Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004585-40	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 1 of 14	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1218.20 / U11-1485-03	**Dates of trial:** 12 FEB 2008 to 21 DEC 2010	**Date of revision:** 06 JUN 2012

Title of trial:	A randomised, double-blind, active-controlled parallel group efficacy and safety study of linagliptin (5 mg, administered orally once daily) compared to glimepiride (1 to 4 mg once daily) over two years, in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy
Coordinating Investigator:	[redacted] Germany
Trial sites:	Multi-national, multi-centre trial: 209 trial sites in 16 countries (Bulgaria, Denmark, France, Germany, Hong Kong, Hungary, India, Ireland, Italy, Netherlands, Norway, Poland, South Africa, Sweden, UK, USA)
Publication (reference):	Data of this study have not been published
Clinical phase:	III
Objectives:	The objective of this trial was to investigate the efficacy, safety, and tolerability of linagliptin (5 mg) versus glimepiride (1 mg to 4 mg) administered for 104 weeks as an add-on therapy to metformin in patients with type 2 diabetes mellitus (T2DM) and insufficient glycaemic control.
Methodology:	Randomised, double-blind, double-dummy, active-controlled, parallel group comparison of 2 groups over 104 weeks. Before randomisation, patients pre-treated with 1 additional oral antidiabetic agent in addition to metformin underwent a washout period of 6 weeks followed by an open-label placebo run-in period of 2 weeks; patients previously treated with metformin only underwent a 2-week placebo run-in period.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004585-40	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 2 of 14	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1218.20 / U11-1485-03	**Dates of trial:** 12 FEB 2008 to 21 DEC 2010	**Date of revision:** 06 JUN 2012

No. of patients:	
planned:	Entered: 1414 patients (707 per group)
actual:	Enrolled: 2283 patients (17 patients from non-compliant site 91025 not included; for more information, please see Section 11.1) Entered: 1552 patients (8 patients from non-compliant site 91025 not included; for more information, please see Section 11.1) Linagliptin (5 mg) Entered: 777 treated: 776 analysed (for primary endpoint): 764 Glimepiride (1 mg to 4 mg) Entered: 775 treated: 775 analysed (for primary endpoint): 755
Diagnosis and main criteria for inclusion:	Patients must have had T2DM previously treated with metformin monotherapy or metformin plus not more than 1 other oral antidiabetic agent (unchanged for 10 weeks). For patients undergoing washout of previous antidiabetic medication glycosylated haemoglobin (HbA_{1c}) at screening was to be ≥6.0% and ≤9.0%. For patients not undergoing washout of previous antidiabetic medication HbA_{1c} was to be ≥6.5% and ≤10.0%. Patients were to have been ≥18 and ≤80 years old with a body mass index (BMI) ≤40 kg/m^2.
Test product:	Linagliptin, tablet
dose:	5 mg, once daily
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6
Reference therapy:	Glimepiride, overencapsulated tablet
dose:	1 mg to 4 mg, once daily
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004585-40	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 3 of 14	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1218.20 / U11-1485-03	**Dates of trial:** 12 FEB 2008 to 21 DEC 2010	**Date of revision:** 06 JUN 2012

Duration of treatment:	A 6-week washout period was followed by a 2-week, open-label, placebo run-in (for patients pre-treated with 1 additional oral antidiabetic agent apart from metformin) or a 2-week placebo run-in (for patients not previously treated with an additional oral antidiabetic agent apart from metformin). During the first 12 weeks of treatment, glimepiride could have been up-titrated (in intervals of 4 weeks). After the treatment period, which was 104-weeks long, there was a 1-week follow-up period. Background medication (metformin) was taken during the entire trial duration (including the washout and placebo run-in periods) in an unchanged dosage.
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The 2 co-primary endpoints in this study were the change in HbA_{1c} from baseline to 52 and 104 weeks of treatment. The 52-week outcomes are discussed in an interim report (U10-1465-02). The 2 key secondary 104-week endpoints were the change in body weight and the occurrence of hypoglycaemic events from baseline to Week 104 (the latter is described in the safety results section). Other important secondary endpoints were the occurrence of a treat-to-target response (HbA_{1c} on treatment <7.0% or <6.5%) and the occurrence of a relative efficacy response (reduction of HbA_{1c} by at least 0.5%) at Week 104, the change in HbA_{1c} over time, the change in fasting plasma glucose (FPG) from baseline to 104 weeks, and the change in 2 h post-prandial glucose (2h PPG) from baseline to 104 weeks of treatment.
Safety:	Safety was assessed based on the incidence and intensity of adverse events (AEs), withdrawals due to AEs, physical examination, changes in vital signs, clinically relevant findings in 12-lead electrocardiogram (ECG) reported as AEs, and changes from baseline in clinical laboratory parameters.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004585-40	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 4 of 14	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1218.20 / U11-1485-03	**Dates of trial:** 12 FEB 2008 to 21 DEC 2010	**Date of revision:** 06 JUN 2012

