Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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.

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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: Trajenta®		**EudraCT No.:** 2008-008296-33	
Name of active ingredient: Linagliptin (BI 1356)		**Page:** 1 of 10	**Synopsis No.:**
Module:		**Volume:**	
Disclosure Synopsis date: 18 JUN 2014	**Trial No. / U No.:** 1218.36 / U12-1511-01	**Dates of trial:** 05 AUG 2009 - 17 SEP 2011	**Date of revision:** Not applicable

Title of trial:	A Phase III randomised, double-blind, placebo-controlled, parallel group efficacy and safety study of Linagliptin (5 mg), administered orally once daily for at least 52 weeks in type 2 diabetic patients in combination with basal insulin therapy
Coordinating Investigator:	[redacted]
Trial sites:	Multinational trial conducted in 167 centres in 19 countries worldwide (Argentina, Belgium, Brazil, Canada, Czech Republic, Finland, Germany, Greece, Italy, Korea, Mexico, Netherlands, Norway, Peru, Russia, Slovakia, Spain, Taiwan, United States)
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	The objective of this trial was to investigate the efficacy and safety of linagliptin 5 mg versus placebo administered for at least 52 weeks as add-on to basal insulin therapy to patients with type 2 diabetes mellitus and insufficient glycaemic control, the primary endpoint being efficacy after 24 weeks.
Methodology:	This was a multicentre, randomised, double-blind, parallel-group, placebo-controlled study. Before randomisation, patients underwent a 2-week placebo run-in period.
No. of subjects:	
planned:	entered: 1200
actual:	enrolled: 1848
	Linagliptin 5 mg: entered: 633 treated: 631 analysed (for primary endpoint): 618
	Placebo: entered: 630 treated: 630 analysed (for primary endpoint): 617

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Diagnosis and main criteria for inclusion:	Patients ≥18 years with type 2 diabetes mellitus (T2DM) who were being treated with subcutaneous basal insulin alone or in combination with metformin and/or pioglitazone. Glycosylated haemoglobin (HbA_{1c}) at screening was to be ≥7.0% and ≤10.0%. Body mass index (BMI) at screening was to be ≤45 kg/m^2.
Test product:	Linagliptin, tablet
dose:	5 mg, once daily
mode of admin.:	Oral
batch no.:	956146
Reference therapy:	Placebo, tablet
dose:	Not applicable
mode of admin.:	Oral
batch no.:	4000015
Duration of treatment:	A 2-week placebo run-in period was followed by a randomised, double-blind treatment period of at least 52 weeks. During the first 24 weeks of randomised treatment, the background dose of basal insulin was to remain stable. After 24 weeks, the dose of basal insulin could be adjusted according to the clinical judgement of the investigator. The dose of oral antidiabetics (metformin and/or pioglitazone) was to remain stable throughout the whole study. After the treatment period, there was a 1-week follow-up period.
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary endpoint was the change from baseline in HbA_{1c} after 24 weeks of treatment. Important secondary endpoints were the change from baseline in fasting plasma glucose (FPG) after 24 and 52 weeks of treatment, and the occurrence of treat-to-target response that was an HbA_{1c} under treatment of <7.0% (or <6.5%) or a relative efficacy response (HbA_{1c} lowering by at least 0.5% from baseline) after 24 and 52 weeks of treatment. Other important endpoints were the use of rescue therapy, and the change in body weight from baseline to Week 24 and end of treatment. Primary and secondary endpoints after 24 weeks were reported in an interim analysis which was performed to provide data required for regulatory submissions.

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Safety:	Safety endpoints were the frequency and intensity of adverse events (AEs), clinically relevant new or worsening findings in physical examination, 12-lead ECG, vital signs, and clinical laboratory parameters.
Statistical methods:	Primary endpoint: Testing of superiority hypothesis versus placebo with an analysis of covariance (ANCOVA) with treatment, concomitant oral antidiabetics, and baseline renal function impairment category as fixed classification effects, and baseline HbA_{1c} as covariate The primary endpoint was assessed after 24 weeks of treatment and was reported in an interim analysis which was performed to provide data required for regulatory submissions. The current final study report includes the analysis of the complete study period (52 weeks) including the primary endpoint. Secondary and other endpoints: ANCOVA (exploratory); for use of rescue medication logistic regression and Kaplan-Meier analysis Safety endpoints: Descriptive statistics; for hypoglycaemic events logistic regression and Kaplan-Meier analysis

SUMMARY – CONCLUSIONS:

Efficacy results:

In this study, 1848 patients were enrolled by 167 centres in 19 countries in Asia, Europe, North America, and South America. A total of 1263 patients were randomised in a 1:1 ratio to receive treatment with either placebo (630 patients) or linagliptin (633 patients) in addition to their basal insulin therapy. A total of 1261 patients (630 patients placebo; 631 patients linagliptin) were treated with randomised study medication. Of those, 198 patients (15.7%) prematurely discontinued study medication (17.5% placebo, 13.9% linagliptin). The main reason for discontinuation was the occurrence of adverse events (5.2% placebo; 4.0% linagliptin).

The demographic baseline characteristics of the treated set of patients were comparable between the treatment groups. Just over half of the patients were male (52.2%). The majority of patients were White (80.3%) or Asian (12.2%). The mean age was 60.0 years. The mean body mass index at baseline was similar in both treatment groups (31.16 kg/m^2 placebo; 30.78 kg/m^2 linagliptin).

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Efficacy results: (continued)

At baseline, 43.8% of patients had normal renal function (estimated Glomerular Filtration Rate; eGFR ≥90 mL/min), 45.6% had mild renal impairment (eGFR 60 to <90 mL/min), 10.1% had moderate renal impairment (eGFR 30 to <60 mL/min), while 0.6% had severe or end-stage renal impairment (eGFR <30 mL/min).

