Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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..

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-001640-40	
Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 1 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

Title of trial:	A Phase III randomised, double-blind, placebo-controlled parallel group study to compare the efficacy and safety of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg, or of linagliptin 2.5 mg + metformin 1000 mg, with the individual components of metformin (500 mg or 1000 mg, twice daily) and linagliptin (5 mg, once daily) over 24 weeks in drug naïve or previously treated (4 weeks washout and 2 weeks placebo run-in) type 2 diabetic patients with insufficient glycaemic control
Coordinating Investigator:	[redacted]
Trial sites:	Multinational, multicentre trial: 133 sites in 14 countries (Canada, Croatia, Estonia, France, Germany, India, Lithuania, Mexico, Romania, Russia, Sweden, The Netherlands, Tunisia, and Ukraine)
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	Randomised part Efficacy and safety of linagliptin + metformin versus linagliptin or metformin alone for 24 weeks Open-label arm To estimate the efficacy and safety of linagliptin + metformin for 24 weeks
Methodology:	Randomised, placebo-controlled, double-blind, parallel group comparison of 6 groups over 24 weeks with an additional open-label arm. Before randomisation, patients pre-treated with one oral antidiabetic agent underwent a washout period of 6 weeks that included a placebo run-in period during the last 2 weeks of the washout period; patients not pre-treated with an oral antidiabetic agent performed a 2-week placebo run-in period. Patients with a baseline glycosylated haemoglobin (HbA_{1c}) of ≥11% were enrolled into the open-label arm. All patients who received metformin 1000 mg had to undergo a 2-week forced titration phase for metformin. Patients who regularly completed the randomised period of this study were offered to participate in an extension trial (BI trial no. 1218.52).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-001640-40	
Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 2 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

No. of patients:	
planned:	entered: 791
actual:	enrolled: 1770
	Placebo: entered: 72 treated: 72 analysed (for primary endpoint): 65
	Linagliptin 5 mg: entered: 142 treated: 142 analysed (for primary endpoint): 135
	Metformin 500 mg entered: 144 treated: 144 analysed (for primary endpoint): 141
	Metformin 1000 mg entered: 147 treated: 147 analysed (for primary endpoint): 138
	Linagliptin 2.5 mg + Metformin 500 mg entered: 143 treated: 143 analysed (for primary endpoint): 137
	Linagliptin 2.5 mg + Metformin 1000 mg entered: 143 treated: 143 analysed (for primary endpoint): 140
	Linagliptin 2.5 mg + Metformin 1000 mg (open-label) entered: 66 treated: 66 analysed (for primary endpoint): 66
Diagnosis and main criteria for inclusion:	Patients with type 2 diabetes mellitus and insufficient glycaemic control either drug naïve or despite therapy with one oral antidiabetic agent (patients undergoing washout of previous antidiabetic medication: HbA_{1c} ≥7.0 to ≤10.5%; patients not undergoing washout HbA_{1c} ≥7.5 to <11.0%); age ≥18 and ≤80 years; BMI ≤40 kg/m^2 Patients with very poor glycaemic control (HbA_{1c} ≥11%) who were not eligible for randomisation could participate in the open-label arm of the trial.
Test product:	Linagliptin + metformin administered as a free combination
dose:	Linagliptin 2.5 mg + Metformin 500 mg twice daily or Linagliptin 2.5 mg + Metformin 1000 mg twice daily

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Name of finished product: Not applicable		**EudraCT No.:** 2008-001640-40	
Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 3 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

mode of admin.:	Tablets, oral
batch no.:	See Appendix 16.1.6
Reference therapy:	Linagliptin
dose:	5 mg, once daily
mode of admin.:	Tablet, oral
batch no.:	See Appendix 16.1.6
Reference therapy:	Metformin
dose:	500 mg or 1000 mg, twice daily
mode of admin.:	Tablet, oral
batch no.:	See Appendix 16.1.6
Reference therapy:	Placebo
dose:	n.a.
mode of admin.:	Tablet, oral
batch no.:	See Appendix 16.1.6
Test product (open-label):	Linagliptin + metformin administered as a free combination
dose:	Linagliptin 2.5 mg + Metformin 1000 mg twice daily
mode of admin.:	Tablets, oral
batch no.:	See Appendix 16.1.6
Duration of treatment:	24 weeks treatment followed by 1 week follow-up after study drug termination for both the double-blind arm of the study and the additional open-label active treatment arm of the study

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-001640-40	
Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 4 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

Criteria for evaluation:

Efficacy / clinical pharmacology:

Randomised part
The primary endpoint was the HbA_{1c} change from baseline after 24 weeks of treatment. Important secondary endpoints were the change from baseline in fasting plasma glucose (FPG) after 24 weeks of treatment, occurrence of treat-to-target response (i.e. HbA_{1c} on treatment <7.0% or <6.5%), occurrence of relative efficacy response (i.e. HbA_{1c} lowering by 0.5%), change from baseline in 2h post-prandial glucose (2h PPG), and use of rescue medication.

Open-label arm
The primary endpoint was the HbA_{1c} change from baseline after 24 weeks of treatment. Secondary endpoints were HbA_{1c} reduction over time and FPG reduction over time.

Safety:

Randomised part and open-label arm
Incidence and intensity of adverse events (AEs), withdrawals due to AEs, physical examination, 12-lead ECG, vital signs, clinical laboratory parameters

Statistical methods:

Randomised part
Primary endpoint: Testing of superiority hypothesis of the combination therapies over the monotherapies in a hierarchical manner with an analysis of covariance (ANCOVA) with treatment and prior use of antidiabetic therapy as factors and baseline HbA_{1c} as covariate
Secondary and other endpoints: ANCOVA (exploratory), descriptive statistics, for use of rescue medication logistic regression and Kaplan-Meier analysis
Safety endpoints: descriptive statistics, for hypoglycaemic events logistic regression and Kaplan-Meier analysis

Open-label arm
Primary and secondary endpoint: descriptive statistics
Safety endpoints: descriptive statistics, for hypoglycaemic events logistic regression and Kaplan-Meier analysis

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Randomised part
A total of 1770 patients were enrolled in this study, out of these 791 patients

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Name of finished product: Not applicable		**EudraCT No.:** 2008-001640-40	
Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 5 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

were randomised in a 1:2:2:2:2:2 ratio to either placebo (72 patients), linagliptin 5 mg (142 patients), metformin 500 mg (144 patients), metformin 1000 mg (147 patients), linagliptin 2.5 mg + metformin 500 mg (143 patients), or linagliptin 2.5 mg + metformin 1000 mg (143 patients). The main reason for non-randomisation was in-/exclusion criteria not met (42.8% of the enrolled patients). All of the randomised patients were treated. The most frequent reasons for discontinuation were due to adverse events (3.3%), refusal to continue trial medication (2.9%), and lack of efficacy (2.3%).