Statistical methods:

Primary endpoint
First, the non-inferiority of treatment with linagliptin to treatment with glimepiride was tested in terms of change in HbA_{1c} from baseline to Week 104 (non-inferiority margin of 0.35%), at the level of α=0.0125 (1-sided) through a 2-sided 97.5% confidence interval (CI). If the non-inferiority of treatment with linagliptin was confirmed in terms of HbA_{1c} change from baseline to Week 104 at the margin of 0.35%, then superiority of treatment with linagliptin to treatment with glimepiride was to be tested in terms of change in HbA_{1c} from baseline to Week 104 at the level of α=0.0125 (1-sided). An analysis of covariance (ANCOVA) was performed to compare the change from baseline in HbA_{1c} after 104 weeks treatment with linagliptin or glimepiride, with 'treatment' and 'prior use of antidiabetic agents' as fixed classification effects and 'baseline HbA_{1c}' as a linear covariate.

Key secondary endpoints
If the superiority of treatment with linagliptin was established over treatment with glimepiride in the primary endpoint, the superiority of treatment with linagliptin over treatment with glimepiride was to be tested in terms of both change in body weight and occurrence of hypoglycaemic events from baseline to Week 104 of treatment, each at the level of α=0.0125 (1-sided) in a hierarchical fashion. The change from baseline in body weight was analysed using an ANCOVA model with 'treatment' and 'prior use of antidiabetic agents' as fixed classification effects and 'baseline HbA_{1c}' and 'baseline weight' as linear covariates. The Cochran-Mantel-Haenszel test was performed to compare the proportion of patients with hypoglycaemic events between the linagliptin and glimepiride groups. The impact of treatment on the occurrence of hypoglycaemia was explored using logistic regression including 'treatment', 'baseline HbA_{1c}' and 'prior OADs' in the model. Time to the onset of the first hypoglycaemia was analysed by Kaplan-Meier estimates.

Other secondary endpoints (exploratory)
The change in 2h PPG was analysed using an ANCOVA model with the factors 'treatment', 'prior use of antidiabetic agents' as well as 'HbA_{1c} baseline' and 'postprandial glucose after 2 hours at baseline' as covariates. Responder status (HbA_{1c} on treatment <7.0% or <6.5%, reduction of HbA_{1c} by at least 0.5%) was analysed by using logistic regression, and rescue therapy was examined by using Kaplan-Meier analysis.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004585-40	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 5 of 14	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1218.20 / U11-1485-03	**Dates of trial:** 12 FEB 2008 to 21 DEC 2010	**Date of revision:** 06 JUN 2012

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

A total of 2283 patients were enrolled into this study; 1552 patients were randomised in a 1:1 ratio to linagliptin (777 patients) or glimepiride (775 patients). The main reason for non-randomisation was inclusion criteria not met (21.7%), with 15.9% of patients excluded because HbA_{1c} was out of range at Visit 1A. All but 1 of the randomised patients were treated (1 patient in the linagliptin group was not treated). Of the treated patients, 23.2% discontinued prematurely. The most frequent reasons for discontinuation were the occurrence of AEs (7.9% linagliptin; 11.6% glimepiride) and lack of efficacy (5.8% linagliptin; 1.9% glimepiride).