Concomitant diagnoses and therapies at screening were generally comparable between the two treatment groups, as were baseline efficacy parameters. The mean prescribed basal insulin dose at baseline was 40.1 IU for the placebo group and 41.5 IU for the linagliptin group. The majority of patients (75.6%) were taking metformin, while a further 7.4% were taking metformin in combination with pioglitazone as background oral antidiabetic medication. Pioglitazone alone was taken by 1.0% of patients as background therapy in addition to basal insulin. Mean baseline HbA_{1c} was similar in both treatment groups (8.29% placebo; 8.31% linagliptin). Mean baseline FPG was also similar in both treatment groups (151.3 mg/dL placebo; 147.2 mg/dL linagliptin). The efficacy endpoint analyses were performed on the full analysis set (FAS) of patients, comprising all treated patients who had a baseline and at least one on-treatment HbA_{1c} measurement available (617 patients placebo; 618 patients linagliptin). The last observation carried forward approach was applied to impute missing data.

Compliance was maintained at more than 95% for both treatment groups up to the end of 52 weeks of treatment.

Primary endpoint

Superiority of linagliptin over placebo was demonstrated for the primary endpoint by a treatment difference in HbA_{1c} adjusted mean change from baseline of -0.65% (95% CI: -0.74, -0.55; $p<0.0001$) after 24 weeks of randomised treatment. The adjusted mean change from baseline in the linagliptin group was -0.58% (SE 0.08), compared with 0.07% (SE 0.08) in the placebo group.

Sensitivity analyses confirmed the superiority of linagliptin shown in the primary efficacy analysis. One of these sensitivity analyses, a mixed model for repeated measurement analysis performed on the FAS applying an observed cases approach (without imputation of missing data), showed a significant ($p<0.0001$) difference between both treatments in the adjusted mean HbA_{1c}

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Efficacy results: (continued)

change from baseline that increased over time to Week 12 (-0.62%) and was sustained up to the timepoint for the analysis of the primary endpoint at 24 weeks (-0.67%).

The subgroup variables that had significant ($p<0.10$) interactions with treatment were baseline HbA_{1c} ($p=0.0725$), region ($p=0.0548$), race ($p=0.0603$), and time since diagnosis of diabetes ($p=0.0017$). The treatment group interaction with renal impairment category was not significant ($p=0.5784$), indicating that renal impairment did not alter the efficacy of linagliptin.

Secondary endpoints

At Week 52, the difference between treatments in terms of adjusted mean change from baseline in HbA_{1c} was -0.53% (95% CI: -0.64, -0.43; $p<0.0001$). The adjusted mean change from baseline in the linagliptin group was -0.48% (SE 0.08), compared with 0.05% (SE 0.08) in the placebo group. For those patients with data beyond 52 weeks, the treatment difference between linagliptin and placebo was maintained.

The analyses performed to assess how many patients reached target HbA_{1c} levels of <7.0% or <6.5% after 52 weeks of treatment (i.e. had an absolute efficacy response) and how many patients had a 0.5% reduction or more after 52 weeks of randomised treatment (i.e. had a relative efficacy response) all confirmed the superiority of linagliptin over placebo. For patients with a baseline HbA_{1c} of 7.0% or greater, those in the linagliptin group were more likely to attain an HbA_{1c} below 7.0% after 52 weeks than patients in the placebo group (6.6% placebo; 15.8% linagliptin; odds ratio 2.935, $p<0.0001$). For patients with a baseline HbA_{1c} of 6.5% or greater, those in the linagliptin group were more likely to attain an HbA_{1c} below 6.5% after 52 weeks than patients in the placebo group (2.0% placebo; 7.3% linagliptin; odds ratio 4.327, $p<0.0001$). Patients in the linagliptin group were also more likely to have a reduction in HbA_{1c} of at least 0.5% after 52 weeks than patients in the placebo group (16.9% placebo; 37.4% linagliptin; odds ratio 2.958, $p<0.0001$).

The difference between the treatment groups in the change in adjusted mean HbA_{1c} from baseline to 24 weeks was similar for patients with normal renal function (-0.70%; $p<0.0001$), mild renal impairment (-0.59%; $p<0.0001$), and moderate renal impairment (-0.69%; $p<0.0001$).

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Efficacy results: (continued)

Within these subgroup categories, the reduction in HbA_{1c} from baseline that was achieved at 24 weeks was generally maintained until 52 weeks for patients in the linagliptin group. However, as was the case for the overall patient population, there was a reduction in HbA_{1c} in most subgroup categories of patients receiving placebo after 24 weeks, when the investigators could adjust the prescribed basal insulin dose according to their medical judgement. There was no evidence of a differential effect across subgroup categories beyond 24 weeks. Overall, the results show comparable efficacy for linagliptin for patients with normal renal function and those with mild or moderate renal impairment. The responses in terms of HbA_{1C} reduction from baseline were generally consistent and clinically relevant across subgroups.

Linagliptin was also superior to placebo with respect to the FPG reduction from baseline. The adjusted mean change from baseline after 24 weeks was 4.52 mg/dL for placebo and -7.09 mg/dL for linagliptin. The difference in the adjusted mean change from baseline at 24 weeks was -11.60 mg/dL (95% CI: -16.49, -6.71; $p<0.0001$).

Other endpoints

During randomised treatment, patients on treatment with linagliptin were less likely to require the use of rescue therapy than patients on treatment with placebo (50.4% placebo; 38.2% linagliptin), with an associated odds ratio of 0.575 ($p<0.0001$). More patients in the placebo group than in the linagliptin group had increases in their prescribed basal insulin dose of more than 10% of their baseline dose during randomised treatment (44.4% placebo; 33.7% linagliptin). The mean change of basal insulin dose up to Week 24 was 0.4 IU for patients treated with placebo and 0.1 IU for patients treated with linagliptin. The mean change of basal insulin dose up to Week 52 was 4.1 IU for patients treated with placebo and 2.5 IU for patients treated with linagliptin and the respective change up to Week 76 was 6.6 IU for patients treated with placebo and 2.8 IU for patients treated with linagliptin.

The mean change in body weight from baseline to Week 52 was minimal and similar between the treatment groups (-0.04 kg placebo; -0.30 kg linagliptin).

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Safety results:

All 1261 patients who took at least one dose of study medication during the randomised treatment period were included in the analysis of safety.

Exposure

The mean exposure was 422.4 days for the placebo group and 435.5 days for the linagliptin group. The duration of exposure to linagliptin was 752.4 patient years.