Overall, the demographic profile was balanced between the treatment groups. About half of the population was male (53.9%). The patient population consisted mainly of White (66.8%) and Asian (32.5%) patients; 1 patient (0.1%) was [redacted], and 5 patients (0.6%) were Black. The lina 2.5 + met 500 group comprised more White (72.0%) and less Asian (25.9%) patients compared to the other treatment groups. In all treatment groups, 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; 51.7%) or mild renal impairment (eGFR 60 to <90 mL/min; 42.2%). The total percentage of patients with moderate renal impairment (eGFR 30 to <60 mL/min) was 1.5%. There were no patients with severe renal impairment (eGFR <30 mL/min). The treatment groups differed with regard to renal impairment; the percentages of patients with no renal impairment ranged from 47.2% to 56.3%, the percentages of patients with mild renal impairment ranged from 36.1% to 49.3%.

Primary endpoint
65 patients of the placebo group, 135 patients of the lina 5 group, 141 patients of the met 500 group, 138 patients of the met 1000 group, 137 patients of the lina 2.5 + met 500 group, and 140 patients of the lina 2.5 + met 1000 group were included in the full analysis set (FAS). The FAS was a subset of the treated set including all patients who had a baseline and at least one on-treatment HbA_{1c} measurement available. All efficacy analyses were based on the FAS; the MTT analyses were based on the FAS MTT.

Superiority of both free combination therapies, consisting of the twice daily administration of linagliptin 2.5 mg and metformin (500 mg or 1000 mg), was shown over the individual metformin components (500 mg and 1000 mg, both

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-001640-40	
Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 6 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

b.i.d.) and over linagliptin 5 mg (q.d.) for the change in HbA_{1c} from baseline at Week 24. The mean treatment difference in HbA_{1c} from baseline to Week 24 was -0.51% (95% CI -0.73, -0.30; p<0.0001) for the free combination of lina 2.5 + met 1000 compared to the individual component met 1000, -1.14% (95% CI -1.36, -0.92; p<0.0001) for the free combination of lina 2.5 + met 1000 compared to lina 5, -0.58% (95% CI -0.79, -0.36; p<0.0001) for the free combination of lina 2.5 + met 500 compared to the individual component met 500, and -0.77% (95% CI -0.99, -0.55; p<0.0001) for the free combination of lina 2.5 + met 500 compared to lina 5. Sensitivity analyses confirmed the results observed for the primary endpoint. From baseline to Week 24, across visits, the p-values for the differences in the adjusted means of HbA_{1c} of all treatment comparisons were <0.0001. Subgroup analyses for the unadjusted mean change in HbA_{1c} from baseline showed a consistent treatment effect across the different subgroups. No relevant treatment-subgroup interaction was shown, except for gender (p = 0.0621).

Secondary endpoints
The mean treatment difference in FPG from baseline to Week 24 was -17.2 mg/dL (95% CI -27.1, -7.3; p = 0.0006) for the free combination of linagliptin 2.5 + met 1000 compared to the individual component met 1000, -40.8 mg/dL (95% CI -50.6, -31.0; p<0.0001) for the free combination of linagliptin 2.5 + met 1000 compared to lina 5, -17.4 mg/dL (95% CI -27.2, -7.6; p = 0.0005) for the free combination of lina 2.5 + met 500 compared to the individual component met 500, and -24.6 mg/dL (95% CI -34.4, -14.8; p<0.0001) for the free combination of lina 2.5 + met 500 compared to lina 5. Sensitivity analyses confirmed the observed results. From baseline to Week 24, across visits, the p-values for the differences in the adjusted means of FPG of all treatment comparisons were <0.05.

Concerning the treat-to-target efficacy response, among patients with a baseline $HbA_{1c} \geq 7.0\%$, 10.8% of patients of the placebo group, 10.4% of the lina 5 group, 18.6% of the met 500 group, 30.7% of the met 1000 group, 30.1% of the lina 2.5 + met 500 group, and 53.6% of the lina 2.5 + met 1000 group achieved a response of $HbA_{1c} < 7.0\%$. Among patients with a baseline $HbA_{1c} \geq 6.5\%$, 3.1% of patients of the placebo group, 3.7% of the lina 5 group, 5.0% of the met 500 group, 12.3% of the met 1000 group, 13.1% of the lina 2.5 + met 500 group, and

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Name of finished product: Not applicable		**EudraCT No.:** 2008-001640-40	
Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 7 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

27.1% of the lina 2.5 + met 1000 group achieved a response of HbA_{1c} <6.5%. Overall, the percentages of patients with a reduction of at least 0.5% in HbA_{1c} were higher in the active treatment groups compared to placebo. A reduction of at least 0.5% in HbA_{1c} was seen at a higher frequency among patients with higher baseline HbA_{1c} for most of the treatment groups except for the met 500 and lina 2.5 + met 1000 groups. In both efficacy response categories (i.e. HbA_{1c} on treatment <7.0% or <6.5% after 24 weeks of treatment) as well as in the relative efficacy response (i.e. HbA_{1c} lowering by at least 0.5% after 24 weeks of treatment) the odds of achieving an HbA_{1c} reduction were higher for patients treated with free combination therapy (lina 2.5 + met 500 or lina 2.5 + met 1000) compared to monotherapy (metformin or linagliptin), with the odds ratio being highest for patients treated with lina 2.5 + met 1000 compared to lina 5 and comparable odds ratios for the remaining treatments.

Difference in the adjusted mean changes from baseline in 2h PPG at Week 24 with p-values <0.05 were observed for lina 2.5 + met 1000 compared to lina 5 with -73.9 mg/dL (95% CI -119.3, -28.6; p = 0.0018) and linagliptin 2.5 + met 500 compared to lina 5 with -50.8 mg/dL (95% CI -98.5, -3.1; p = 0.0373).