Overall, the demographic profile was balanced between the treatment groups. The study population contained slightly more male patients (60.2%). The majority of patients were White (85.0%), the mean age was 59.8 years, and the mean BMI was 30 kg/m^2. The majority of patients had either normal renal function (estimated glomerular filtration rate [eGFR] based on modification of diet in renal disease [MDRD] staging ≥90 mL/min; 49.5%) or mild renal impairment (eGFR 60 to <90 mL/min; 45.7%) at baseline; 4.8% of patients had moderate renal impairment (eGFR 30 mL/min to <60 mL/min), and there were no patients with severe renal impairment or endstage renal disease (eGFR <30 mL/min) at baseline. Baseline concomitant diagnoses and efficacy parameters were similar between the 2 groups; the only exceptions were that the percentage of patients with musculoskeletal and connective tissue disorders (42.3% linagliptin; 37.5% glimepiride) was higher in the linagliptin group, while more patients in the glimepiride group had a concomitant diagnosis of cardiac disorders (16.9% linagliptin; 19.5% glimepiride), metabolism and nutrition disorders (61.6% linagliptin; 67.0% glimepiride), and eye disorders (12.0% linagliptin; 14.6% glimepiride).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004585-40	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 6 of 14	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1218.20 / U11-1485-03	**Dates of trial:** 12 FEB 2008 to 21 DEC 2010	**Date of revision:** 06 JUN 2012

Efficacy / clinical pharmacology results (continued):

The treated set (TS) was composed of all randomised patients who received at least 1 dose of study medication (N=1551). All safety analyses were carried out on the TS. The full analysis set (FAS) was defined as all treated patients who had a baseline and at least 1 on-treatment HbA_{1c} measurement (N=1519). The primary efficacy analysis was carried out on the FAS. The per-protocol set (PPS) was a subset of the FAS that included all patients without an important protocol violation (PV; N=1160). The FAS-completers and PPS-completers were subsets of the FAS and PPS, respectively, that consisted of all patients who completed at least 684 days of treatment and had a HbA_{1c} measurement at Week 104 (N=1158 FAS-completers; N=905 PPS-completers). The meal tolerance test (MTT) set was a subset of the FAS that included all patients with a valid MTT at baseline and at least 1 valid on-treatment MTT (N=462). Selected analyses were carried out using last observation carried forward (LOCF), observed cases (OC; in which missing data were not imputed), non-completers considered failure (NCF; in which missing data due to premature discontinuation of a patient were considered as failure), or with observations after the start of rescue therapy accepted as observed cases (ROC).

Primary efficacy endpoint

The primary endpoint was the change from baseline in HbA_{1c} after 104 weeks of treatment. The treatment difference between linagliptin and glimepiride in the adjusted mean HbA_{1c} change from baseline to 104 weeks was 0.20% (97.5% CI: 0.094, 0.299) for the FAS(LOCF); this showed the non-inferiority of linagliptin compared to glimepiride (1-sided p-value for non-inferiority=0.0004), based on a pre-defined non-inferiority margin of 0.35%. The PPS(LOCF) analysis showed a larger difference between linagliptin and glimepiride (0.28%) in the adjusted mean HbA_{1c} change from baseline to Week 104 than was observed for the FAS(LOCF). The upper limits of both the 97.5% CI (0.17, 0.40) and 95% CI (0.18, 0.39) in this PPS(LOCF) analysis were above the pre-defined non-inferiority margin of 0.35%. For the FAS-completers(OC) and the PPS-completers(OC), the upper limits of the 97.5% CIs were within the pre-defined non-inferiority margin of 0.35% (97.5% CIs: 0.02, 0.21 and 0.07, 0.28, respectively). Superiority of linagliptin over glimepiride could not be shown in terms of change in HbA_{1c} from baseline to Week 104 (2-sided p-value for superiority <0.0001 for the FAS(LOCF)).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004585-40	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 7 of 14	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1218.20 / U11-1485-03	**Dates of trial:** 12 FEB 2008 to 21 DEC 2010	**Date of revision:** 06 JUN 2012

Efficacy / clinical pharmacology results (continued):

A further sensitivity analysis was performed, in the form of a retrospective 'completers cohort' analysis. In this post-hoc 'completers cohort' analysis, from which patients were excluded once they failed to attain certain FPG or HbA_{1c} levels at particular points in time, the adjusted mean change in HbA_{1c} after 104 weeks was −0.56% for patients taking linagliptin and −0.63% for patients taking glimepiride; the difference between treatments at 104 weeks was only 0.08% (95% CI: 0.00, 0.15, p=0.0468) in this analysis. This further supports the efficacy findings.

Key secondary efficacy endpoints
The difference between treatment with linagliptin versus treatment with glimepiride was tested in terms of change in body weight and occurrence of hypoglycaemic events from baseline to 104 weeks of treatment. These analyses were considered 'exploratory' tests; as superiority of linagliptin over glimepiride was not shown for the second hierarchical primary endpoint, the superiority of linagliptin over glimepiride in terms of change in body weight and occurrence of hypoglycaemic events could not be tested in a hierarchal fashion.

