Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim
Name of finished product: Tradjenta™, Trajenta™, Trayenta™		**EudraCT No.:** 2011-004158-24	**Synopsis No.:**
Name of active ingredient: linagliptin, BI 1356		**Page:** 1 of 7	
Module:		**Volume:**	
Report date: 06 AUG 2013	**Trial No. / U No.:** 1218.83 / U13-3654-01	**Date of trial:** 24 Jan 2012 –15 Apr 2013	**Date of revision:** Not Applicable

Title of trial:	A 24-week, randomized, double-blind, active-controlled, parallel group trial to assess the superiority of oral linagliptin and metformin compared to linagliptin monotherapy in newly diagnosed, treatment-naïve, uncontrolled Type 2 Diabetes Mellitus patients
Coordinating Investigator:	Stuart Ross, M.B., CH.B., FRACP, FRCP(C) LMC Endocrinology Centres (Calgary) 5940 MacLeod Trail SW Suite 102 Calgary, AB Canada T2H 2G4
Trial sites:	Multi-center trial, refer to Appendix 16.1.4
Publication (reference):	Data from this trial have not been published
Clinical phase:	IV
Objectives:	To investigate the efficacy, safety and tolerability of linagliptin 5 mg once daily compared to an initial combination of linagliptin 5 mg and metformin IR (1500 to 2000 mg per day, total daily dose) given orally for 24 weeks in newly diagnosed, treatment-naïve patients with uncontrolled type 2 diabetes mellitus (T2DM) [i.e., glycated (or glycosylated) haemoglobin (HbA_{1c}) between 8.5% and 12.0%]; to show superiority of the initial combination of linagliptin 5 mg and metformin IR (1500 to 2000 mg total daily dose) over linagliptin 5 mg.
Methodology:	Randomized, double-blind, active-controlled, parallel design comparison of 2 treatment groups over 24 weeks.
No. of subjects:	
planned:	entered: 270
actual:	enrolled: 316 Treatment linagliptin 5 mg: entered: 157; treated: 157; analyzed (for primary endpoint): 113 Treatment linagliptin 5 mg and metformin: entered: 159; treated: 159; analyzed (for primary endpoint): 132

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Tradjenta™, Trajenta™, Trayenta™		**EudraCT No.:** 2011-004158-24	
Name of active ingredient: Tradjenta™, Trajenta™, Trayenta™, linagliptin, BI 1356		**Page:** 2 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 06 AUG 2013	**Trial No. / U No.:** 1218.83 / U13-3654-01	**Date of trial:** 24 Jan 2012 –15 Apr 2013	**Date of revision:** Not Applicable

Diagnosis and main criteria for inclusion:	Newly diagnosed (diagnosis <12 month prior to screening) uncontrolled T2DM patients who were 18 years of age or older with HbA_{1c} levels of 8.5% to 12.0%; had a Body Mass Index (BMI) of less than or equal to 45 kg/m^2; and had not taken any oral antidiabetic therapy, injectable glucagon−like peptide−1 (GLP−1) receptor agonist (e.g., liraglutide) or insulin for 12 weeks prior to randomisation.
Test product:	linagliptin tablet
dose:	5 mg
mode of admin.:	by mouth (p.o.), once daily each morning
batch no.:	4000427, 4000428
Reference therapy:	linagliptin tablet and metformin immediate release (IR) tablet
dose:	linagliptin: 5 mg metformin: 1000 mg, 1500 mg or 2000 mg
mode of admin.:	linagliptin: p.o., once daily each morning metformin: 1000 mg (one 500 mg tablet twice daily) to be given for 7 days with up titration to 1500 mg (one 500 mg tablet each morning and two 500 mg tablets each evening) for 7 days, then a total daily dose of 1500 mg or 2000 mg (two 500 mg tablets each morning and two 500 mg tablets each evening) based on tolerability from Day 14 to Day 168
batch no.:	11504, 251354, X2042
Duration of treatment:	A 1 to 2 week Screen period with no study medication, leading into a 1 to 2 week placebo Run-in period, followed by a double-blind treatment period for 24 weeks, and a 1 week post-treatment period with no study medication.
Criteria for evaluation:	

Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim
Name of finished product: Tradjenta™, Trajenta™, Trayenta™		**EudraCT No.:** 2011-004158-24	
Name of active ingredient: Tradjenta™, Trajenta™, Trayenta™, linagliptin, BI 1356		**Page:** 3 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 06 AUG 2013	**Trial No. / U No.:** 1218.83 / U13-3654-01	**Date of trial:** 24 Jan 2012 –15 Apr 2013	**Date of revision:** Not Applicable

Efficacy / clinical pharmacology:	The primary endpoint in this trial was the change from baseline in HbA_{1c} after 24 weeks of treatment. Key secondary endpoints were: • Change from baseline in fasting plasma glucose (FPG) after 24 weeks of treatment • Change from baseline in HbA_{1c} by visit over time Secondary endpoints were: • Occurrence of relative efficacy response I (HbA_{1c} lowering by at least 0.5% after 24 weeks of treatment) • Occurrence of relative efficacy response II (HbA_{1c} lowering by at least 1.0% after 24 weeks of treatment) • Occurrence of treat to target efficacy response, that was an HbA_{1c} of < 7.0% after 24 weeks of treatment • Change from baseline in FPG by visit over time • Change in body weight from baseline to Week 24 • Homeostasis Model Assessment (HOMA) indices for insulin resistance and insulin secretion (at baseline and Week 24) • Use of rescue medication Biomarkers investigated included fasting C-peptide, proinsulin, insulin, and proinsulin/insulin ratio.
Safety:	Adverse events (AEs) including relevant new or worsening findings [including those found from physical examinations and/or 12 lead electrocardiograms (ECGs)], hypoglycaemic events, protocol-specified adverse events of special interest, use of rescue therapy, changes from baseline in routine laboratory tests, blood pressure, and pulse.
Statistical methods:	The primary analysis, including testing of superiority of linagliptin and metformin versus linagliptin, was performed with an analysis of covariance (ANCOVA) model that compared the HbA_{1c} change from baseline after 24 weeks of treatment. The statistical model included treatment as a fixed effect and baseline HbA_{1c} as a linear covariate. Baseline HbA_{1c} was defined as the last observation prior to administration of any randomized study medication. If rescue-medication was used (allowed by the protocol) or any other antidiabetic medication, all subsequent measurements of the endpoints (HbA_{1c}, FPG)

Statistical methods (cont): were set to missing and those values were then imputed by the Last Observation Carried Forward (LOCF)-technique.

The analysis population for the primary analysis was the Per Protocol Completers Cohort (PPCC) and a sensitivity analysis was conducted on the Full Analysis Set (FAS).

Key secondary efficacy endpoints were analysed by a mixed model for repeated measurements (MMRM) (change from baseline in HbA_{1c} by visit over time) and an ANCOVA model (FPG change from baseline after 24 weeks of treatment), based on the PPCC.

Descriptive statistical methods were completed for the remaining secondary endpoints, the other endpoints and the safety parameters.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

A total of 556 patients were enrolled and 316 patients were entered (randomized) into the trial. Overall, 316 randomised patients (159 linagliptin and metformin; 157 linagliptin) were included in the pre-specified efficacy and safety analyses. Of the 316 treated patients, 275 patients (87.0%) did not prematurely discontinue trial medication while 41 patients (13.0%) prematurely discontinued trial medication (11.9% linagliptin and metformin; 14.0% linagliptin) most frequently due to 'other' reasons. Most patients were White (57.6%) or Asian (38.3%) and the mean age was 48.8 years.