Adverse events

The proportion of patients with at least one reported AE was similar for both treatment groups (81.4% placebo, 78.4% linagliptin). The system organ class with the highest incidence of reported AEs was metabolism and nutrition disorders (49.0% placebo; 46.0% linagliptin). The AEs reported with an incidence of at least 5% in either treatment group at the preferred term level were hypoglycaemia (31.4% placebo; 30.7% linagliptin), hyperglycaemia (18.1% placebo; 14.3% linagliptin), nasopharyngitis (9.8% placebo; 11.3% linagliptin), urinary tract infection (7.1% placebo; 4.9% linagliptin), hypertension (5.6% placebo; 4.8% linagliptin), back pain (4.8% placebo, 5.5% linagliptin), headache (4.3% placebo; 5.5% linagliptin), dizziness (4.8% placebo; 5.4% linagliptin), influenza (5.4% placebo, 4.1% linagliptin), and diarrhoea (4.8% placebo; 5.2% linagliptin).

During the first 24 weeks of randomised treatment (period of stable basal insulin dose), investigator-defined hypoglycaemic AEs were reported for 23.2% of patients in the placebo group and 22.0% of patients in the linagliptin group. Up to the end of treatment, investigator-defined hypoglycaemic AEs were reported for 32.9% of patients in the placebo group and 31.4% of patients in the linagliptin group.

Most of the AEs were of mild or moderate intensity. Adverse events of severe intensity were reported in 8.3% of patients in the placebo group and 8.2% of patients in the linagliptin group.

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Safety results: (continued)

Adverse events considered by the investigator to be drug-related were reported for 22.2% of patients in the placebo group and 18.7% of patients in the linagliptin group. The drug-related AE with the highest incidence was hypoglycaemia (15.1% placebo; 13.2% linagliptin).

All other drug-related AEs were reported with an incidence of ≤2% with no imbalance towards placebo or linagliptin. Adverse events leading to discontinuation of trial medication were reported for 4.4% of patients in the placebo group and 3.3% of patients in the linagliptin group. All individual reported AEs had a low incidence of <1% with no imbalance towards placebo or linagliptin.

The incidence of AEs was similar in both treatment groups for patients with normal renal function (78.2% placebo; 77.3% linagliptin) and mild renal impairment (82.7% placebo; 78.8% linagliptin). For patients with moderate renal impairment, the incidence of AEs was lower in the linagliptin group than in the placebo group (88.2% placebo; 81.4% linagliptin). The overall incidence of AEs was higher for patients with mild or moderate renal impairment, compared with patients with normal renal function at baseline. Analysis of the established side effect profile of linagliptin (nasopharyngitis, cough, hypersensitivity, and pancreatitis) did not reveal a clinically meaningful increased risk for patients with mild or moderate renal impairment. There was also no evidence for an increased risk of hypoglycaemia in patients treated with linagliptin with mild or moderate renal impairment, compared to patients with normal renal function.

A total of 11 patients (1.7%) in the placebo group and 18 patients (2.9%) in the linagliptin group were reported with cardiovascular deaths, myocardial infarction, stroke, or hospitalisation due to unstable angina that were confirmed by adjudication by the clinical event committee. Six patients were reported with cardiovascular death, 1 patient (0.2%) in the placebo group and 5 patients (0.8%) in the linagliptin group.

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Safety results: (continued)

Serious adverse events were reported for 83 patients (13.2%) in the placebo group and 87 patients (13.8%) in the linagliptin group. The SAE with the highest incidence by system organ class was cardiac disorders (2.7% placebo; 3.2% linagliptin). Ten deaths were reported, 5 in the placebo and 5 in the linagliptin group.

Pre-specified significant AEs and other AEs of special interest were renal AEs, hepatic AEs, hypersensitivity reactions, cutaneous skin lesions, and pancreatitis. Renal AEs were reported for 5 patients (0.8%) in the placebo group and 2 patients (0.3%) in the linagliptin group. Hepatic AEs were reported for 11 patients (1.7%) in the placebo group and 18 patients (2.9%) in the linagliptin group. Hypersensitivity reactions were reported for 4 patients (0.6%) in the placebo group and 7 patients (1.1%) in the linagliptin group. Of these, there was an imbalance between treatment groups for urticaria, which was reported for 1 patient (0.2%) in the placebo group and 5 patients (0.8%) in the linagliptin group. Cutaneous skin lesions were reported for 1 patient (0.2%) in the linagliptin group and for no patient in the placebo group. Pancreatitis was reported for 1 patient (0.2%) in the placebo group and 3 patients (0.5%) in the linagliptin group.

'Other significant' AEs (as defined by the ICH E3 guideline) were reported for 10 patients (1.6%) in the placebo group and for 7 patients (1.1%) in the linagliptin group.

Laboratory parameters and vital signs

Laboratory analyses (haematology, clinical chemistry, and urinalysis) did not reveal any clinically relevant or unexpected changes. One patient in the placebo group fulfilled the search criteria for a potential Hy's Law case; however, the abnormal liver function tests coincided with an episode of hepatitis B in this patient. Because of the clear alternative aetiology, this was not considered as a Hy´s Law case. There was no imbalance between treatment groups with respect to shifts in renal impairment stage. There were no clinically relevant changes in vital signs during this trial in either treatment group.

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Conclusions:

In a population of patients with insufficient glycaemic control despite treatment with basal insulin, treatment with 5 mg linagliptin once daily was superior to placebo in the reduction of HbA_{1c} and fasting plasma glucose levels. The difference after 24 weeks in the adjusted means of -0.65% HbA_{1c} lowering between linagliptin and placebo treatment is clinically relevant and was achieved without additional risk of hypoglycaemia for patients treated with linagliptin. It was also achieved with stable basal insulin dose and without changes in body weight. The difference in HbA_{1c} was well maintained beyond 24 weeks, when investigators were free to adjust insulin doses. At Week 52, the difference between linagliptin and placebo treatments in terms of adjusted mean change from baseline in HbA_{1c} was -0.53%. For those patients who continued in the study beyond 52 weeks, the treatment difference between linagliptin and placebo was maintained until 76 weeks of treatment. The efficacy beyond Week 24 was maintained with minimal insulin dose changes. Hypoglycaemia rates and weight remained comparable beyond 24 weeks. The assessment of safety did not reveal any major concerns for treatment with linagliptin. There was also no evidence of an altered efficacy or safety profile for linagliptin, as a 5 mg daily dose, in patients with mild or moderate renal impairment. For patients with insufficient glycaemic control on basal insulin therapy, treatment with linagliptin was efficacious, safe, and well-tolerated.