The proportion of patients requiring rescue therapy was higher in the placebo group compared to the active treatment groups and the onset of use of rescue therapy (relative day) was earlier in patients of the placebo group compared to patients receiving active treatment. The odds of requiring rescue medication were lower for patients treated with free combination therapy (lina 2.5 + met 500 or lina 2.5 + met 1000) compared to monotherapy (metformin or linagliptin).

Other endpoints
Differences in change in body weight were observed between the treatment groups, however no distinct pattern was observed and overall no meaningful change in body weight was noted in any of the treatment groups. No differences between the treatment groups were shown for waist circumference or any of the questionnaires (Euro Quality of Life - 5 Dimensions [EQ-5D], Health Care Resource Utilisation [HCRU], and Diabetes Treatment Satisfaction Questionnaire [DTSQ]).

Biomarker, pharmacokinetic, and pharmacodynamic results
Linagliptin trough levels at Week 24 were comparable between the treatment

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-001640-40	
Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 8 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

groups (7.31 mmol/L lina 5, 6.34 mmol/L lina 2.5 + met 500, and 7.23 mmol/L lina 2.5 + met 1000), indicating no meaningful interaction of linagliptin and metformin as well as equivalence of treatment with linagliptin 5 mg q.d. and 2.5 mg b.i.d.. At Week 24, the median dipeptidyl-peptidase 4 (DPP-4) inhibition was >80% in all patients who received linagliptin given either alone or in free combination with metformin. The p-values were >0.05 for the observed treatment differences for indices of β-cell function, insulin sensitivity, and glucagon-like peptide 1 (GLP-1). With regard to homeostasis model assessment - insulin resistance (HOMA-IR), a change from baseline to Week 24 was observed for treatment with metformin (given alone or in combination), as expected. The estimated insulin secretion rate (ISR) increased in all treatment groups from baseline to Week 24. Of the meal tolerance test (MTT) parameters, the p-value for the difference in total glucose area under the concentration curve (AUC) at Week 24 between lina 2.5 + met 1000 and lina 5 was <0.05).

Open-label arm

In total, 66 patients entered the open-label arm of the study and were treated with linagliptin 2.5 mg + metformin 1000 mg. The most frequent reasons for discontinuation were due to adverse events (6.1%), other reasons (4.5%), and lack of efficacy (3.0%).

The open-label study population comprised more female (60.6%) than male (39.4%) patients. The patient population consisted only of White (63.6%) and Asian (36.4%) patients. The majority of patients had either normal renal function (eGFR based on MDRD ≥90 mL/min; 62.1%) or mild renal impairment (eGFR 60 to <90 mL/min; 30.3%). The total percentage of patients with moderate renal impairment (eGFR 30 to <60 mL/min) was 3.0%. There were no patients with severe renal impairment (eGFR <30 mL/min).

Primary endpoint

66 patients were included in the open-label set (OLS). The OLS comprised those patients who entered the open-label treatment after run-in. All efficacy analyses of the open-label arm were based on the OLS.

The mean change in HbA_{1c} from baseline to Week 24 was -3.74% for patients who received open-label lina 2.5 + met 1000 (observed cases). Sensitivity analyses confirmed the results observed for the primary endpoint.

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Name of finished product: Not applicable		**EudraCT No.:** 2008-001640-40	
Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 9 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

	Secondary endpoints From baseline to Week 24, across visits, a decrease in both HbA_{1c} (maximum change from baseline -3.90% at Week 18) and FPG (maximum change from baseline -85.10 mg/dL at Week 6) over time was observed.
Safety results:	Randomised part *Exposure* The mean exposure was 144.0 days for patients treated with placebo, 158.4 days for patients treated with lina 5, 160.0 days for patients treated with metformin monotherapy, and 161.3 days for patients treated with free combination therapy. The median exposure was 169 days in the placebo group and 170 days each in the remaining treatment groups. A large majority of patients completed their planned exposure to the drug: 59.7% of patients in the placebo group, 71.8% in the lina 5 group, 75.6% in the metformin mono group, and 79.0% in the free combination group. The duration of exposure was 28.4 patient years in the placebo group, 61.6 years in the lina 5 group, 127.5 years in the metformin mono groups, and 126.3 years in the free combination groups. *Adverse events* Overall, the percentages of patients reported with AEs were comparable between treatment groups: 54.2% of patients in the placebo group, 56.3% in the lina 5 group, 52.1% in the met 500 group, 50.3% in the met 1000 group, 49.0% in the lina 2.5 + met 500 group, and 56.6% in the lina 2.5 + met 1000 group. The majority of the AEs were of mild or moderate intensity. Patients with AEs were most frequently (occurring with a frequency of at least 2% in any treatment group on preferred term [PT] level) reported in the system organ classes (SOCs) gastrointestinal disorders (ranging from 9.7% to 19.6%), infections and infestations (ranging from 16.3% to 23.1%), metabolism and nutrition disorders (ranging from 4.9% to 16.7%), and nervous system disorders (ranging from 3.4% to 13.9%). The percentage of patients with vascular disorders was comparable between the treatment groups, ranging from 2.8% to 5.6%. Further AEs which are of interest in the development of antidiabetic drugs or are seen in connection with DPP-4 inhibitors occurred with a frequency of less than 2% on PT level in the SOCs cardiac disorders (with single patient events noted), renal and urinary disorders, and skin and subcutaneous tissue disorders. There was no case of pancreatitis reported in any of the treatment groups.

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Name of finished product: Not applicable		**EudraCT No.:** 2008-001640-40	
Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 10 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

In the placebo group, 10 patients (13.9%) were reported with drug-related AEs (as assessed by the investigator), in the lina 5 group 15 patients (10.6%), in the met 500 group 14 patients (9.7%), in the met 1000 group 13 patients (8.8%), in the lina 2.5 + met 500 group 16 patients (11.2%), and in the lina 2.5 + met 1000 group 13 patients (9.1%). Within metabolism and nutrition disorders, hyperglycaemia was the most frequently reported PT in nearly all treatment groups (the incidence being highest in the met 500 group compared to the remaining treatment groups). There were no drug-related renal and urinary disorders, and vascular disorders. There were 2 cases of drug-related skin and subcutaneous tissue disorders: 1 patient in the placebo group with pruritus generalised, and 1 patient in the met 1000 group with seborrhoea.

