Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2008-008127-15	
Name of active ingredient: Linagliptin (BI 1356) and Pioglitazone		**Page:** 1 of 16	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Report date: 13 March 2014	**Trial No. / U No.:** 1264.3 / C01655906-01	**Date of trial:** 25 Aug 2010 – 11 Feb 2013	**Date of revision:** Not applicable

Title of trial:	A randomized, double-blind parallel group study to compare the efficacy and safety of initial combination therapy with linagliptin 5 mg + pioglitazone 15 mg, 30 mg, or 45 mg, vs. monotherapy with pioglitazone (15 mg, 30 mg, or 45 mg) or linagliptin 5 mg once daily for 30 weeks, followed by a blinded trial period on linagliptin 5 mg + pioglitazone 30 or 45 mg versus pioglitazone monotherapy 30 or 45 mg or linagliptin 5 mg for up to 54 weeks in type 2 diabetic patients with insufficient glycemic control on diet and exercise This trial was prematurely discontinued. The Sponsor decided not to pursue registration for the fixed dose combinations.
Principal/Coordinating Investigator:	[redacted]
Trial sites:	This multi-center, multinational trial included trial sites in the following participating countries: Estonia, Germany, Great Britain, Latvia, Spain, and the United States of America.
Publication (reference):	Data of this study have not been published
Clinical phase:	III
Objectives:	The primary objective was to demonstrate superior glycemic control (HbA_{1c} reduction) of the linagliptin/pioglitazone FDC versus the respective pioglitazone and linagliptin monotherapies.
Methodology:	Randomized, multi-center, multi-national, double-blind, double-dummy, parallel group design
No. of subjects	
planned:	896 (128 patients from all countries randomized equally to each of the 7 treatment groups in Part A)
actual:	enrolled (screened): 1849

entered (randomly assigned to treatment): 936

Treated in Part A (first 30 weeks): 936

Treatment: linagliptin/pioglitazone 5 mg/15 mg FDC

- entered: 126
- treated: 126
- analyzed (for primary endpoint): 120

Treatment: linagliptin/pioglitazone 5 mg/30 mg FDC

- entered: 133
- treated: 133
- analyzed (for primary endpoint): 125

Treatment: linagliptin/pioglitazone 5 mg/45 mg FDC

- entered: 133; treated: 133
- analyzed (for primary endpoint): 126

Treatment: linagliptin 5 mg monotherapy

- entered: 135
- treated: 135
- analyzed (for primary endpoint): 130

Treatment: pioglitazone 15 mg monotherapy

- entered: 131; treated: 131
- analyzed (for primary endpoint): 124

Treatment: pioglitazone 30 mg monotherapy

- entered: 140
- treated: 140
- analyzed (for primary endpoint): 134

Treatment: pioglitazone 45 mg monotherapy

- entered: 138
- treated: 138

	• analyzed (for primary endpoint): 134
	
	Treated in Part B (following Part A, an additional 54 weeks): 557
	Note: Patients who received linagliptin/pioglitazone 5 mg/15 mg FDC in Part A received linagliptin/pioglitazone 5 mg/30 mg FDC in Part B. Patients who received pioglitazone 15 mg monotherapy in Part A received pioglitazone 30 mg monotherapy in Part B.
	• <u>linagliptin/pioglitazone 5 mg/30 mg FDC</u>
	  • entered: 157
	  • treated: 157
	• <u>linagliptin/pioglitazone 5 mg/45 mg FDC</u>
	  • entered: 80
	  • treated: 80
	• <u>linagliptin 5 mg monotherapy</u>
	  • entered: 85
	  • treated: 85
	• <u>pioglitazone 30 mg monotherapy</u>
	  • entered: 156
	  • treated: 156
	• <u>pioglitazone 45 mg monotherapy</u>
	  • entered: 79
	  • treated: 79