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 endpoints defined in the trial protocol are presented in this synopsis because their number was too large to allow meaningful presentation in this format.

Results for	**presented in**
HbA_{1c} (%) change from baseline by visit to week 52	Table 15.2.1.2.2: 1
FPG (mg/dL) change from baseline to week 52	Table 15.2.2.3: 3
FPG (mg/dL) over time, including changes from baseline	Table 15.2.2.3: 4
Weighted mean daily glucose (mmol.h/L) over time	Table 15.2.2.8: 1
Incremental post-prandial glucose (iPPG) (mmol.h/L) over time	Table 15.2.2.8: 2

Table 15.2.1.2.2: 1 Adjusted means for HbA1c (%) change from baseline by visit - FAS (LOCF)

	Placebo			Linagliptin			Difference Linagliptin - Placebo				
	N	Adj* mean	SE	N	Adj* mean	SE	Adj* mean	SE	95% CI LL	95% CI UL	p-value
Baseline (unadjusted means)	617	8.29	0.03	618	8.31	0.03					
Change from baseline at Week 6	617	0.00	0.05	618	-0.45	0.05	-0.45	0.03	-0.51	-0.39	<.0001
Change from baseline at Week 12	617	0.02	0.07	618	-0.59	0.07	-0.61	0.04	-0.69	-0.52	<.0001
Change from baseline at Week 18	617	0.03	0.08	618	-0.64	0.08	-0.67	0.05	-0.76	-0.57	<.0001
Change from baseline at Week 24	617	0.07	0.08	618	-0.58	0.08	-0.65	0.05	-0.74	-0.55	<.0001
Change from baseline at Week 32	617	0.01	0.08	618	-0.56	0.08	-0.57	0.05	-0.67	-0.47	<.0001
Change from baseline at Week 40	617	0.05	0.08	618	-0.50	0.08	-0.55	0.05	-0.65	-0.45	<.0001
Change from baseline at Week 52	617	0.05	0.08	618	-0.48	0.08	-0.53	0.05	-0.64	-0.43	<.0001

* Model includes treatment, baseline HbA1c, cat. renal function impairment and concomitant OADs

Table 15.2.2.3: 3 Mean (SE) change from baseline in FPG (mg/dL) at week 52 - FAS (LOCF, LOCF-ROC)

	Placebo (N=617)							Lina (N=618)						
	N	Mean	SD	SEM	Min	Median	Max	N	Mean	SD	SEM	Min	Median	Max
LOCF	609	0.63	56.44	2.29	-206.0	0.00	198.0	614	-2.55	55.01	2.22	-218.0	-6.00	274.0
LOCF-ROC	612	-6.18	56.07	2.27	-206.0	-9.00	196.4	615	-4.04	55.45	2.24	-218.0	-6.00	274.0

Table 15.2.2.3: 4 Descriptive statistics of FPG (mg/dL) over time - FAS (OC, OC-ROC)