In the placebo group, 5 patients (6.9%) were reported with AEs leading to discontinuation, in the lina 5 group 6 patients (4.2%), in the met 500 group 3 patients (2.1%), in the met 1000 group 6 patients (4.1%), in the lina 2.5 + met 500 group 5 patients (3.5%), and in the lina 2.5 + met 1000 group 3 patients (2.1%); 14 of the events were assessed as not related to the study medication. In addition, AEs leading to discontinuation were checked manually for any changes in vital signs (bradycardia, tachycardia, hypertension, and hypotension). No such events were reported in any of the treatment groups.

Investigator-defined hypoglycaemic events were reported by 1 patient (1.4%) in the placebo group, 2 patients (1.4%) in the met 500 group, 5 patients (3.4%) in the met 1000 group, and 5 patients in the lina 2.5 + met 500 group. There were no hypoglycaemic events as defined by the investigator in the lina 5 and lina 2.5 + met 1000 treatment groups. Only 1 event in the met 1000 group required assistance. No patient received rescue medication at the time of the event.

Out of the patients using rescue medication, 42.1% in the placebo group, 40.0% in the lina 5 group, 26.3% in the met 500 group, 50.0% in the met 1000 group, 30.0% in the lina 2.5 + met 500 group, and 66.7% in the lina 2.5 + met 1000 group were reported with adverse events. Overall, the observed pattern of adverse events did not change when rescue medication was used.

All reported treatment-emergent fatal events and events suspected of stroke or cardiac ischaemia and cardiac death were adjudicated in a blinded fashion by an external committee. Confirmed events were reported for 1 patient in the

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-001640-40	
Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 11 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

met 1000 group (sudden death), 2 patients in the lina 5 group (non-ST elevation myocardial infarction [NSTEMI] and unstable angina), and 1 patient in the lina 2.5 + met 1000 group (stable angina).

There was one fatal event during randomised treatment: patient [redacted] of the met 1000 group died due to MI; the event was assessed as not related to the study medication. Overall, the number of patients with serious AEs (SAEs) was low: 1 patient (1.4%) in the placebo group (bradycardia), 3 patients (2.1%) in the lina 5 group (1 patient with unstable angina, left ventricular failure, MI, and hypertension; 1 patient with breast cancer stage III, and 1 patient with myocardial ischaemia), 3 patients (2.1%) in the met 500 group (1 patient with thrombocytopenia, malaria, plasmodium falciparum infection, urinary tract infection, and haematuria; 1 patient with hyperglycaemia, and 1 patient with bile duct cancer), 6 patients (4.1%) in the met 1000 group (1 patient each with MI, haemorrhoids, erysipelas, femoral neck fracture, rotator cuff syndrome, and 1 patient with nephrolithiasis and renal colic), 2 patients (1.4%) in the lina 2.5 + met 500 group (1 patient with hyperparathyroidism primary and 1 patient with femur fracture), and 2 patients (1.4%) in the lina 2.5 + met 1000 group (1 patient with angina pectoris, cardiac failure congestive, and myocardial ischaemia; and 1 patient with Hodgkin's disease). All SAEs except one were considered as not being drug-related (hyperglycaemia in the met 500 group was assessed as related).

Hypersensitivity reactions, renal AEs, hepatic AEs, severe cutaneous adverse reactions, and acute pancreatitis were defined as significant AEs and analysed by narrow standardised MedDRA query (SMQ)s. Hypersensitivity reactions were reported by 1 patient (0.7%, periorbital oedema) in the lina 5 group; no hypersensitivity reactions were reported in the remaining treatment groups. Hepatic events were reported by 5 patients (3.5%) in the lina 5 group (2 patients with increased alanine transaminase (ALT), 1 patient with increased ALT and increased aspartate transaminase (AST), 1 patient with increased γ-glutamyl-transferase (GGT), and 1 patient with increased hepatic enzyme), 5 patients (3.5%) in the met 500 group (1 patient with increased ALT, 1 patient with increased ALT and increased AST, 1 patient with increased blood bilirubin, and 2 patients with increased GGT), 6 patients (4.1%) in the met 1000 group (2 patients with both increased ALT and increased AST, 3 patients with

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-001640-40	
Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 12 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

increased ALT, and 1 patient with perihepatic discomfort), 5 patients (3.5%) in the lina 2.5 + met 500 group (1 patient with hepatic steatosis, 1 patient with increased ALT and increased AST, 1 patient with increased ALT and increased GGT, and 2 patients with increased hepatic enzyme), and 2 patients (1.4%) in the lina 2.5 + met 1000 group (1 patient with increased ALT and increased AST, and 1 patient with increased ALT, increased AST, and increased GGT); no hepatic events were reported in the placebo group. There were no patients with renal events, severe cutaneous adverse reactions, and pancreatitis in any of the treatment groups. 'Other significant' AEs (based upon ICH E3) were reported by 5 patients (6.9%) in the placebo group (1 patient with increased glycosylated haemoglobin, 3 patients with hyperglycaemia, and 1 patient with renal colic), 4 patients (2.8%) in the lina 5 group (1 patient each with abdominal pain, increased GGT, hyperglycaemia, and headache), 2 patients (1.4%) in the met 500 group (hyperchlorhydria and hyperglycaemia), 3 patients (2.0%) in the met 1000 group (diarrhoea, diabetes mellitus, and headache), 5 patients (3.5%) in the lina 2.5 + met 500 group (1 patient with diarrhoea and nausea, and 1 patient each with diarrhoea, increased hepatic enzyme, muscle spasms, and headache), and 2 patients (1.4%) in the lina 2.5 + met 1000 group (diarrhoea and headache). All events led to treatment discontinuation.

Laboratory evaluation and vital signs
Laboratory analyses (haematology, clinical chemistry, and urinalysis) did not reveal any clinically relevant findings. Few patients were reported with possible clinically significant abnormalities (PCSAs). There were no patients who fulfilled the criteria for Hy's law in the randomised part of this study and no notable differences between treatments were observed for changes in renal function.