Diagnosis and main criteria for inclusion:	Male or female patients, aged ≥ 18 and ≤ 80 and body mass index (BMI) ≤ 45 kg/m2, and with type 2 diabetes mellitus and insufficient glycemic control (HbA_{1c} ≥ 7.0 to ≤ 10.5%) on diet and exercise alone, without oral antidiabetic drug therapy within 10 weeks prior to start of the run-in period
Test product:	linagliptin/pioglitazone fixed dose combination (FDC)
dose:	5 mg/ 15 mg; 5 mg/ 30 mg; 5 mg / 45 mg

mode of admin.:	oral (po)
batch nos.:	005577, B101001456; 005213, B101000833, 101905; 005214, B101000711, 101906
Reference therapy:	placebo matching linagliptin/pioglitazone FDC5mg/15mg; 5mg/30mg; 5mg/45mg
dose:	n/a
mode of admin.:	oral (po)
batch nos.:	90467, B101001164; 90460, B101001227, B111001936; 90589, B101001312, B101001334, B111001935
Test product:	pioglitazone
dose:	15 mg; 30 mg; 45 mg
mode of admin.:	oral (po)
batch nos.:	B101004845, B101001633; B101004834, 101001632, B111002403; B101004847, B101001630, B111002404
Reference therapy:	placebo matching pioglitazone15 mg; 30 mg; 45 mg
dose:	n/a
mode of admin.:	oral (po)
batch nos.:	B101001122, B101003886, B111002634
Test product:	linagliptin monotherapy
dose:	5 mg
mode of admin.:	oral (po)
batch nos.:	4000427, 4000297, 4000553
Reference therapy:	placebo matching linagliptin monotherapy5 mg
dose:	n/a
mode of admin.:	oral (po)

batch nos.:	4000428, 4000551, 4000280
Duration of treatment:	30 weeks (Visits 3 through 8; Part A) plus up to 54 weeks (Visits 9 through 13; Part B)
Criteria for evaluation:	
Efficacy:	The primary efficacy endpoint was the change from baseline in HbA_{1c} after 30 weeks of treatment. No key secondary endpoints were specified. Additional secondary endpoints were as follows: • Occurrence of cumulative treat-to-target efficacy response, ie, an HbA_{1c} under treatment of < 7.0% after 30 weeks of treatment • Occurrence of cumulative treat-to-target efficacy response, ie, an HbA_{1c} under treatment of < 6.5% after 30 weeks of treatment • Occurrence of relative efficacy response, ie, HbA_{1c} lowering by at least 0.5% after 30 weeks of treatment • HbA_{1c} reduction from baseline by visit over time • Change from baseline in FPG after 30 weeks of treatment • Change from baseline in FPG by visit over time • Change from baseline in post-prandial glucose (PPG) 2 hours after the start of the MTT after 30 weeks of treatment (in the relevant subgroup of participating patients) • Time to first use of rescue therapy during the first 30 weeks of treatment; rescue therapy including any new antidiabetic medication taken for hyperglycemia and introduced on or after the start date of study treatment and before the end date of study treatment • Incidence of rescue therapy during the first 30 weeks of treatment
Safety:	Safety evaluations included the following: • Adverse events • Hypoglycemic events • Protocol-specified significant adverse events • Incidence and severity of edema • Change in use of diuretics • Changes from baseline in vital signs (blood pressure and pulse)