A decrease in adjusted mean body weight was seen in the linagliptin group, whereas a steady increase in adjusted mean body weight was seen in the glimepiride group (−1.39 kg linagliptin; 1.29 kg glimepiride). The difference between the 2 groups in terms of change in adjusted mean body weight from baseline to Week 104 was −2.68 kg (−3.17, −2.19; p<0.0001), which was statistically significant and favoured linagliptin.

Fewer patients taking linagliptin experienced hypoglycaemic events as compared with patients taking glimepiride (7.5% linagliptin; 36.1% glimepiride); the difference between the groups for the incidence of hypoglycaemic events was statistically significant and favoured linagliptin (p<0.0001). Further discussion of hypoglycaemic events can be found under safety results.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004585-40	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 8 of 14	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1218.20 / U11-1485-03	**Dates of trial:** 12 FEB 2008 to 21 DEC 2010	**Date of revision:** 06 JUN 2012

Efficacy / clinical pharmacology results (continued):

Other secondary efficacy endpoints

Fewer patients in the linagliptin group than in the glimepiride group achieved absolute and relative efficacy responses. Among patients with a baseline HbA_{1c} of 7.0% or more, 21.0% of the linagliptin group and 28.3% of the glimepiride group achieved an HbA_{1c} less than 7.0% at Week 104. Among patients with baseline HbA_{1c} of 6.5% or more, 10.9% of the linagliptin group and 14.7% of the glimepiride group achieved HbA_{1c} less than 6.5% at Week 104. Further, a lower percentage of patients in the linagliptin group had an HbA_{1c} reduction of at least 0.5% compared with patients in the glimepiride group (26.2% linagliptin; 33.5% glimepiride). Post-hoc analyses revealed that more patients taking linagliptin than glimepiride achieved an HbA_{1c} at Week 104 of less than 7.0% without using rescue therapy or experiencing a hypoglycaemic event (26.6% linagliptin; 19.7% glimepiride); more linagliptin patients than glimepiride patients had an HbA_{1c} at 104 weeks of less than 7.0% without using rescue medication, without significant weight gain (<1 kg), and with no or only mild hypoglycaemic events (23.8% linagliptin; 15.2% glimepiride).

Overall, for the FAS(LOCF) adjusted mean HbA_{1c} decreased until Week 16 for both treatment groups and then increased to Week 78. From Week 78 until the end of the study, HbA_{1c} remained relatively constant for patients in both treatment groups. This plateau in mean HbA_{1c} was also observed for the PPS(LOCF), FAS(LOCF-ROC) and PPS(LOCF-ROC), but not for the FAS-completers(OC), PPS-completers(OC), FAS(OC), PPS(OC), FAS(OC-ROC), or PPS(OC-ROC).

The difference between the 2 treatment groups in terms of the change in adjusted mean FPG from baseline to 104 weeks was 6.38 mg/dL (95% CI: 2.51, 10.25; p=0.0012), with glimepiride showing the greater decrease. The change from baseline in adjusted mean 2h PPG at Week 104 showed no significant difference between the groups (treatment difference: −9.74 mg/dL; 95% CI: −21.07, 1.59; p=0.0918).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004585-40	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 9 of 14	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1218.20 / U11-1485-03	**Dates of trial:** 12 FEB 2008 to 21 DEC 2010	**Date of revision:** 06 JUN 2012

Efficacy / clinical pharmacology results (continued):

Other endpoints

The proportion of patients using rescue therapy was slightly higher in the linagliptin group than the glimepiride group (24.7% linagliptin; 21.5% glimepiride), although this difference between treatments was not statistically significant (p=0.1170). The mean change from baseline in waist circumference was small in both groups, with a mean decrease of 1.0 cm in the linagliptin group and a mean increase of 0.6 cm in the glimepiride group at Week 104. In terms of coefficient of durability, the yearly rise in adjusted mean HbA_{1c} was slightly less for the linagliptin group than for the glimepiride group (0.44% linagliptin; 0.54% glimepiride); thus, linagliptin treatment was slightly more durable than glimepiride treatment, although this difference was not significant (95% CI: −0.24, 0.04; p=0.1659).