	Placebo (N=617)							Lina (N=618)						
	N	Mean	SD	SEM	Min	Median	Max	N	Mean	SD	SEM	Min	Median	Max
OC														
Baseline	613	151.28	46.43	1.88	49.0	148.00	319.0	615	147.24	45.99	1.85	58.0	144.00	357.0
Week 6	601	154.26	47.64	1.94	58.0	148.00	340.0	607	141.61	43.99	1.79	52.0	135.00	373.0
Week 12	557	149.78	47.44	2.01	58.0	146.00	375.0	590	138.61	42.34	1.74	41.0	133.00	299.0
Week 18	533	151.55	48.72	2.11	41.0	148.00	420.0	568	143.14	47.77	2.00	45.0	137.00	533.0
Week 24	499	148.62	48.15	2.16	52.0	144.00	378.0	534	137.56	41.78	1.81	50.0	131.00	292.0
Week 32	437	143.95	45.64	2.18	52.0	137.00	304.0	491	136.55	40.48	1.83	40.0	131.00	274.0
Week 40	358	139.92	42.50	2.25	61.0	135.00	315.0	429	134.30	39.19	1.89	54.0	128.00	328.0
Week 52	293	135.96	41.24	2.41	52.0	133.00	322.0	378	136.41	44.36	2.28	47.0	130.50	423.0
Week 64	156	137.46	47.06	3.77	50.0	131.00	378.0	227	125.80	32.40	2.15	65.0	124.00	247.0
Week 76	74	129.07	38.36	4.46	63.0	120.00	270.0	122	133.66	45.92	4.16	67.0	127.00	367.0
Week 88	27	119.15	25.71	4.95	67.0	121.00	180.0	38	127.79	34.51	5.60	81.0	123.50	229.0
Week 100	3	128.00	26.06	15.04	103.0	126.00	155.0	8	121.38	29.41	10.40	97.0	103.50	173.0
Change from baseline at Week 6	600	2.97	50.89	2.08	-206.0	3.00	182.0	606	-5.29	44.74	1.82	-179.0	-5.50	227.0
Change from baseline at Week 12	556	-0.33	51.09	2.17	-215.0	-2.00	231.0	590	-7.59	48.50	2.00	-265.0	-10.00	177.0
Change from baseline at Week 18	533	2.10	53.21	2.30	-211.0	2.00	227.0	567	-3.30	55.51	2.33	-238.0	-3.00	434.0
Change from baseline at Week 24	499	0.04	54.94	2.46	-224.0	0.00	198.0	533	-7.07	44.70	1.94	-200.0	-8.00	146.0
Change from baseline at Week 32	436	-2.67	52.43	2.51	-179.0	-1.72	196.0	491	-6.30	48.16	2.17	-204.0	-7.00	186.0
Change from baseline at Week 40	357	-3.99	50.29	2.66	-206.0	-2.00	193.0	429	-6.50	50.00	2.41	-218.0	-5.00	212.0
Change from baseline at Week 52	292	-4.62	48.13	2.82	-197.0	-7.00	166.0	377	-4.27	53.71	2.77	-218.0	-7.27	274.0
Change from baseline at Week 64	155	-5.40	54.11	4.35	-126.0	-5.00	288.0	227	-11.31	44.42	2.95	-242.0	-11.00	141.0
Change from baseline at Week 76	73	-10.78	49.25	5.76	-129.0	-13.00	170.0	122	-2.34	50.51	4.57	-81.0	-7.50	209.0
Change from baseline at Week 88	26	-14.19	40.89	8.02	-156.0	-8.50	40.0	38	-1.89	35.20	5.71	-81.0	-3.00	58.0
Change from baseline at Week 100	3	2.00	34.39	19.86	-27.0	-7.00	40.0	8	1.38	42.99	15.20	-54.0	-5.00	90.0
OC-ROC														
Baseline	613	151.28	46.43	1.88	49.0	148.00	319.0	615	147.24	45.99	1.85	58.0	144.00	357.0
Week 6	604	154.15	47.71	1.94	58.0	148.00	340.0	608	141.76	44.11	1.79	52.0	136.00	373.0
Week 12	575	150.02	47.70	1.99	54.0	146.00	375.0	600	139.10	42.80	1.75	41.0	133.00	299.0
Week 18	571	151.95	48.55	2.03	41.0	148.00	420.0	588	143.15	47.73	1.97	45.0	137.00	533.0
Week 24	566	150.31	47.87	2.01	52.0	145.00	378.0	575	138.90	42.93	1.79	50.0	131.00	292.0
Week 32	547	146.37	45.57	1.95	52.0	140.00	322.0	563	137.91	40.71	1.72	40.0	133.00	274.0
Week 40	537	144.66	44.20	1.91	58.0	140.00	366.0	569	139.92	43.23	1.81	50.0	133.00	328.0
Week 52	522	141.46	44.90	1.97	52.0	137.00	322.0	548	141.65	46.96	2.01	47.0	135.00	423.0
Week 64	324	141.28	46.00	2.56	50.0	135.00	378.0	359	133.99	38.73	2.04	65.0	130.00	308.0
Week 76	200	136.49	42.82	3.03	63.0	130.50	342.0	219	138.50	43.94	2.97	67.0	131.00	367.0
Week 88	71	129.06	35.19	4.18	67.0	126.00	238.0	73	134.15	37.70	4.41	76.0	130.00	272.0

Source data: Appendix 16.2.6, Listing 2.1 efficacy\fpg-ds.sas 10APR2012

Table 15.2.2.3: 4 Descriptive statistics of FPG (mg/dL) over time - FAS (OC, OC-ROC)

	Placebo (N=617)							Lina (N=618)						
	N	Mean	SD	SEM	Min	Median	Max	N	Mean	SD	SEM	Min	Median	Max
Week 100	12	123.17	32.84	9.48	74.0	117.00	191.0	18	127.78	32.91	7.76	90.0	121.50	211.0
Change from baseline at Week 6	603	2.87	50.79	2.07	-206.0	3.00	182.0	607	-5.29	44.70	1.81	-179.0	-6.00	227.0
Change from baseline at Week 12	574	-0.88	51.83	2.16	-215.0	-2.00	231.0	600	-7.51	48.84	1.99	-265.0	-10.00	177.0
Change from baseline at Week 18	571	0.81	54.19	2.27	-211.0	0.00	227.0	587	-3.71	55.16	2.28	-238.0	-3.00	434.0
Change from baseline at Week 24	566	-1.00	55.65	2.34	-224.0	0.00	198.0	574	-7.13	45.09	1.88	-200.0	-7.50	146.0
Change from baseline at Week 32	546	-5.38	53.21	2.28	-179.0	-4.00	196.0	562	-7.77	49.16	2.07	-204.0	-7.00	186.0
Change from baseline at Week 40	536	-6.24	52.47	2.27	-206.0	-7.00	193.0	569	-6.16	53.98	2.26	-218.0	-5.00	212.0
Change from baseline at Week 52	520	-9.23	52.63	2.31	-197.0	-11.00	177.0	546	-4.39	54.69	2.34	-218.0	-7.00	274.0
Change from baseline at Week 64	323	-12.08	56.01	3.12	-182.0	-11.00	288.0	357	-13.76	49.89	2.64	-242.0	-13.00	141.0
Change from baseline at Week 76	199	-18.53	53.75	3.81	-173.0	-19.00	179.0	217	-8.35	48.93	3.32	-144.0	-11.00	209.0
Change from baseline at Week 88	70	-17.91	40.85	4.88	-156.0	-16.00	148.0	72	-7.91	37.90	4.47	-99.0	-4.50	61.0
Change from baseline at Week 100	12	-22.08	32.09	9.27	-56.0	-32.00	40.0	18	-10.06	50.24	11.84	-97.0	-8.50	99.0

Table 15.2.2.8: 1 Descriptive statistics of weighted mean daily glucose (mmol.h/L) over time - FAS (OC)

	Placebo (N=109)							Lina (N=103)						
	N	Mean	SD	SEM	Min	Median	Max	N	Mean	SD	SEM	Min	Median	Max
OC														
Baseline	75	9.47	2.20	0.25	4.0	9.27	15.2	67	9.33	2.27	0.28	4.8	8.92	18.3
Week 24	84	9.38	2.43	0.26	5.4	9.04	21.1	84	9.34	2.23	0.24	5.3	8.91	15.2
Week 52	36	9.17	1.88	0.31	6.0	9.27	14.3	34	8.59	1.90	0.33	4.6	8.42	13.6
Change from baseline at Week 24	55	0.03	2.28	0.31	-5.4	-0.14	5.8	52	-0.01	1.98	0.28	-5.0	-0.15	6.3
Change from baseline at Week 52	25	0.10	3.06	0.61	-6.3	0.28	6.4	15	-0.50	2.35	0.61	-4.2	-0.29	4.5

