutral, and was safe and well tolerated when compared with placebo and with glimepiride.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement results for secondary endpoints of the trial. Note that not all secondary endpoints defined in the trial protocol are presented in this synopsis because their number was too large to allow meaningful presentation in this format.

Results for	**presented in**
HbA_{1c} (%) change from baseline over time up to Week 52	Table 15.2.2.1.1: 1
FPG (mg/dL) change from baseline over time up to Week 52	Table 15.2.2.1.3: 1

Table 15.2.2.1.1: 1 Adjusted HbA1c (%) mean change from baseline over time up to Week 52 - FAS (LOCF)

	Placebo/Glimepiride			Linagliptin			Difference Linagliptin - Placebo/Glimepiride				
	N	Adj* mean	SE	N	Adj* mean	SE	Adj* mean	SE	95% CI LL	95% CI UL	p-value
Baseline (unadjusted means)	120	8.03	0.09	113	8.08	0.08					
Change from baseline at Week 4	120	-0.16	0.06	113	-0.37	0.06	-0.21	0.05	-0.31	-0.11	<.0001
Change from baseline at Week 8	120	-0.11	0.10	113	-0.49	0.09	-0.39	0.08	-0.54	-0.23	<.0001
Change from baseline at Week 12	120	-0.11	0.11	113	-0.53	0.11	-0.42	0.09	-0.60	-0.24	<.0001
Change from baseline at Week 16	120	-0.38	0.12	113	-0.54	0.11	-0.15	0.10	-0.34	0.04	0.1108
Change from baseline at Week 20	120	-0.64	0.12	113	-0.63	0.12	0.01	0.10	-0.18	0.21	0.8805
Change from baseline at Week 24	120	-0.74	0.13	113	-0.73	0.12	0.01	0.10	-0.20	0.21	0.9341
Change from baseline at Week 28	120	-0.71	0.13	113	-0.72	0.12	-0.01	0.10	-0.21	0.20	0.9325
Change from baseline at Week 34	120	-0.66	0.13	113	-0.72	0.12	-0.06	0.10	-0.27	0.14	0.5489
Change from baseline at Week 40	120	-0.53	0.13	113	-0.70	0.13	-0.17	0.11	-0.38	0.04	0.1204
Change from baseline at Week 46	120	-0.54	0.13	113	-0.68	0.13	-0.14	0.11	-0.36	0.08	0.2133
Change from baseline at Week 52	120	-0.50	0.13	113	-0.64	0.13	-0.14	0.11	-0.36	0.07	0.1977

* Model includes treatment, baseline HbA1c, renal function impairment and prior use of antidiabetic agents

Table 15.2.2.1.3: 1 Adjusted FPG (mg/dL) mean change from baseline over time up to Week 52 - FAS(LOCF)

	Placebo/Glimepiride			Linagliptin			Difference Linagliptin - Placebo/Glimepiride				
	N	Adj* mean	SE	N	Adj* mean	SE	Adj* mean	SE	95% CI LL	95% CI UL	p-value
Baseline (unadjusted means)	119	148.05	4.59	112	155.96	4.28					
Change from baseline at Week 4	119	2.66	7.59	112	-14.85	7.31	-17.51	6.25	-29.83	-5.19	0.0055
Change from baseline at Week 8	119	4.98	7.16	112	-11.99	6.90	-16.97	5.90	-28.59	-5.35	0.0044
Change from baseline at Week 12	119	9.53	8.01	112	0.24	7.71	-9.29	6.59	-22.28	3.70	0.1602
Change from baseline at Week 16	119	-18.13	8.15	112	-2.87	7.85	15.26	6.71	2.03	28.49	0.0240
Change from baseline at Week 20	119	-14.84	8.63	112	-6.69	8.31	8.15	7.11	-5.86	22.15	0.2528
Change from baseline at Week 24	119	-19.73	8.08	112	-18.41	7.78	1.32	6.65	-11.79	14.43	0.8430
Change from baseline at Week 28	119	-14.00	8.38	112	-8.90	8.06	5.09	6.90	-8.49	18.68	0.4608
Change from baseline at Week 34	119	-16.88	8.53	112	-4.87	8.21	12.01	7.02	-1.83	25.85	0.0887
Change from baseline at Week 40	119	-11.57	8.98	112	-7.90	8.65	3.67	7.40	-10.90	18.25	0.6200
Change from baseline at Week 46	119	-9.19	9.00	112	-2.47	8.67	6.72	7.41	-7.89	21.33	0.3656
Change from baseline at Week 52	119	-6.62	8.73	112	5.01	8.41	11.63	7.19	-2.54	25.79	0.1071

* Model includes baseline HbA1c, baseline FPG, renal function impairment group, prior use of anti-diabetic drugs and treatment group