Biomarkers, pharmacokinetic, and pharmacodynamic results

The geometric mean (gMean) plasma concentrations of linagliptin at trough remained constant over the study (from 5.23 nmol/L to 5.73 nmol/L). Categorised by eGFR (MDRD staging), gMean linagliptin trough levels over time were comparable between patients with normal renal function (from 4.99 nmol/L to 5.47 nmol/L) and mild renal impairment (from 5.37 nmol/L to 5.95 nmol/L), while levels in patients with moderate renal impairment (from 6.89 nmol/L to 8.06 nmol/L) were slightly higher. Due to the small sample size of patients with moderate renal impairment (N≤21 for all timepoints), these results should be interpreted with caution. GMean linagliptin trough levels were also slightly higher in patients continuously using a P-gp (from 5.78 mmol/L to 6.79 mmol/L) or CYP3A4 (from 4.83 mmol/L to 6.75 mmol/L) inhibitor than in patients not using any concomitant P-gp (from 5.29 mmol/L to 5.71 mmol/L) or CYP3A4 (from 5.28 mmol/L to 5.72 mmol/L) inhibitor. Because of the small sample size of patients taking concomitant P-gp (N≤13 at all timepoints) or CYP3A4 inhibitors (N≤12 at all timepoints), these results should be interpreted with caution. Median DPP-4 inhibition remained constant during the study and was above 80% at all timepoints.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004585-40	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 10 of 14	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1218.20 / U11-1485-03	**Dates of trial:** 12 FEB 2008 to 21 DEC 2010	**Date of revision:** 06 JUN 2012

Efficacy / clinical pharmacology results (continued):

Results for biomarkers and derived indices were difficult to interpret because they did not point in a clear direction. While significant differences between the treatment groups in terms of the adjusted mean change from baseline to Week 104 were observed for the proinsulin to insulin ratio (−0.04 pmol/mU; 95% CI: −0.06, −0.03; p<0.0001) and HOMA-IR (−0.85 [mU/L] × [mmol/L]; 95% CI: −1.37, −0.33; p=0.0014) in favour of linagliptin, significant differences between the treatments in favour of glimepiride were observed for HOMA-%B (−15.29 [mU/L]/[mmol/L] 95% CI: −21.03, −9.55; p<0.0001) and the disposition index (−1.95 [1/((mmol/L)×(mmol/L))]; 95% CI: −3.36, −0.54; p=0.0067).

The parameters measured over 2 h during a meal challenge, including adjusted mean total glucose AUC (−2.90 mmol×h/L linagliptin; −1.70 mmol×h/L glimepiride), adjusted mean total insulin AUC to total glucose AUC ratio (0.26 linagliptin; 8.05 glimepiride), and adjusted mean C-peptide AUC (497.92 pmol×h/L linagliptin; 958.68 pmol×h/L glimepiride) improved for both groups during the course of the study. The difference between the treatment groups in terms of adjusted mean change from baseline to Week 104 in total glucose AUC (−1.21 mmol×h/L; 95% CI: −2.33, −0.09; p=0.0347) was significant in favour of linagliptin, while the difference between treatments groups for the adjusted mean change in total insulin AUC to total glucose AUC ratio (−7.79; 95% CI: −11.12, −4.46; p<0.0001) and the adjusted mean change in C-peptide AUC (−460.77 pmol×h/L; 95% CI: −779.3, −142.2; p=0.0048) was significant in favour of glimepiride. Adjusted mean total insulin AUC over 2 h after a meal challenge decreased for the linagliptin group (−44.57 pmol×h/L) and increased for the glimepiride group (151.74 pmol×h/L) during the course of this study; the difference between treatments in this case was also significant (−196.31 pmol×h/L, 95% CI: −263.8, −128.8; p<0.0001) in favour of glimepiride. These results should be interpreted with caution, because some MTT parameters may not provide clear results for individuals who change body mass over time.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004585-40	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 11 of 14	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1218.20 / U11-1485-03	**Dates of trial:** 12 FEB 2008 to 21 DEC 2010	**Date of revision:** 06 JUN 2012

Safety results

Exposure
Mean exposure was 627.2 days for patients randomised to linagliptin and 624.8 days for patients randomised to glimepiride. The median exposure was 729 days in the linagliptin group (range 1 to 776 days), and 729 days in the glimepiride group (range 3 to 804 days). Overall, 24.4% of patients in the linagliptin group and 22.1% of patients in the glimepiride group prematurely discontinued trial medication. The most frequent reasons for discontinuation were the occurrence of AEs (7.9% linagliptin; 11.6% glimepiride) and lack of efficacy (5.8% linagliptin; 1.9% glimepiride).