Overall, no clinically significant differences between the treatment groups were observed in blood pressure and pulse rate from baseline to end of treatment. The majority of patients had inconspicuous values at the end of treatment and only a small proportion of patients shifted from inconspicuous to conspicuous values at end of treatment (≤2.8% for systolic blood pressure [SBP], ≤1.4% for diastolic blood pressure [DBP], and ≤0.7% pulse rate), with no relevant differences between treatments. The percentages of patients with marked increases in blood pressure were comparable between the treatment groups (overall ≤4.9%). The

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-001640-40	
Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 13 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

analysis of marked outliers did also not reveal any differences between treatments, with single patient events being observed in the different treatment groups.

Open-label arm

Exposure

The mean exposure was 156.3 days, the median exposure was 170 days, and a large proportion of patients (69.7%) completed their planned exposure to the open-label study medication (>24 weeks). The duration of exposure was 28.2 patient years.

Adverse events

Of the patients in the open-label arm, 53.0% were reported with an AE. The majority of the AEs were of mild or moderate intensity. Patients with AEs were most frequently (occurring with a frequency of at least 2% on PT level) reported in the SOCs gastrointestinal disorders (19.7%), infections and infestations (16.7%), metabolism and nutrition disorders (15.2%), and nervous system disorders (13.6%). Vascular disorders were reported by 4.5% of patients. Further AEs which are of interest in the development of antidiabetic drugs or are seen in connection with DPP-4 inhibitors occurred with a frequency of less than 2% on PT level in the SOCs cardiac disorders, renal and urinary disorders, and skin and subcutaneous tissue disorders.

In total, 6 patients (9.1%) were reported with drug-related AEs (as assessed by the investigator), with diarrhoea (4.5%) and nausea (4.5%) being the most frequently reported preferred terms.

AEs leading to treatment discontinuation were reported by 4 patients (6.1%). One patient was reported with 5 events (bradycardia, exertional dyspnoea, diarrhoea, nausea, and peripheral oedema), the remaining 3 patients were reported with 1 event each (1 patient with nausea and 2 patients with hyperglycaemia). In addition, AEs leading to discontinuation were checked manually for any changes in vital signs (bradycardia, tachycardia, hypertension, and hypotension). There was 1 patient reported with bradycardia; the event was of mild intensity and assessed as drug-related.

Investigator-defined hypoglycaemic events were reported by 1 patient (1.5%); the episode was asymptomatic, the patient had 4 or more hypoglycaemic

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Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 14 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

episodes, and did not receive rescue medication at the time of the event. Of the patients using rescue medication, 31.3% were reported with an adverse event. Overall, the observed pattern of adverse events did not change when rescue medication was used. No patients were reported in the open-label arm with cardiac and cerebrovascular events that qualified for adjudication and therefore there were no events to be confirmed.

There were no fatal events in the open-label arm of the study. One patient (1.5%) was reported with a SAE (induced abortion), which was assessed as not related to the study medication.

Hypersensitivity reactions, renal AEs, hepatic AEs, severe cutaneous adverse reactions, and acute pancreatitis were defined as significant AEs and analysed by narrow SMQs. No patients were reported with hypersensitivity reactions, hepatic events, renal events, severe cutaneous adverse reactions, and pancreatitis. 'Other significant' AEs (based upon ICH E3) were reported by 4 patients (6.1%); 1 patient was reported with bradycardia, exertional dyspnoea, diarrhoea, nausea, and peripheral oedema; 1 patient with nausea, and 2 patients with hyperglycaemia. All events led to discontinuation.

Laboratory evaluation and vital signs
Laboratory analyses (haematology, clinical chemistry, and urinalysis) did not reveal any clinically relevant findings. Only 2 patients were reported with PCSAs. There were no patients who fulfilled the criteria for Hy's law in the open-label arm of this study and 2 patients were observed for changes in renal function (shifting from moderate renal impairment to no/mild renal impairment).

The mean change from baseline to Visit 7/end of treatment (EoT) was 2.03 mmHg for SBP, -0.31 mmHg for DBP, and 1.02 bpm for PR. The majority of patients had inconspicuous values at the end of treatment (93.9% SBP, 97.0% DBP, and 97.0% pulse rate). The percentage of patients with marked increases was ≤1.5%. No patients were reported with marked outliers in blood pressure and pulse rate.

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Name of active ingredient: Linagliptin (BI 1356) and metformin (free combination)		**Page:** 15 of 15	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 SEP 2010	**Trial No. / U No.:** 1218.46 / U10-2372-02	**Dates of trial:** 05 DEC 2008 – 26 MAY 2010	**Date of revision:** 09 FEB 2012

Conclusions:	A clinically relevant reduction in HbA_{1c} change from baseline to Week 24 was observed for both free combination therapies compared to the monotherapies. Superiority of the free combination therapies over the monotherapies was shown and the treatment with the free combination therapies was well tolerated. The reported safety results were comparable between all treatment groups (placebo and active treatments). The incidence of hypoglycaemic events during treatment with the free combination therapies was low. In this study, the free combination therapy of linagliptin and metformin was efficacious and well tolerated and no safety concerns arose.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement the results for patient disposition and the secondary endpoints of the trial.

Note that not all 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**
Patient Disposition	Table 15.1.1: 1
Adjusted FPG mean change from baseline over time (at weeks 2, 6 12, 18, and 24)	Table 15.2.2.1.1: 6
Patients with HbA_{1c} <7.0% at week 24	Table 15.2.2.2: 1
Patients with HbA_{1c} <6.5% at week 24	Table 15.2.2.3: 1
Patients with HbA_{1c} reduction by 0.5% at week 24	Table 15.2.2.4: 1
Adjusted 2h PPG mean change from baseline at week 24	Table 15.2.2.6: 2
Use of Rescue Therapy	Table 15.2.2.7: 1
HbA_{1c} mean change from baseline by visit over time (at weeks 6 12, 18, and 24)	Table 15.2.1.2.2.1: 1