For the FAS, both treatment groups were well balanced across baseline efficacy variables. The primary efficacy variable was HbA_{1c}, which was based on the FAS for this trial. Most patients (75.6%) had a baseline HbA_{1c} greater than or equal to 9% (mean = 9.83%): 9.79% in the linagliptin and metformin group and 9.88% in the linagliptin group. The mean baseline HbA_{1c} for the PPCC was 9.71%. Other baseline efficacy variables (mean values) included mean fasting plasma proinsulin (38.92 pmol/L), mean fasting plasma insulin (16.39 mU/L), plasma C−peptide (511.98 pmol/L), proinsulin/insulin ratio (0.44), HOMA index for insulin resistance (7.67 mU/L), and HOMA index for insulin secretion (54.20 mU/mmol).

Efficacy / clinical pharmacology result (cont):

The primary endpoint in this trial was the change from baseline in HbA_{1c} after 24 weeks of treatment. There were 132 patients in the linagliptin and metformin group and 113 patients in the linagliptin group included in the primary analysis. Linagliptin and metformin showed superiority compared to linagliptin with an adjusted mean treatment difference of −0.79% for change in HbA_{1c} [95% Confidence Interval (CI) −1.13%, −0.46%] from baseline to 24 weeks ($p<0.0001$). Linagliptin and metformin led to change from baseline in HbA_{1c} of −2.81% (adjusted mean) at Week 24. In addition, linagliptin monotherapy led to change from baseline in HbA_{1c} of −2.02% (adjusted mean) at Week 24.

For the FAS (LOCF), the adjusted mean change from baseline in HbA_{1c} after 24 weeks was −2.66% in the linagliptin and metformin compared to −1.68% in the linagliptin group, the difference between linagliptin and metformin versus linagliptin was −0.99% (95% CI −1.33, −0.64) and was statistically significant ($p < 0.0001$).

FPG after 24 weeks was analyzed based on PPCC (LOCF). The adjusted mean change from baseline in FPG after 24 weeks was −47.1 mg/dL in the linagliptin and metformin compared to −30.2 mg/dL in the linagliptin group, the difference between linagliptin and metformin versus linagliptin was −16.9 mg/dL (95% CI −28.0, −5.7) and was statistically significant ($p = 0.0032$).

HbA_{1c} change from baseline over time on the PPCC (OC) was analyzed using a MMRM. From baseline to Week 24, across all visits, the difference between the adjusted means of HbA_{1c} (linagliptin and metformin - linagliptin) was statistically significant ($p < 0.0001$). The difference between treatments for adjusted mean change from baseline in HbA_{1c} was maintained across visits, from −0.63% (95% CI −0.90,−0.36) at Week 6 to −0.79% (95% CI −1.13,−0.46) at Week 24.

Sensitivity analyses based on different analysis population sets confirmed the superiority of the combination of linagliptin and metformin over linagliptin.

Overall, 61.4% of the patients in the linagliptin and metformin group and 39.8% of the patients in the linagliptin group achieved $HbA_{1c} < 7.0\%$ at Week 24, based on the PPCC [non-completers considered failures (NCF)]. At Week 24, the odds for patients with a baseline HbA_{1c} of $\geq 7.0\%$ to achieve an HbA_{1c} reduction to < 7.0% were almost 2.5 times greater for patients treated with linagliptin and metformin compared to patients treated with linagliptin alone (odds ratio = 2.448; 95% CI 1.453, 4.123) ($p = 0.0008$).