Table 15.2.2.8: 2 Descriptive statistics of incremental post-prandial glucose (mmol.h/L) over time - FAS (OC)

	Lina 5mg							Placebo						
	N	Mean	SD	Min	Q1	Median	Q3	Max	N	Mean	SD	Min	Q1	Median	Q3	Max
Fasting glucose																
Baseline	82	140.30	49.97	48.0	101.00	135.50	171.00	289.0	87	136.28	44.43	63.0	98.00	132.00	163.00	241.0
Week 24	92	134.17	37.32	67.0	108.00	130.75	157.00	317.0	97	129.43	41.29	46.0	101.00	122.50	154.00	250.0
Week 52	63	129.94	42.20	67.0	99.00	126.00	154.00	254.0	62	127.24	31.63	73.0	105.00	125.00	143.00	224.0
Change from basel. week 24	71	-9.39	55.28	-169.0	-42.00	-3.60	18.00	122.5	72	-5.43	44.00	-95.5	-39.80	-8.00	21.00	98.0
Change from basel. week 52	46	-21.30	58.17	-151.0	-56.00	-14.50	16.20	87.0	47	-2.69	49.77	-136.0	-30.60	-1.00	25.00	149.0
Post-breakfast glucose																
Baseline	78	198.47	59.99	69.0	156.80	187.70	246.00	373.0	78	195.15	60.21	79.0	142.00	196.00	250.00	348.0
Week 24	80	189.18	57.93	90.0	144.60	173.50	222.00	353.0	85	194.80	59.49	59.0	153.00	188.00	229.00	353.0
Week 52	58	186.40	57.36	93.0	140.60	177.60	230.70	330.0	52	199.57	53.61	101.0	164.00	194.50	232.00	368.0
Change from basel. week 24	62	-11.83	75.05	-239.0	-67.00	-10.50	34.00	181.0	62	2.77	56.19	-136.0	-39.00	-2.50	42.00	153.0
Change from basel. week 52	44	-11.29	64.29	-173.0	-55.00	-6.10	26.50	125.0	39	1.74	80.55	-157.0	-45.00	1.80	41.00	233.0
Post-breakfast incr. glucose																
Baseline	77	56.92	50.95	-49.0	21.00	60.00	93.70	165.0	78	60.48	49.36	-69.0	30.60	52.50	98.00	177.0
Week 24	80	54.17	49.18	-45.0	16.50	48.00	69.50	185.0	83	67.16	54.88	-55.0	26.00	69.00	113.00	215.0
Week 52	57	57.12	50.96	-34.2	22.00	54.00	76.00	237.0	52	71.98	43.50	-20.0	44.00	66.50	98.50	183.0
Change from basel. week 24	61	-3.78	63.63	-190.0	-37.80	-9.00	37.00	142.3	60	9.31	44.02	-97.0	-15.00	6.50	43.50	92.0
Change from basel. week 52	43	9.86	53.95	-122.5	-25.00	7.00	32.00	161.0	39	7.91	54.41	-108.0	-18.00	4.00	35.00	210.0
Pre-lunch glucose																
Baseline	68	151.98	58.81	43.0	113.65	139.50	178.50	360.0	69	148.52	45.32	73.0	113.00	147.80	171.00	272.1
Week 24	73	143.29	49.61	51.0	112.00	139.00	166.00	300.9	76	158.88	60.98	61.0	115.15	145.00	182.00	369.0
Week 52	49	144.82	57.09	72.0	91.00	141.00	179.00	288.0	51	149.69	49.58	60.0	106.00	148.00	180.00	303.0
Change from basel. week 24	47	-4.15	59.03	-138.0	-51.00	0.00	39.00	99.0	48	1.22	66.71	-167.0	-38.50	-0.80	30.00	201.0
Change from basel. week 52	31	-4.72	71.68	-135.0	-48.00	-19.00	40.00	176.0	28	4.37	60.64	-114.0	-29.50	-2.50	62.15	108.0
Post-lunch glucose																
Baseline	72	187.87	58.21	89.0	151.00	179.00	219.00	406.0	74	185.66	50.96	85.0	144.00	179.50	223.00	309.0
Week 24	82	176.56	53.07	103.0	136.00	166.50	205.40	342.0	82	189.15	67.77	78.0	147.80	183.00	224.00	465.0
Week 52	53	175.76	63.44	72.0	122.00	176.00	221.00	349.0	49	196.81	53.12	110.0	149.60	197.00	223.00	320.8
Change from basel. week 24	58	-13.09	63.32	-201.0	-52.00	-12.00	27.00	139.0	51	-3.27	66.38	-153.0	-34.00	-6.00	30.00	155.0
Change from basel. week 52	38	-26.72	75.39	-271.0	-72.10	-13.50	16.00	129.0	30	10.75	70.12	-126.0	-32.00	11.80	54.00	197.0

*Analysis is based on patients that have measurements for all timepoints

Source data: Appendix 16.2.6, Listing 6.1 eff\ippg_des.sas 11APR2012

Table 15.2.2.8: 2 Descriptive statistics of incremental post-prandial glucose (mmol.h/L) over time - FAS (OC)