	• Changes from baseline in clinical laboratory values, including lipid profiles, bone markers and BNP • Changes from baseline in physical examination as reported as adverse event • Changes from baseline in 12-lead ECG as reported as adverse event
Statistical methods:	The primary analysis was an analysis of covariance (ANCOVA) on the full analysis set (FAS), with terms for Part A treatment, continuous HbA_{1c} baseline, prior use of antidiabetic agents and country, comparing the change from baseline in HbA_{1c} after 30 weeks of randomized treatment in Part A. The last-observation-carried-forward (LOCF) method was used to handle missing data. Various sensitivity analyses on the primary endpoint were also performed. Change from baseline in fasting plasma glucose (FPG) after 30 weeks of randomized treatment in Part A was also analysed using an ANCOVA (LOCF) on the FAS, with the same terms as the primary analysis model, plus continuous FPG baseline. For secondary analyses, descriptive statistics were produced for changes in HbA_{1c} and fasting plasma glucose (FPG) over time, and for the responder criteria based on HbA_{1c} (< 7.0% and < 6.5% and change from baseline <-0.5%). For meal tolerance test (MTT) results: 2-hour postprandial glucose (PPG) after 30 weeks of randomized treatment was analyzed for the subset of participating patients (MTT set) using an ANCOVA model with the same terms as the primary analysis model, plus continuous 2-hour PPG baseline. A logistic regression model was fitted using the FAS to each of the binary response variables defining i) use of rescue therapy during the first 30 weeks of treatment, and ii) the various HbA_{1c} responder endpoints, with the same terms as for the primary analysis model. This model was used to estimate the odds ratios for the comparison of linagliptin + pioglitazone combination therapy against linagliptin and pioglitazone monotherapies, together with their 95% confidence intervals, for each pioglitazone dose. Time to first rescue therapy use during the first 30 weeks of treatment was presented graphically by Part A treatment for the FAS using Kaplan-Meier survival probability estimates. Safety data were analyzed using descriptive summaries.

Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2008-008127-15	**Synopsis No.:**
Name of active ingredient: Lnagliptin (BI 1356) and Pioglitazone		**Page:** **7 of 16**	
Module:		**Volume:** **{hyperlink }**	
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SUMMARY – CONCLUSIONS:

Efficacy results:

Patient disposition:

Patient disposition is summarized in the table below.

	P15/P30 N (%)	P30 N (%)	P45 N (%)	L5 N (%)	L5P15/ L5P30 N (%)	L5P30 N (%)	L5P45 N (%)	Total N (%)
Randomised	131	140	138	135	126	133	133	936
Treated [1]	131 (100.0)	140 (100.0)	138 (100.0)	135 (100.0)	126 (100.0)	133 (100.0)	133 (100.0)	936 (100.0)
Not prematurely discontinued trial medication	86 (65.6)	101 (72.1)	97 (70.3)	105 (77.8)	90 (71.4)	88 (66.2)	96 (72.2)	663 (70.8)
Prematurely discontinued trial medication	45 (34.4)	39 (27.9)	41 (29.7)	30 (22.2)	36 (28.6)	45 (33.8)	37 (27.8)	273 (29.2)
AEs	6 (4.6)	8 (5.7)	5 (3.6)	5 (3.7)	10 (7.9)	10 (7.5)	6 (4.5)	50 (5.3)
AE study dis. worse	1 (0.8)	1 (0.7)	0 (0.0)	2 (1.5)	1 (0.8)	1 (0.8)	1 (0.8)	7 (0.7)
AE other dis. worse	2 (1.5)	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	5 (0.5)
AE other	3 (2.3)	6 (4.3)	4 (2.9)	3 (2.2)	9 (7.1)	8 (6.0)	5 (3.8)	38 (4.1)
Lack of efficacy [2]	3 (2.3)	2 (1.4)	1 (0.7)	2 (1.5)	1 (0.8)	2 (1.5)	0 (0.0)	11 (1.2)
Non compl. protocol	5 (3.8)	2 (1.4)	4 (2.9)	0 (0.0)	4 (3.2)	3 (2.3)	3 (2.3)	21 (2.2)
Lost to follow-up	7 (5.3)	3 (2.1)	4 (2.9)	3 (2.2)	2 (1.6)	6 (4.5)	5 (3.8)	30 (3.2)
Refused cont. medic.	9 (6.9)	13 (9.3)	10 (7.2)	8 (5.9)	7 (5.6)	9 (6.8)	10 (7.5)	66 (7.1)
Other	15 (11.5)	11 (7.9)	17 (12.3)	12 (8.9)	12 (9.5)	15 (11.3)	13 (9.8)	95 (10.1)

This table includes patients in study Parts A and B combined.
[1]Treated' refers to treatment with randomised study drug.
[2] Includes patients discontinued due to hyperglycemia.