Adverse events
Overall, fewer patients in the linagliptin group were reported with AEs than in the glimepiride group (85.4% linagliptin; 91.1 % glimepiride). The most frequently reported AEs in both treatment groups were in the system organ classes (SOCs) infections and infestations (48.7% linagliptin; 50.7% glimepiride), musculoskeletal and connective tissue disorders (33.1% linagliptin; 31.5% glimepiride), gastrointestinal disorders (27.7% linagliptin; 28.4% glimepiride), nervous system disorders (19.2% linagliptin; 23.4% glimepiride), and metabolism and nutrition disorders (18.6% linagliptin; 44.1% glimepiride). On a preferred term (PT) level, the only differences of note between the treatment groups was in the incidence of hypoglycaemia, which occurred at a notably lower frequency in the linagliptin group compared to the glimepiride group (7.1% linagliptin; 34.8% glimepiride).

The majority of all AEs were mild or moderate in intensity; a total of 13.8% of patients in the linagliptin group and 13.2% of patients in the glimepiride group were reported with AEs of severe intensity. AEs assessed as being drug-related by the investigator were observed in a lower number of patients in the linagliptin group compared to the glimepiride group (15.2% linagliptin; 38.7% glimepiride); a lower incidence of drug-related hypoglycaemia in the linagliptin group was the primary reason for this difference (5.8% linagliptin; 29.8% glimepiride). A lower percentage of patients in the linagliptin group than in the glimepiride group were reported with AEs leading to study discontinuation (7.7% linagliptin; 11.0% glimepiride); again, the most common AE reported as leading to discontinuation was hypoglycaemia, which occurred at a lower frequency in the linagliptin group than in the glimepiride group (0.4% linagliptin; 2.3% glimepiride).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004585-40	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 12 of 14	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1218.20 / U11-1485-03	**Dates of trial:** 12 FEB 2008 to 21 DEC 2010	**Date of revision:** 06 JUN 2012

Safety results (continued):

Overall, 7.5% of patients in the linagliptin group and 36.1% of patients in the glimepiride group had investigator-reported hypoglycaemic events. The difference between the groups in terms of the proportion of patients with hypoglycaemic events on treatment was significant ($p<0.0001$ from the Cochran-Mantel-Haenszel test) in favour of linagliptin. Because the superiority of linagliptin was not shown for the primary endpoint, the superiority of linagliptin over glimepiride in terms of hypoglycaemic events could not be tested in a hierarchal fashion, and thus is considered an 'exploratory' endpoint. The majority of hypoglycaemic events in both groups were either asymptomatic (37.9% linagliptin; 33.6% glimepiride) or symptomatic but mild (i.e., plasma glucose ≥54 mg/dL and ≤70 mg/dL; 34.5%linagliptin; 63.2% glimepiride). Only 1 patient in the linagliptin group compared with 12 patients in the glimepiride group experienced a severe episode (i.e., that required assistance). The odds ratio of having a hypoglycaemic episode for patients treated with linagliptin compared with patients receiving glimepiride was 0.136 (95% CI: 0.100, 0.186; $p<0.0001$); patients treated with glimepiride had 7.35-fold the odds of having a hypoglycaemic event as compared with patients receiving linagliptin.

All cardiac and cerebrovascular events were reviewed by an adjudication committee composed of external and independent specialists; 6.4% of patients in the linagliptin group and 9.5% of patients in the glimepiride group were identified with cardiac and cerebrovascular events that qualified for adjudication. A total of 1.5% of patients taking linagliptin and 3.4% of patients taking glimepiride had cardiovascular (CV) death, myocardial infarction (MI), stroke, or unstable angina that was confirmed by the adjudication committee. In an analysis that was carried out to support a planned CV meta-analysis on the project level, non-fatal stroke (3 patients linagliptin, 11 patients glimepiride; $p=0.0315$) and combined CV events (including overall CV death, MI, stroke, or hospitalisation due to unstable angina; 12 patients linagliptin; 26 patients glimepiride; $p=0.0213$) occurred at a significantly lower frequency for linagliptin patients than for glimepiride patients. Further, a post-hoc analysis showed that patients in the linagliptin group had a reduced risk of experiencing these events as compared with patients in the glimepiride group (relative risk of non-fatal stroke: 0.27, 95% CI: 0.08, 0.97; relative risk of combined events 0.46, 95% CI: 0.23, 0.91), even though both treatment groups were well-balanced in terms of important CV risk factors at baseline.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004585-40	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 13 of 14	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1218.20 / U11-1485-03	**Dates of trial:** 12 FEB 2008 to 21 DEC 2010	**Date of revision:** 06 JUN 2012