Table 15.1.1: 1 Disposition of randomised patients – SCR

	Placebo N (%)	M500 N (%)	M1000 N (%)	Lina5 N (%)	L2.5+M500 N (%)	L2.5+M1000 N (%)	Total N (%)
Enrolled							1770
Started wash-out							598
Started placebo run-in							957
Not randomised							913
Open label							66
Randomised	72	144	147	142	143	143	791
Not treated	0	0	0	0	0	0	0
Treated *	72 (100.0)	144 (100.0)	147 (100.0)	142 (100.0)	143 (100.0)	143 (100.0)	791 (100.0)
Not prematurely discontinued trial medication	54 (75.0)	127 (88.2)	126 (85.7)	121 (85.2)	127 (88.8)	132 (92.3)	687 (86.9)
Prematurely discontinued trial medication	18 (25.0)	17 (11.8)	21 (14.3)	21 (14.8)	16 (11.2)	11 (7.7)	104 (13.1)
Adverse events	3 (4.2)	4 (2.8)	6 (4.1)	6 (4.2)	5 (3.5)	2 (1.4)	26 (3.3)
AE study dis. worse	1 (1.4)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
AE other dis. worse	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	2 (0.3)
AE other	2 (2.8)	3 (2.1)	5 (3.4)	5 (3.5)	5 (3.5)	2 (1.4)	22 (2.8)
Lack of efficacy #	6 (8.3)	4 (2.8)	2 (1.4)	3 (2.1)	1 (0.7)	2 (1.4)	18 (2.3)
Non compl. protocol	2 (2.8)	1 (0.7)	3 (2.0)	3 (2.1)	3 (2.1)	2 (1.4)	14 (1.8)
Lost to follow-up	1 (1.4)	3 (2.1)	4 (2.7)	3 (2.1)	4 (2.8)	0 (0.0)	15 (1.9)
Refused cont. medic.	5 (6.9)	4 (2.8)	5 (3.4)	4 (2.8)	2 (1.4)	3 (2.1)	23 (2.9)
Other	1 (1.4)	1 (0.7)	1 (0.7)	2 (1.4)	1 (0.7)	2 (1.4)	8 (1.0)

* In all tables 'treated' refers to treatment with randomised study drug
\# Includes patients discontinued due to hyperglycemia

Table 15.2.2.1.1: 6 Adjusted FPG (mg/dL) mean change from baseline over time − FAS (LOCF)

Time point number = Baseline

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	61	136	132
Baseline unadjusted mean (SD)	203.3 (51.5)	190.6 (46.6)	190.6 (52.2)
Lina 5 od/ Lina 2.5 bid*			
N	134	135	136
Baseline unadjusted mean (SD)	195.3 (50.2)	198.6 (60.2)	195.6 (50.4)

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid
* Model includes treatment, baseline FPG, continuous baseline HbA1c and prior OADs.

Table 15.2.2.1.1: 6 Adjusted FPG (mg/dL) mean change from baseline over time − FAS (LOCF)

Time point number = Week 2

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	61	136	132
Week 2 adjusted mean (SE)	200.2 (4.3)	175.3 (2.9)	173.2 (2.9)
Change to Week 2 adjusted mean (SE)	5.3 (4.3)	−19.6 (2.9)	−21.8 (2.9)
Lina 5 od/ Lina 2.5 bid*			
N	134	135	136
Week 2 adjusted mean (SE)	181.9 (2.9)	160.4 (2.9)	156.3 (2.9)
Change to Week 2 adjusted mean (SE)	−13.0 (2.9)	−34.5 (2.9)	−38.6 (2.9)
Difference to Met component		−14.9 (4.1)	−16.8 (4.1)
95% CI		(−22.9, −6.8)	(−24.9, −8.8)
p−value		0.0003	<.0001
Difference to Lina 5		−21.5 (4.1)	−25.6 (4.1)
95% CI		(−29.5, −13.4)	(−33.6, −17.6)
p−value		<.0001	<.0001

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid
* Model includes treatment, baseline FPG, continuous baseline HbA1c and prior OADs.

Table 15.2.2.1.1: 6 Adjusted FPG (mg/dL) mean change from baseline over time − FAS (LOCF)

Time point number = Week 6

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	61	136	132
Week 6 adjusted mean (SE)	201.1 (4.7)	174.2 (3.2)	163.4 (3.2)
Change to Week 6 adjusted mean (SE)	6.2 (4.7)	−20.8 (3.2)	−31.6 (3.2)
Lina 5 od/ Lina 2.5 bid*			
N	134	135	136
Week 6 adjusted mean (SE)	184.2 (3.2)	156.3 (3.2)	146.6 (3.2)
Change to Week 6 adjusted mean (SE)	−10.8 (3.2)	−38.7 (3.2)	−48.3 (3.2)
Difference to Met component		−17.9 (4.5)	−16.8 (4.5)
95% CI		(−26.7, −9.1)	(−25.6, −7.9)
p−value		<.0001	0.0002
Difference to Lina 5		−27.9 (4.5)	−37.6 (4.5)
95% CI		(−36.7, −19.1)	(−46.4, −28.8)
p−value		<.0001	<.0001

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid
* Model includes treatment, baseline FPG, continuous baseline HbA1c and prior OADs.

Table 15.2.2.1.1: 6 Adjusted FPG (mg/dL) mean change from baseline over time − FAS (LOCF)

Time point number = Week 12

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	61	136	132
Week 12 adjusted mean (SE)	203.8 (5.0)	173.2 (3.3)	163.0 (3.4)
Change to Week 12 adjusted mean (SE)	8.9 (5.0)	−21.8 (3.3)	−31.9 (3.4)
Lina 5 od/ Lina 2.5 bid*			
N	134	135	136
Week 12 adjusted mean (SE)	186.5 (3.4)	158.7 (3.4)	145.0 (3.3)
Change to Week 12 adjusted mean (SE)	−8.4 (3.4)	−36.2 (3.4)	−49.9 (3.3)
Difference to Met component		−14.4 (4.7)	−18.0 (4.8)
95% CI		(−23.7, −5.1)	(−27.4, −8.7)
p−value		0.0024	0.0002
Difference to Lina 5		−27.8 (4.7)	−41.5 (4.7)
95% CI		(−37.1, −18.5)	(−50.8, −32.2)
p−value		<.0001	<.0001

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid
* Model includes treatment, baseline FPG, continuous baseline HbA1c and prior OADs.