Patients were 54.8% male; mean age was 57 years; and mean baseline HbA_{1c} was 8.11%. The Pio45 group had a higher mean weight at baseline (96.9 kg) than the other groups (93.6 kg, Lina5+Pio15/Lina5+Pio30FDC; 91.8 kg,

Lina5+Pio30FDC; 91.8 kg, Lina5+Pio45FDC; 91.5 kg, Pio15/Pio30; 91.5 kg, Pio30; and 94.7 kg, Lina5). No other important differences were observed between groups in demographic or baseline characteristics.

Primary endpoint:

Adjusted mean HbA_{1c} changes (% [SE]) from baseline and differences between the FDC and the respective monotherapy groups at week 30 from the primary analysis were as follows:

Treatment group (HbA_{1c} change (% [SE])	Lina5Pio15FDC (-0.83 [0.09])	Lina5Pio30FDC (-1.06 [0.09])	Lina5Pio45FDC (-1.28 [0.09])
Lina5 (-0.39 [0.09])	-0.44 (SE 0.12) 95% CI -0.67, -0.20, p=0.0003	-0.68 (SE 0.12) 95% CI -0.91, -0.44, p<.0001	-0.89 (SE 0.12) 95% CI -1.12, -0.66, p<.0001)
Pio monotherapy Pio15 (-0.66 [0.09]) Pio30 (-0.69 [0.09]) Pio45 (-0.87 [0.09])	-0.17 (SE 0.12) 95% CI -0.41, 0.07, p=0.1571	-0.37 (SE 0.12) 95% CI -0.60, -0.14, p=0.0016	-0.41 (SE 0.12) 95% CI -0.64, -0.18, p=0.0006

Changes for each treatment are shown with each treatment name. Differences between treatments are shown in body of table.

Sensitivity analyses on the primary endpoint were consistent with the primary analysis results.

Key secondary endpoints: None.

Other secondary endpoints:

Within group frequencies and between-group comparisons (odds ratios) between FDC and the respective monotherapies of patients with baseline HbA_{1c} ≥7.0% and week 30 HbA_{1c} <7.0% at week 30 are shown below.

Treatment group (Frequency n/N [%])	Lina5Pio15FDC (45/112 [40.2])	Lina5Pio30FDC (61/118 [51.7])	Lina5Pio45FDC (81/121 [66.9])
Lina5 (29/124 [23.4])	2.804 (0.872) 95% CI 1.524, 5.159, p=0.0009	5.429 (1.692) 95% CI 2.947, 10.001, p<.0001	9.614 (3.027) 95% CI 5.187, 17.821, p<.0001

Pio monotherapy Pio15 (39/121 [32.2]) Pio30 (55/125 [44.0]) Pio45 (68/129 [52.7])	1.246 (0.373) 95% CI 0.692, 2.242, p=0.4639	1.746 (0.507) 95% CI 0.989, 3.083, p=0.0546	1.903 (0.548) 95% CI 1.083, 3.345, p=0.0254

Frequencies for each treatment are shown with each treatment name. Comparisons between treatments are shown in body of table.

Within group frequencies and between-group comparisons (odds ratios) between FDC and the respective monotherapies of patients with baseline HbA_{1c} ≥6.5% and week 30 HbA_{1c} <6.5% are shown below.