Safety results (continued):

Serious adverse events (SAEs) were reported for a slightly lower percentage of patients in the linagliptin group (17.4% linagliptin; 20.9% glimepiride). The most commonly reported SOCs for SAEs included cardiac disorders (3.2% linagliptin; 4.3% glimepiride), infections and infestations (3.0% linagliptin; 3.2% glimepiride), benign, malignant, and unspecified neoplasms (including cysts and polyps) (2.3% linagliptin; 2.5% glimepiride), and nervous system disorders (1.4% linagliptin; 3.4% glimepiride).

There were 10 deaths in this study: 4 deaths in the linagliptin group (including 1 patient each cardio-respiratory arrest, sudden cardiac death, bronchial carcinoma, and aortic aneurysm), 4 deaths in the glimepiride group (including 1 patient each with abdominal infection, sudden cardiac death, and MI, and 1 patient with both metastatic bronchial carcinoma and acute renal failure) and 2 deaths in the post-treatment period (including 1 patient previously in the linagliptin treatment group with haemorrhage and 1 patient previously in the glimepiride treatment group with accidental death); none of the deaths were considered related to the study drugs.

Overall, 4.5% of patients in the linagliptin group and 10.1% of patients in the glimepiride group were reported with 'other significant AEs' (according to ICH E3). In terms of 'other significant AEs', the most commonly reported SOC was metabolism and nutrition disorders (1.8% linagliptin; 5.8% glimepiride), and the most commonly reported PT was hypoglycaemia (0.6% linagliptin; 5.7% glimepiride).

Hypersensitivity reactions, renal AEs, and hepatic AEs were pre-defined as significant AEs and were analysed based on standardised MedDRA queries (SMQs); cutaneous skin lesions and pancreatitis were analysed post-hoc by SMQs based on regulatory recommendations. The frequency of hypersensitivity reactions (8 patients linagliptin; 6 patients glimepiride), renal AEs (4 patients linagliptin; 6 patients glimepiride), hepatic AEs (11 patients linagliptin; 10 patients glimepiride), was low and similar between the 2 treatment groups. Pancreatitis was reported for 1 patient in the linagliptin group and no patients in the glimepiride group, while no cutaneous skin lesions were reported for patients in either group during this study.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004585-40	
Name of active ingredient: Linagliptin, BI 1356		**Page:** 14 of 14	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 APR 2011	**Trial No. / U No.:** 1218.20 / U11-1485-03	**Dates of trial:** 12 FEB 2008 to 21 DEC 2010	**Date of revision:** 06 JUN 2012

Safety results (continued):	**Laboratory parameters and vital signs** Laboratory analyses (haematology, clinical chemistry, and urinalysis) did not reveal any clinically relevant findings. There were no cases of Hy's law in this study and no notable difference between treatments was observed for changes in renal function. No clinically significant differences between the treatment groups were observed in vital signs measured from baseline to the end of treatment.
Conclusions:	Linagliptin was shown to be non-inferior to glimepiride in its ability to reduce adjusted mean HbA_{1c} levels over 104 weeks. While treatment with linagliptin was associated with a decrease in adjusted mean body weight, patients treated with glimepiride were observed to gain weight on average, leading to a significant difference between groups. Although the safety profiles of linagliptin and glimepiride were generally comparable, linagliptin treatment was associated with a significantly lower risk of hypoglycaemia than treatment with glimepiride. Further, the overall risk of combined cardiovascular events was seen to be significantly lower for patients treated with linagliptin than with glimepiride. Overall, treatment with linagliptin was efficacious, well tolerated, and safe over the course of this 104-week study.