Table 15.2.2.1.1: 6 Adjusted FPG (mg/dL) mean change from baseline over time − FAS (LOCF)

Time point number = Week 18

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	61	136	132
Week 18 adjusted mean (SE)	202.2 (5.1)	181.2 (3.4)	164.6 (3.5)
Change to Week 18 adjusted mean (SE)	7.3 (5.1)	−13.7 (3.4)	−30.3 (3.5)
Lina 5 od/ Lina 2.5 bid*			
N	134	135	136
Week 18 adjusted mean (SE)	185.7 (3.4)	160.3 (3.4)	146.8 (3.4)
Change to Week 18 adjusted mean (SE)	−9.2 (3.4)	−34.6 (3.4)	−48.1 (3.4)
Difference to Met component		−20.9 (4.8)	−17.9 (4.9)
95% CI		(−30.4, −11.4)	(−27.4, −8.3)
p−value		<.0001	0.0003
Difference to Lina 5		−25.4 (4.9)	−39.0 (4.9)
95% CI		(−35.0, −15.9)	(−48.5, −29.4)
p−value		<.0001	<.0001

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid
* Model includes treatment, baseline FPG, continuous baseline HbA1c and prior OADs.

Table 15.2.2.1.1: 6 Adjusted FPG (mg/dL) mean change from baseline over time − FAS (LOCF)

Time point number = Week 24

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	61	136	132
Week 24 adjusted mean (SE)	205.1 (5.3)	179.1 (3.5)	162.8 (3.6)
Change to Week 24 adjusted mean (SE)	10.2 (5.3)	−15.8 (3.5)	−32.2 (3.6)
Lina 5 od/ Lina 2.5 bid*			
N	134	135	136
Week 24 adjusted mean (SE)	186.3 (3.6)	161.7 (3.5)	145.6 (3.5)
Change to Week 24 adjusted mean (SE)	−8.6 (3.6)	−33.2 (3.5)	−49.4 (3.5)
Difference to Met component		−17.4 (5.0)	−17.2 (5.0)
95% CI		(−27.2, −7.6)	(−27.1, −7.3)
p−value		0.0005	0.0006
Difference to Lina 5		−24.6 (5.0)	−40.8 (5.0)
95% CI		(−34.4, −14.8)	(−50.6, −31.0)
p−value		<.0001	<.0001

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid
* Model includes treatment, baseline FPG, continuous baseline HbA1c and prior OADs.

Table 15.2.2.2: 1 Logistic regression of HbA1c < 7.0% at Week 24 − FAS patients with baseline HbA1c >=7.0% (NCF)

		Met 0	Met 500 bid	Met 1000 bid
Lina 0				
N		65	140	137
HbA1c < 7.0%		7 (10.8)	26 (18.6)	42 (30.7)
Lina 5 od/ Lina 2.5 bid*				
N		135	136	138
HbA1c < 7.0%		14 (10.4)	41 (30.1)	74 (53.6)
Comparison to Met component				
	Odds ratio		2.372 (0.748)	4.163 (1.221)
	95% CI		(1.278, 4.402)	(2.343, 7.397)
	p−value		0.0062	<.0001
Comparison to Lina 5				
	Odds ratio		4.854 (1.783)	17.094 (6.367)
	95% CI		(2.363, 9.973)	(8.238,35.471)
	p−value		<.0001	<.0001

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid

Table 15.2.2.3: 1 Logistic regression of HbA1c < 6.5% at Week 24 − FAS patients with baseline HbA1c >= 6.5% (NCF)

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	65	141	138
HbA1c < 6.5%	2 (3.1)	7 (5.0)	17 (12.3)
Lina 5 od/ Lina 2.5 bid*			
N	135	137	140
HbA1c < 6.5%	5 (3.7)	18 (13.1)	38 (27.1)
Comparison to Met component			
Odds ratio		3.465 (1.676)	3.521 (1.258)
95% CI		(1.342, 8.943)	(1.747, 7.094)
p−value		0.0102	0.0004
Comparison to Lina 5			
Odds ratio		4.521 (2.449)	11.947 (6.208)
95% CI		(1.564,13.069)	(4.314,33.080)
p−value		0.0053	<.0001

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid

Table 15.2.2.4: 1 Logistic regression of HbA1c lowering by 0.5% at Week 24 − FAS (NCF)

		Met 0	Met 500 bid	Met 1000 bid
Lina 0				
N		65	141	138
HbA1c lowering by 0.5%		19 (29.2)	65 (46.1)	91 (65.9)
Lina 5 od/ Lina 2.5 bid*				
N		135	137	140
HbA1c lowering by 0.5%		57 (42.2)	98 (71.5)	114 (81.4)
Comparison to Met component				
	Odds ratio		3.181 (0.834)	2.382 (0.688)
	95% CI		(1.903, 5.316)	(1.352, 4.196)
	p−value		<.0001	0.0027
Comparison to Lina 5				
	Odds ratio		3.622 (0.961)	6.529 (1.870)
	95% CI		(2.153, 6.093)	(3.724,11.445)
	p−value		<.0001	<.0001

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid

Table 15.2.2.6: 2 Adjusted means for 2h PPG (mg/dL) change from baseline at Week 24 − MTT (OC)

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	6	15	14
Baseline unadjusted mean (SD)	254.7 (64.0)	289.4 (72.4)	287.6 (94.6)
End of study adjusted mean (SE)	265.1 (23.2)	217.6 (14.4)	213.3 (14.8)
Change to end of study adjusted mean (SE)	−35.4 (23.2)	−82.9 (14.4)	−87.2 (14.8)
Lina 5 od/ Lina 2.5 bid*			
N	12	10	12
Baseline unadjusted mean (SD)	298.2 (71.3)	325.1 (87.5)	334.1 (91.4)
End of study adjusted mean (SE)	265.2 (16.1)	214.5 (17.5)	191.3 (16.2)
Change to end of study adjusted mean (SE)	−35.3 (16.1)	−86.0 (17.5)	−109.2 (16.2)
Difference to Met component		−3.2 (22.7)	−22.0 (22.1)
95% CI		(−48.5, 42.2)	(−66.2, 22.2)
p−value		0.8893	0.3234
Difference to Lina 5		−50.8 (23.8)	−73.9 (22.7)
95% CI		(−98.5, −3.1)	(−119.3, −28.6)
p−value		0.0373	0.0018

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid
* Model includes treatment, baseline PPG, continuous baseline HbA1c and prior OADs.