Treatment group (Frequency n/N [%])	Lina5Pio15FDC (24/120 [20.0])	Lina5Pio30FDC (38/123 [30.9])	Lina5Pio45FDC (43/125 [34.4])
Lina5 (14/129 [10.9])	2.220 (0.837) 95% CI 1.060, 4.649, p=0.0345	4.580 (1.647) 95% CI 2.263, 9.266, p<.0001	5.066 (1.795) 95% CI 2.530, 10.145, p<.0001
Pio monotherapy Pio15 (20/124 [16.1]) Pio30 (28/132 [21.2]) Pio45 (39/134 [29.1])	1.126 (0.396) 95% CI 0.565, 2.243, p=0.7359	1.905 (0.587) 95% CI 1.042, 3.484, p=0.0363	1.269 (0.361) 95% CI 0.726, 2.217, p=0.4039

Frequencies for each treatment are shown with each treatment name. Comparisons between treatments are shown in body of table.

Within group frequencies and between-group comparisons (odds ratios) between FDC and the respective monotherapies of patients with HbA_{1c} decrease of ≥0.5% from baseline at week 30 are shown below.

Treatment group (Frequency n/N [%])	Lina5Pio15FDC (79/120 [65.8])	Lina5Pio30FDC (91/125 [72.8])	Lina5Pio45FDC (107/126 [84.9])
Lina5 (54/130 [41.5])	2.696 (0.722) 95% CI 1.594, 4.559, p=0.0002	4.017 (1.101) 95% CI 2.348, 6.873, p<.0001	8.521 (2.652) 95% CI 4.630, 15.681, p<.0001
Pio monotherapy Pio15 (79/124 [63.7]) Pio30 (83/134 [61.9]) Pio45 (90/134 [67.2])	1.090 (0.298) 95% CI 0.637, 1.863, p=0.7540	1.707 (0.467) 95% CI 0.999, 2.918, p=0.0506	2.966 (0.930) 95% CI 1.604, 5.485, p=0.0005

Frequencies for each treatment are shown with each treatment name. Comparisons between treatments are shown in body of table.

The change from baseline in mean HbA_{1c} by visit over time was assessed for all groups by visit (weeks 6, 12, 18, 24 and 30 in Part A). For this synopsis, descriptive statistics (observed cases) are shown at 30 weeks of treatment as follows:

	HbA_{1c} reduction from baseline over time
	Mean % change (SD), n
Lina5Pio15FDC	-1.07 (0.76) n=86
Lina5Pio30FDC	-1.23 (1.00) n=87
Lina5Pio45FDC	-1.36 (0.94) n=97
Lina5	-0.61 (0.73) n=79
Pio15	-1.07 (0.70) n=78
Pio30	-0.91 (0.78) n=93
Pio45	-1.21 (0.97) n=91

Adjusted mean FPG (mg/dL, SE) changes from baseline and differences between the FDC and the respective monotherapy groups at week 30 are shown below.

Treatment group Mean change (SE)	Lina5Pio15FDC -18.84 (3.47) n=119	Lina5Pio30FDC -27.33 (3.46) n=123	Lina5Pio45FDC -35.19 (3.40) n=125
Lina5 -1.46 (3.35) n=130	-17.38 (SE 4.57) 95% CI -26.35, -8.41, p=0.0002	-25.87 (SE 4.53) 95% CI -34.77, -16.98, p<.0001	-33.73 (SE 4.50) 95% CI -42.57, -24.89, p<.0001
Pio monotherapy Pio15 -15.16 (3.49) n=123 Pio30 -25.49 (3.28) n=133 Pio45 -28.69 (3.29) n=134	-3.68 (SE 4.63) 95% CI -12.77, 5.42, p=0.4275	-1.84 (SE 4.51) 95% CI -10.69, 7.02, p=0.6839	-6.50 (SE 4.48) 95% CI -15.29, 2.28, p=0.1466

Changes for each treatment are shown with each treatment name. Differences between treatments are shown in body of table.