Efficacy / clinical pharmacology result (cont):	After 24 weeks of treatment, patients in the linagliptin and metformin group experienced a decrease in adjusted mean body weight (−1.07 kg) compared with a minor body weight gain for patients in the linagliptin group (0.24 kg), for an adjusted mean difference from baseline in body weight of −1.31 kg (95% CI −2.18,−0.44, p = 0.0033) for the PPCC (OC).
Safety results:	The safety profile of linagliptin in this trial was similar to previous trial experience. No deaths occurred in this trial. The overall frequency of serious adverse events (SAEs) during the treatment period was very low (≤ 1.9% in each treatment group); 5 individual SAEs occurred without any trends noted. One patient in the linagliptin group experienced an SAE of benign thyroid neoplasm that was not related to trial medication and resolved with treatment. There were no pancreatitis or pancreatic cancer, thyroid cancer, renal, or cutaneous skin lesion AEs of Special Interest that occurred during the treatment period. Hepatic and hypersensitivity reactions AEs of Special Interest were similar between both treatment groups and occurred in ≤3.2% of patients in each treatment group. Other significant AEs occurred in less than 1.5% of patients in each treatment group without any trends noted. Overall, 56.0% of patients in the linagliptin and metformin group and 61.1% of patients in the linagliptin group experienced AEs. The incidence of AEs was higher in the linagliptin group for hyperglycemia (12.7% compared to 3.1% for linagliptin and metformin), which was expected because combination therapy is generally more effective than monotherapy, and dyslipidemia (14.0% compared to 8.8% for linagliptin and metformin). However, when reviewing all reported preferred terms associated with lipid abnormalities (i.e., dyslipidaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia), there was no observed difference between treatment groups. Additionally, the lipid laboratory values measured throughout the trial did not show any particular difference between treatment groups. Drug related AEs, as assessed by the investigator, occurred in 8.8% of the patients for the linagliptin and metformin group and 5.7% of the patients for the linagliptin group and were generally comparable between treatment groups. There were very few patients who experienced AEs that led to premature discontinuation (1.3% in each treatment group) and no trends were noted. The majority of patients (94.8 % linagliptin and metformin; 87.3 % linagliptin) did not use rescue medication and there were no clinically relevant trends in patients reporting AEs with respect to the use of rescue medication.

Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim
Name of finished product: Tradjenta™, Trajenta™, Trayenta™		**EudraCT No.:** 2011-004158-24	
Name of active ingredient: Tradjenta™, Trajenta™, Trayenta™, linagliptin, BI 1356		**Page:** 7 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 06 AUG 2013	**Trial No. / U No.:** 1218.83 / U13-3654-01	**Date of trial:** 24 Jan 2012 –15 Apr 2013	**Date of revision:** Not Applicable

Safety results (cont):	The proportion of patients experiencing investigator defined hypoglycemic adverse events was comparable between treatment groups, with less than 3.2% in each treatment group. No patients had severe episodes of hypoglycemic events requiring assistance. Laboratory analyses, blood pressures, and pulses did not reveal any clinically meaningful differences. Mean changes in blood pressures and pulse were small with no trends noted between treatment groups.
Conclusions:	Linagliptin and metformin showed superiority compared to linagliptin with an adjusted mean treatment difference of −0.79% for change in HbA_{1c} (95% CI −1.13%, −0.46%) from baseline to 24 weeks ($p<0.0001$) for the PPCC (OC). Linagliptin and metformin led to change from baseline in HbA_{1c} of −2.81% (adjusted mean) at Week 24. In addition, linagliptin monotherapy led to change from baseline in HbA_{1c} of −2.02% (adjusted mean) at Week 24. In both treatment groups, HbA_{1c} continued to decrease up to 18 weeks and appeared to plateau between 18 and 24 weeks. These results were confirmed by sensitivity analyses on the FAS (LOCF). Overall, 61.4% of the patients in the linagliptin and metformin group and 39.8% of the patients in the linagliptin group achieved $HbA_{1c} < 7.0\%$ at Week 24 based on the PPCC (NCF). The linagliptin and metformin and linagliptin groups demonstrated consistent patterns with known safety profiles, including low risk for hypoglycaemia. After 24 weeks of treatment, patients in the linagliptin and metformin group experienced a decrease in adjusted mean body weight (−1.07 kg) compared with a minor body weight gain for patients in the linagliptin group (0.24 kg).