	Lina 5mg							Placebo						
	N	Mean	SD	Min	Q1	Median	Q3	Max	N	Mean	SD	Min	Q1	Median	Q3	Max
Post-lunch incr. glucose																
Baseline	61	39.09	50.39	-96.0	8.00	43.00	68.50	142.0	59	41.34	40.61	-52.0	11.00	33.00	72.10	149.0
Week 24	65	32.14	53.50	-105.0	-1.00	24.00	59.00	173.0	64	26.10	53.29	-92.0	-3.50	24.50	53.00	161.0
Week 52	44	28.88	55.66	-90.1	0.50	21.50	60.65	157.0	42	52.91	63.53	-55.0	11.00	35.90	82.00	260.0
Change from basel. week 24	41	-11.00	68.04	-124.0	-61.30	-3.00	29.00	175.0	34	-17.80	61.94	-181.0	-41.00	-6.95	25.00	98.0
Change from basel. week 52	25	-18.14	67.82	-142.0	-56.00	-19.80	39.00	105.0	19	7.51	89.60	-70.0	-55.00	-24.00	23.00	234.0
Pre-dinner glucose																
Baseline	73	171.68	58.31	57.0	135.00	167.00	201.80	306.0	80	170.46	62.57	45.0	129.50	168.00	207.50	331.0
Week 24	85	170.05	57.52	75.7	125.00	160.00	211.00	322.0	87	170.36	63.32	90.0	122.50	158.00	202.00	439.0
Week 52	57	164.01	55.65	65.0	127.00	161.00	190.00	323.0	58	171.35	62.75	55.0	132.00	170.50	202.00	437.0
Change from basel. week 24	60	-2.94	74.56	-193.0	-37.80	3.00	47.00	190.0	61	-0.43	77.61	-213.0	-23.00	-5.00	20.00	223.0
Change from basel. week 52	40	-22.70	72.35	-136.0	-77.35	-21.75	19.50	161.0	40	-3.11	80.87	-136.0	-60.50	-18.00	70.75	164.0
Post-dinner glucose																
Baseline	74	202.56	57.96	107.0	162.00	189.60	227.00	365.0	76	208.08	57.31	92.0	166.50	195.50	260.00	337.0
Week 24	82	202.33	60.83	107.0	159.00	192.90	239.00	344.0	81	195.35	67.77	80.0	150.00	185.00	229.00	480.0
Week 52	54	191.95	54.04	92.0	156.00	187.20	220.00	337.0	48	187.64	68.03	66.7	145.90	184.00	225.00	426.0
Change from basel. week 24	60	-5.49	71.12	-241.0	-48.50	-4.50	36.00	182.0	56	-9.69	67.75	-166.0	-47.50	-2.00	31.50	122.0
Change from basel. week 52	36	-18.49	79.63	-144.0	-90.50	-21.00	40.00	158.0	32	-27.93	94.34	-209.0	-92.50	-43.50	21.50	193.0
Post-dinner inc. glucose																
Baseline	70	33.01	48.07	-50.0	-3.60	30.50	59.00	172.0	72	33.75	49.55	-128.0	4.50	34.00	69.00	138.0
Week 24	78	31.37	42.59	-66.0	3.60	30.00	58.00	163.0	70	31.34	40.64	-62.0	3.00	34.50	54.00	166.0
Week 52	48	27.94	53.97	-153.0	-6.50	26.00	61.00	149.0	47	13.24	48.87	-135.1	-11.00	21.00	38.00	116.0
Change from basel. week 24	57	-3.26	66.51	-164.0	-39.60	-9.00	27.00	207.0	46	-1.71	68.15	-134.0	-49.00	-5.50	31.00	197.0
Change from basel. week 52	35	-3.68	65.82	-199.0	-39.70	-2.00	49.00	92.0	28	-25.24	68.50	-151.3	-54.00	-35.50	23.50	139.0
Fasting glucose*																
Baseline	40	147.20	52.65	65.0	111.50	141.20	175.50	289.0	32	134.48	43.46	75.0	98.00	128.50	155.90	232.0
Week 24	40	136.52	33.35	67.0	111.85	141.00	159.00	216.2	32	129.11	40.55	72.0	100.00	127.50	149.50	248.0
Week 52	40	126.31	36.17	67.0	103.25	125.50	149.30	214.0	32	122.91	25.28	73.0	105.50	125.55	140.30	190.0
Change from basel. week 24	40	-10.69	61.22	-169.0	-41.50	-4.50	17.50	122.5	32	-5.37	45.64	-68.0	-41.65	-15.80	24.00	94.0
Change from basel. week 52	40	-20.90	59.14	-151.0	-56.00	-12.00	16.10	87.0	32	-11.58	49.71	-136.0	-39.50	-4.50	20.50	61.0

*Analysis is based on patients that have measurements for all timepoints

Source data: Appendix 16.2.6, Listing 6.1 eff\ippg_des.sas 11APR2012

Table 15.2.2.8: 2 Descriptive statistics of incremental post-prandial glucose (mmol.h/L) over time - FAS (OC)