Table 15.2.2.7: 1 Logistic regression of use of rescue therapy − FAS (OC)

		Met 0	Met 500 bid	Met 1000 bid
Lina 0				
N		65	141	138
Rescue medication		19 (29.2)	19 (13.5)	11 (8.0)
Lina 5 od/ Lina 2.5 bid*				
N		135	137	140
Rescue medication		15 (11.1)	10 (7.3)	6 (4.3)
Compare to Met component				
	Odds ratio		0.420 (0.185)	0.326 (0.182)
	95% CI		(0.177, 0.996)	(0.109, 0.973)
	p−value		0.0490	0.0445
Compare to Lina 5				
	Odds ratio		0.598 (0.274)	0.274 (0.146)
	95% CI		(0.244, 1.467)	(0.096, 0.779)
	p−value		0.2617	0.0151

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid

Table 15.2.1.2.2.1: 1 Adjusted HbA1c (%) mean change from baseline over time − FAS (LOCF)

Time point number = Baseline

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	65	141	138
Baseline unadjusted mean (SD)	8.67 (0.95)	8.66 (0.90)	8.52 (0.87)
Lina 5 od/ Lina 2.5 bid*			
N	135	137	140
Baseline unadjusted mean (SD)	8.70 (0.97)	8.71 (0.95)	8.68 (1.03)

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid
Model includes treatment, continuous baseline HbA1c and prior OADs

Table 15.2.1.2.2.1: 1 Adjusted HbA1c (%) mean change from baseline over time − FAS (LOCF)

Time point number = Week 6

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	65	141	138
Week 6 adjusted mean (SE)	8.68 (0.08)	8.20 (0.05)	8.04 (0.05)
Change to Week 6 adjusted mean (SE)	0.03 (0.08)	−0.45 (0.05)	−0.61 (0.05)
Lina 5 od/ Lina 2.5 bid*			
N	135	137	140
Week 6 adjusted mean (SE)	8.29 (0.06)	7.79 (0.05)	7.66 (0.05)
Change to Week 6 adjusted mean (SE)	−0.36 (0.06)	−0.86 (0.05)	−1.00 (0.05)
Difference to Met component		−0.41 (0.08)	−0.38 (0.08)
95% CI		(−0.56, −0.26)	(−0.53, −0.23)
p−value		<.0001	<.0001
Difference to Lina 5		−0.50 (0.08)	−0.64 (0.08)
95% CI		(−0.65, −0.35)	(−0.79, −0.48)
p−value		<.0001	<.0001

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid
Model includes treatment, continuous baseline HbA1c and prior OADs

Table 15.2.1.2.2.1: 1 Adjusted HbA1c (%) mean change from baseline over time − FAS (LOCF)

Time point number = Week 12

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	65	141	138
Week 12 adjusted mean (SE)	8.82 (0.11)	8.04 (0.07)	7.71 (0.07)
Change to Week 12 adjusted mean (SE)	0.16 (0.11)	−0.61 (0.07)	−0.95 (0.07)
Lina 5 od/ Lina 2.5 bid*			
N	135	137	140
Week 12 adjusted mean (SE)	8.24 (0.07)	7.52 (0.07)	7.29 (0.07)
Change to Week 12 adjusted mean (SE)	−0.42 (0.07)	−1.13 (0.07)	−1.37 (0.07)
Difference to Met component		−0.51 (0.10)	−0.42 (0.10)
95% CI		(−0.72, −0.31)	(−0.63, −0.22)
p−value		<.0001	<.0001
Difference to Lina 5		−0.71 (0.11)	−0.95 (0.10)
95% CI		(−0.92, −0.51)	(−1.16, −0.75)
p−value		<.0001	<.0001

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid
Model includes treatment, continuous baseline HbA1c and prior OADs

Table 15.2.1.2.2.1: 1 Adjusted HbA1c (%) mean change from baseline over time − FAS (LOCF)

Time point number = Week 18

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	65	141	138
Week 18 adjusted mean (SE)	8.82 (0.12)	8.00 (0.08)	7.59 (0.08)
Change to Week 18 adjusted mean (SE)	0.16 (0.12)	−0.66 (0.08)	−1.06 (0.08)
Lina 5 od/ Lina 2.5 bid*			
N	135	137	140
Week 18 adjusted mean (SE)	8.20 (0.08)	7.48 (0.08)	7.12 (0.08)
Change to Week 18 adjusted mean (SE)	−0.45 (0.08)	−1.17 (0.08)	−1.54 (0.08)
Difference to Met component		−0.51 (0.11)	−0.47 (0.11)
95% CI		(−0.73, −0.29)	(−0.69, −0.26)
p−value		<.0001	<.0001
Difference to Lina 5		−0.72 (0.11)	−1.08 (0.11)
95% CI		(−0.94, −0.49)	(−1.30, −0.86)
p−value		<.0001	<.0001

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid
Model includes treatment, continuous baseline HbA1c and prior OADs

Table 15.2.1.2.2.1: 1 Adjusted HbA1c (%) mean change from baseline over time − FAS (LOCF)

Time point number = Week 24

	Met 0	Met 500 bid	Met 1000 bid
Lina 0			
N	65	141	138
Week 24 adjusted mean (SE)	8.78 (0.11)	8.01 (0.08)	7.58 (0.08)
Change to Week 24 adjusted mean (SE)	0.13 (0.11)	−0.64 (0.08)	−1.07 (0.08)
Lina 5 od/ Lina 2.5 bid*			
N	135	137	140
Week 24 adjusted mean (SE)	8.21 (0.08)	7.43 (0.08)	7.07 (0.08)
Change to Week 24 adjusted mean (SE)	−0.45 (0.08)	−1.22 (0.08)	−1.59 (0.08)
Difference to Met component		−0.58 (0.11)	−0.51 (0.11)
95% CI		(−0.79, −0.36)	(−0.73, −0.30)
p−value		<.0001	<.0001
Difference to Lina 5		−0.77 (0.11)	−1.14 (0.11)
95% CI		(−0.99, −0.55)	(−1.36, −0.92)
p−value		<.0001	<.0001

* If combined with Metformin 500mg or 1000mg, Linagliptin is administered as 2.5 mg bid
Model includes treatment, continuous baseline HbA1c and prior OADs