The change from baseline in mean FPG (mg/dL) by visit over time was assessed for all groups by visit (weeks 6, 12, 18, 24 and 30 in Part A). For this synopsis, descriptive statistics (observed case) are shown at 30 weeks of treatment as

follows:

	FPG (mg/dL) reduction from baseline over time Mean change (SD), n
Lina5Pio15FDC	-24.11 (32.60) n=82
Lina5Pio30FDC	-27.05 (33.99) n=87
Lina5Pio45FDC	-34.20 (41.43) n=98
Lina5	-0.72 (31.40) n=79
Pio15	-21.92 (31.61) n=76
Pio30	-27.44 (36.44) n=91
Pio45	-38.60 (32.77) n=89

The adjusted mean 2-hour PPG (mg/dL, SE) changes from baseline and differences between the FDC and the respective monotherapy groups at week 30 are shown below.

Treatment group Mean change (SE)	Lina5Pio15FDC -67.26 (11.15), n=28	Lina5Pio30FDC -87.94 (11.14), n=26	Lina5Pio45FDC -84.77 (10.28), n=31
Lina5 -51.61 (11.67), n=22	-15.65 (14.16) 95% CI -43.60, 12.30, p=0.2706	-36.33 (14.42) 95% CI -64.78, -7.89, p=0.0126	-33.16 (13.72) 95% CI -60.23, -6.08, p=0.0167
Pio monotherapy Pio15 -30.65 (10.93), n=29 Pio30 -83.00 (9.85), n=34 Pio45 -82.98 (10.92), n=25	-36.61 (13.08) 95% CI -62.42, -10.80, p=0.0057	-4.94 (12.90) 95% CI -30.39, 20.51, p=0.7021	-1.78 (13.26) 95% CI -27.95, 24.38, p=0.8932

Changes for each treatment are shown with each treatment name. Differences between treatments are shown in body of table.

Medians from the Kaplan-Meier analysis of time to first rescue therapy use were not defined in any treatment group, because there were not sufficient events. The median (min, max) relative days of rescue therapy during the first 30 weeks of treatment for those patients who had rescue therapy were as follows:

	Time (days) to first use of rescue therapy in the first 30 weeks[1] Median (min, max)
Lina5Pio15FDC n=12	171.0 (6, 202)

Lina5Pio30FDC n=10	130.5 (7, 197)
Lina5Pio45FDC n=5	173.0 (38, 201)
Lina5 n=26	134.0 (17, 194)
Pio15 n=20	140.5 (42, 204)
Pio30 n=17	173.0 (15, 199)
Pio45 n=11	173.0 (20, 179)

Within group frequencies and between-group comparisons (odds ratios) between FDC and the respective monotherapies in frequency of rescue therapy use are shown below.

Treatment group Frequency n/N (%)	Lina5Pio15FDC 12/120 (10.0)	Lina5Pio30FDC 10/125 (8.0)	Lina5Pio45FDC 5/126 (4.0)
Lina5 26/130 (20.0)	0.368 (0.151) 95% CI 0.165, 0.821, p=0.0146	0.238 (0.103) 95% CI 0.102, 0.557, p=0.0009	0.141 (0.074) 95% CI 0.050, 0.397, p=0.0002
Pio monotherapy Pio15 20/124 (16.1) Pio30 17/134 (12.7) Pio45 11/134 (8.2)	0.649 (0.273) 95% CI 0.284, 1.482, p=0.3052	0.456 (0.207) 95% CI 0.187, 1.112, p=0.0844	0.443 (0.254) 95% CI 0.143, 1.365, p=0.1561

Frequencies for each treatment are shown with each treatment name. Comparisons between treatments are shown in body of table.

The adjusted mean body weight (kg) changes from baseline and differences between the FDC and the respective monotherapy groups at week 30 are shown below.