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**
Hb_{A1c} <7.0% at week 104 for patients with baseline HbA_{1c} ≥7.0%	Table 15.2.2.2.2: 1
Hb_{A1c} <6.5% at week 104 for patients with baseline HbA_{1c} ≥6.5%	Table 15.2.2.2.3: 1
Hb_{A1c} lowering by ≥0.5% at week 104	Table 15.2.2.2.4: 1
Hb_{A1c} (%) change from baseline over time	Table 15.2.1.2.2: 1

Table 15.2.2.2.2: 1 Logistic regression of HbA1c < 7.0% at week 104 for patients with baseline HbA1c >=7.0% - FAS(NCF)

Factor	Odds ratio	95% CI LL	95% CI UL	Wald Chi-Sq	df	p-value
Treatment Group						
Linagliptin : Glimepiride	0.654	0.494	0.866	8.803	1	0.0030
Baseline HbA1c						
Odds ratio per 1% increase	0.365	0.288	0.463	68.838	1	<.0001
Number of prior antidiabetics drugs						
Two : One	0.523	0.374	0.731	14.368	1	0.0002

Model includes Baseline HBA1c, number of prior OADs, and treatment group

Table 15.2.2.2.3: 1 Logistic regression of HbA1c < 6.5% at week 104 for patients with baseline HbA1c >= 6.5% - FAS(NCF)

Factor	Odds ratio	95% CI LL	95% CI UL	Wald Chi-Sq	df	p-value
Treatment Group						
Linagliptin : Glimepiride	0.689	0.498	0.952	5.095	1	0.0240
Baseline HbA1c						
Odds ratio per 1% increase	0.268	0.200	0.360	76.611	1	<.0001
Number of prior antidiabetics drugs						
Two : One	0.475	0.304	0.741	10.734	1	0.0011

Model includes Baseline HBA1c, number of prior OADs, and treatment group

Table 15.2.2.2.4: 1 Logistic regression of HbA1c lowering by 0.5% at week 104 - FAS(NCF)

Factor	Odds ratio	95% CI LL	95% CI UL	Wald Chi-Sq	df	p-value
Treatment Group						
Linagliptin : Glimepiride	0.700	0.560	0.875	9.778	1	0.0018
Baseline HbA1c						
Odds ratio per 1% increase	1.343	1.180	1.528	19.994	1	<.0001
Number of prior antidiabetics drugs						
Two : One	0.563	0.433	0.733	18.363	1	<.0001

Model includes Baseline HBA1c, number of prior OADs, and treatment group

Table 15.2.1.2.2: 1 Adjusted HbA1c (%) mean change from baseline over time - FAS (LOCF)

	Linagliptin			Glimepiride			Difference Linagliptin - Glimepiride				
	N	Adj* mean	SE	N	Adj* mean	SE	Adj* mean	SE	95% CI LL	95% CI UL	p-value
Baseline (unadjusted means)	764	7.69	0.03	755	7.69	0.03					
Change from baseline at Week 4	764	-0.23	0.02	755	-0.30	0.02	0.07	0.02	0.03	0.11	0.0012
Change from baseline at Week 8	764	-0.32	0.02	755	-0.53	0.02	0.21	0.03	0.16	0.27	<.0001
Change from baseline at Week 12	764	-0.38	0.02	755	-0.70	0.02	0.31	0.03	0.25	0.38	<.0001
Change from baseline at Week 16	764	-0.40	0.02	755	-0.74	0.02	0.33	0.03	0.27	0.40	<.0001
Change from baseline at Week 28	764	-0.37	0.03	755	-0.69	0.03	0.32	0.04	0.24	0.39	<.0001
Change from baseline at Week 40	764	-0.38	0.03	755	-0.64	0.03	0.26	0.04	0.19	0.34	<.0001
Change from baseline at Week 52	764	-0.36	0.03	755	-0.57	0.03	0.22	0.04	0.14	0.30	<.0001
Change from baseline at Week 65	764	-0.26	0.03	755	-0.47	0.03	0.21	0.04	0.13	0.29	<.0001
Change from baseline at Week 78	764	-0.16	0.03	755	-0.37	0.03	0.21	0.04	0.12	0.30	<.0001
Change from baseline at Week 91	764	-0.16	0.03	755	-0.37	0.03	0.22	0.04	0.13	0.30	<.0001
Change from baseline at Week 104	764	-0.16	0.03	755	-0.36	0.03	0.20	0.05	0.11	0.29	<.0001

* Model includes treatment, baseline HbA1c and number of prior OADs