	Lina 5mg							Placebo						
	N	Mean	SD	Min	Q1	Median	Q3	Max	N	Mean	SD	Min	Q1	Median	Q3	Max
Post-breakfast glucose*																
Baseline	40	206.09	54.58	114.0	161.00	193.50	252.50	314.0	32	205.49	62.45	91.0	150.00	205.20	256.45	348.0
Week 24	40	203.37	59.89	103.0	146.90	197.00	256.50	353.0	32	207.97	62.12	91.0	168.20	202.50	245.00	353.0
Week 52	40	193.40	55.69	104.0	144.00	183.00	237.50	315.0	32	199.21	54.15	101.0	162.00	194.00	235.00	296.0
Change from basel. week 24	40	-2.73	75.23	-139.0	-61.50	-10.50	43.00	181.0	32	2.48	56.66	-136.0	-38.00	-2.50	45.00	148.0
Change from basel. week 52	40	-12.70	67.01	-173.0	-58.50	-10.10	26.50	125.0	32	-6.28	70.96	-157.0	-42.50	-3.50	38.00	134.0
Post-breakfast incr. glucose*																
Baseline	40	58.89	46.73	-41.0	26.95	66.50	93.35	153.0	32	71.01	46.21	-7.0	43.00	56.90	108.50	172.0
Week 24	40	66.85	52.36	-18.0	31.00	55.50	104.50	185.0	32	78.85	60.66	-54.0	36.00	75.70	123.50	215.0
Week 52	40	67.09	54.64	-18.0	25.00	61.95	101.50	237.0	32	76.30	44.23	-20.0	46.00	64.00	107.50	169.0
Change from basel. week 24	40	7.96	60.06	-114.0	-27.50	-6.20	50.00	142.3	32	7.85	42.11	-97.0	-15.00	2.50	33.00	85.0
Change from basel. week 52	40	8.20	53.62	-122.5	-23.50	5.00	30.50	161.0	32	5.29	40.95	-92.0	-17.00	2.50	33.50	106.0
Pre-lunch glucose*																
Baseline	23	147.47	48.70	91.0	104.00	134.00	195.00	251.0	11	154.52	47.33	77.0	117.10	156.00	197.00	228.0
Week 24	23	140.65	51.65	62.0	103.00	138.00	166.00	290.0	11	137.11	45.32	61.0	113.50	129.70	168.00	222.0
Week 52	23	151.72	59.26	76.0	93.70	141.00	191.00	288.0	11	144.87	31.86	91.0	126.00	152.00	160.00	203.0
Change from basel. week 24	23	-6.82	64.02	-138.0	-59.00	-9.00	57.00	96.0	11	-17.41	73.52	-167.0	-90.00	-3.60	37.00	74.0
Change from basel. week 52	23	4.25	78.64	-135.0	-45.00	-16.00	48.60	176.0	11	-9.65	62.40	-114.0	-71.00	-19.00	61.30	83.0
Post-lunch glucose*																
Baseline	23	193.38	47.45	95.5	155.00	196.40	224.00	272.0	11	196.24	56.88	105.0	160.40	179.00	271.00	274.0
Week 24	23	180.36	55.82	104.0	137.00	171.00	211.00	297.0	11	161.65	46.80	78.0	126.00	161.00	201.00	226.0
Week 52	23	177.95	70.77	72.0	122.00	171.20	222.00	349.0	11	199.13	54.38	127.0	145.00	197.00	255.00	273.0
Change from basel. week 24	23	-13.02	64.19	-135.0	-72.00	2.00	32.50	88.0	11	-34.58	80.03	-153.0	-137.00	-13.00	36.00	57.0
Change from basel. week 52	23	-15.43	73.75	-150.0	-81.00	-7.20	41.00	129.0	11	2.89	74.23	-126.0	-73.00	12.60	72.00	120.0
Post-lunch incr. glucose*																
Baseline	23	45.90	58.32	-96.0	8.00	61.00	75.60	142.0	11	41.72	47.18	-52.0	13.00	31.00	76.00	111.0
Week 24	23	39.70	58.90	-105.0	1.00	41.00	75.00	156.0	11	24.55	48.91	-58.0	10.90	33.00	48.00	108.1
Week 52	23	26.23	61.62	-90.1	-16.00	29.00	77.50	130.0	11	54.25	75.63	-55.0	-12.60	45.00	126.00	182.0
Change from basel. week 24	23	-6.20	79.48	-124.0	-83.00	1.00	47.00	175.0	11	-17.17	72.91	-169.0	-46.00	-16.00	45.00	98.0
Change from basel. week 52	23	-19.68	70.50	-142.0	-62.00	-21.00	46.00	105.0	11	12.54	90.34	-61.0	-55.00	-31.00	69.00	234.0

*Analysis is based on patients that have measurements for all timepoints

Source data: Appendix 16.2.6, Listing 6.1 eff\ippg_des.sas 11APR2012

Table 15.2.2.8: 2 Descriptive statistics of incremental post-prandial glucose (mmol.h/L) over time - FAS (OC)

	Lina 5mg							Placebo						
	N	Mean	SD	Min	Q1	Median	Q3	Max	N	Mean	SD	Min	Q1	Median	Q3	Max
Pre-dinner glucose*																
Baseline	33	191.24	63.91	86.0	139.00	181.00	246.90	306.0	18	186.72	73.24	63.0	151.40	187.50	250.00	331.0
Week 24	33	189.30	63.36	86.5	135.00	172.00	228.00	322.0	18	174.89	69.35	90.0	118.00	162.50	204.00	322.0
Week 52	33	174.38	61.66	87.0	130.00	172.00	195.00	323.0	18	174.22	53.88	55.0	144.20	176.00	219.80	256.0
Change from basel. week 24	33	-1.93	81.04	-193.0	-36.00	15.00	52.20	134.0	18	-11.83	86.61	-213.0	-58.00	-5.70	27.00	155.0
Change from basel. week 52	33	-16.85	75.90	-136.0	-75.70	-7.00	23.00	161.0	18	-12.49	73.79	-136.0	-64.00	-17.50	55.80	146.0
Post-dinner glucose*																
Baseline	33	210.06	69.46	107.0	162.00	182.00	272.00	365.0	18	231.53	63.20	132.0	171.00	228.00	299.00	337.0
Week 24	33	221.08	70.60	115.3	163.00	206.00	275.00	344.0	18	217.27	58.08	108.0	185.00	210.50	267.00	324.0
Week 52	33	194.01	56.34	98.0	151.00	188.00	221.00	337.0	18	185.77	59.21	76.0	140.00	186.40	236.00	270.3
Change from basel. week 24	33	11.02	83.04	-241.0	-21.00	20.00	47.00	182.0	18	-14.26	73.41	-152.0	-38.00	-17.90	21.00	114.0
Change from basel. week 52	33	-16.05	80.01	-144.0	-89.00	-20.00	40.00	158.0	18	-45.76	83.30	-209.0	-95.00	-51.50	-7.00	102.7
Post-dinner incr. glucose*																
Baseline	33	18.82	48.25	-50.0	-14.40	10.00	45.00	149.0	18	44.81	51.93	-31.0	-3.00	44.60	87.00	138.0
Week 24	33	31.78	47.75	-59.4	3.60	28.80	52.00	163.0	18	42.38	49.11	-55.0	18.00	48.85	68.00	166.0
Week 52	33	19.62	52.41	-153.0	-10.00	25.00	53.00	119.0	18	11.55	43.16	-72.0	-11.00	11.00	33.00	97.3
Change from basel. week 24	33	12.95	60.54	-71.0	-20.00	2.00	32.40	207.0	18	-2.43	81.63	-134.0	-51.00	-12.70	33.00	197.0
Change from basel. week 52	33	0.80	65.07	-199.0	-28.00	5.00	49.00	92.0	18	-33.26	63.56	-151.3	-58.00	-35.50	22.00	84.0

*Analysis is based on patients that have measurements for all timepoints

Source data: Appendix 16.2.6, Listing 6.1 eff\ippg_des.sas 11APR2012