Treatment group Mean change (SE)	Lina5Pio15FDC 0.96 (0.76), n=86	Lina5Pio30FDC 1.50 (0.74), n=87	Lina5Pio45FDC 0.63 (0.70), n=99
Lina5 -0.62 (0.76), n=81	1.58 (0.96) 95% CI -0.31, 3.48, p=0.1007	2.12 (0.96) 95% CI 0.24, 4.00, p=0.0272	1.25 (0.93) 95% CI -0.57, 3.07, p=0.1776

	-0.57 (0.98) 95% CI -2.49, 1.35, p=0.5585		
Pio15 1.53 (0.78), n=76			
		-0.30 (0.93) 95% CI -2.12, 1.52, p=0.7478	
Pio30 1.79 (0.72), n=92			
			-2.61 (0.91) 95% CI -4.39, -0.83, p=0.0042
Pio45 3.24 (0.73), n=90			

Changes for each treatment are shown with each treatment name. Differences between treatments are shown in body of table.

Safety results:

Safety data were analyzed for all 936 patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment in Part A (treated set [TS]), and the 557 patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment in Part B (treated set two [TS2]).

In Parts A and B combined, the mean exposure of patients to treatment ranged from 298 to 334 days among the treatment groups; median exposure ranged from 248 to 337 days. Also in Parts A and B combined, the largest proportions of patients in all groups were exposed to study medication for > 30 to 36 weeks; the overall duration of exposure to study treatment ranged from 106.7 to 123.6 patient years.

The overall frequency of patients with reported AEs was similar among the treatment groups, ranging from 65.7% to 74.6% of patients, in Parts A and B combined.

The frequency of patients in each treatment group with AEs of severe intensity varied among treatment groups, ranging from 1.5% to 8.4%. Important differences between groups were not observed in the intensity of AEs.

Related AEs (as assessed by the investigator), and other significant AEs (according to ICH E3), were reported for similar percentages of patients among the treatment groups.

All treatment groups had patients with AEs leading to treatment discontinuation; the

frequency ranged from 3.6% to 9.5% among the treatment groups. No clinically meaningful differences were observed between treatment groups in percentages of patients with AEs leading to premature discontinuation.

Adjudication results by the independent CEC confirmed no nonfatal strokes, five patients with nonfatal myocardial infarction (n=2, Lina5+Pio30FDC; n=1, Lina5; n=1, Pio15/Pio30; n=1, Pio30), one patient with unstable angina (Lina5), and one patient (Lina5+Pio15/Lina5+Pio30FDC group) hospitalized for heart failure.

One death occurred during the treatment period: a [redacted] patient in the Pio45 group experienced colon cancer on day 313 of treatment; concurrent SAEs included tumor invasion, anaemia, and fatigue; the patient also experienced a post-treatment episode of acute pulmonary edema. In addition, three deaths were reported during the post-treatment period (n=2, Lina5+Pio30FDC; n=1, Pio30). No deaths were considered related to study treatment.

Overall, serious adverse events (SAEs) were reported across treatment groups in both study parts combined at frequencies ranging from 3.6% (Pio45) to 11.3% (Lina5+Pio30FDC). The most frequently occurring SAEs (3 patients each) included acute myocardial infarction (n=2, Lina5+Pio30FDC; n=1, Pio30), myocardial infarction (n=1 each, Lina5, Pio15/Pio30, Pio30) and atrial fibrillation (n=1, Lina5+Pio45FDC; n=1, Lina5+Pio15/Lina5+Pio30FDC; n=1, Pio45).

The frequency of investigator-defined hypoglycemic AEs in Part A and B combined (TS) was ≤1.5% (n≤2) of patients per treatment group. Clinically important differences were not observed between groups. Nine patients had investigator-defined hypoglycemic AEs.

Protocol-specified significant adverse events were defined as hypersensitivity reactions, selected hepatic adverse events, selected renal adverse events, cutaneous skin lesions, and pancreatitis. Overall, protocol-specified significant AEs were rare (≤1.4% of patients in any treatment group with a preferred term of a protocol-specified significant AE). No AEs of bladder cancer were reported. One patient had pancreatic cancer (Lina5+Pio15/Lina5+Pio30FDC group) and one patient had pancreatitis (Pio15/Pio30 group).

Pre-defined AEs of edema (specific terms for edema and peripheral edema) were

	reported in each of the treatment groups in an overall total of 78 patients. The largest frequency occurred in the Lina5+Pio45FDC treatment group (12.8%) and lowest frequency in the Lina5 monotherapy group (4.4%). Peripheral edema was more frequent than edema and was observed in all treatment groups, with the lowest frequency in the Lina5 group (4.4%), a frequency of 6.3% to 11.3% in the FDC groups, and 7.9% to 9.9% in the Pio monotherapy groups. The FDC groups had lower frequencies of AEs of increased weight (1.6%, Lina5+Pio15/Lina5+Pio30FDC; 3.0%, Lina5+Pio30FDC; 0.8%, Lina5+Pio45FDC) compared with the pioglitazone monotherapy groups (3.1%, Pio15/Pio30; 4.3%, Pio30; 2.9%, Pio45) and the Lina monotherapy group (0%); AEs of decreased weight were infrequent. Cardiac failure, based on narrow SMQs, occurred in 0% to 1.5% of patients in the FDC groups (Lina5+Pio30FDC group: chronic cardiac failure [n=1] and cardiopulmonary failure [n=1]; Lina5+Pio15/Lina5+Pio30FDC group: congestive cardiac failure [n=1]). No other cardiac failures were identified per narrow SMQs. Vital signs remained consistent across treatment groups and throughout the treatment periods. No new safety concerns were identified with reported laboratory values. No safety concerns were identified through analyses of changes from baseline in physical examination reported as adverse events. ECG parameters remained consistent across treatment groups and throughout the treatment period. No clinically important differences were noted in safety findings between Part A and Parts A and B combined. The overall safety profiles of the FDCs were similar to the known safety profiles of the individual components. No unexpected safety findings occurred in this study.
Conclusions:	The primary analysis showed that treatment with all of the FDCs of linagliptin 5 mg and pioglitazone 15 mg, 30 mg or 45 mg for 30 weeks led to reductions in HbA_{1c} compared with the respective monotherapies in patients with T2DM and insufficient glycaemic control. The greatest decreases in mean HbA_{1c} were observed in the FDC groups vs. linagliptin monotherapy, followed by the FDC groups vs. pioglitazone monotherapy. Differences were clinically meaningful and statistically significant

($p<0.05$) in all comparisons; except with the Lina5+Pio15FDC vs. Pio15 comparison which showed a modest statistically non-significant reduction. Sensitivity analyses were consistent with the results of the primary analysis.

Consistent efficacy results were also observed with both FDCs after 30 weeks for other secondary endpoints including the occurrence of cumulative treat-to-target efficacy responses in HbA_{1c} ($HbA_{1c} < 7.0\%$; $HbA_{1c} < 6.5\%$, and HbA_{1c} lowering by at least 0.5%), HbA_{1c} reduction from baseline by visit over time, change from baseline in FPG at 30 weeks and by visit over time, and time to first use and incidence of use of rescue therapy. The adjusted mean changes in body weight from baseline to week 30 shown by the different groups may suggest associations with the treatments; further study may be warranted.

The overall safety profiles of the FDCs were similar to the known safety profiles of the individual components in this study. The incidence of hypoglycaemic events during treatment was low. Predefined AEs of edema were reported in each of the treatment groups with the largest frequency in the Lina5+Pio45FDC treatment group and the lowest frequency in the Lina5 monotherapy group. Peripheral edema was more frequent than edema. Cardiac failure was infrequent. No incidences of bladder cancer were observed.

The FDC treatments were efficacious and well tolerated and the safety profile was comparable with the known safety profiles for the individual monotherapies. No unexpected safety findings occurred in this study.