Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
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Title of trial:	A randomised, double-blind, double-dummy, active-comparator controlled study investigating the efficacy and safety of linagliptin co-administered with metformin QD at evening time versus metformin BID over 14 weeks in treatment naive patients with type 2 diabetes mellitus and insufficient glycaemic control
Coordinating Investigator:	[redacted] China
Trial sites:	Multicenter trial in 88 sites in 14 countries (Belgium, Canada, China, Germany, Spain, India, Bangladesh, Guatamala, Mexico, Peru, Taiwan, Hong Kong, Lebanon, and the Philippines)
Publication (reference):	Data from this trial have not been published.
Clinical phase:	IV
Objectives:	To assess the efficacy and safety of linagliptin 5 mg in combination with metformin once daily (maximum daily dose 1000 mg) vs. metformin alone twice daily (minimum daily dose 1000 mg, maximum daily dose 2000 mg)
Methodology:	Randomised, double-blind, double-dummy, active-comparator controlled, parallel-group comparison
No. of subjects:	
planned:	entered: 680
actual:	enrolled: 1149 entered: 689 Linagliptin 5 mg in combination with metformin once daily (lina+met qd): entered: 344 treated: 344 analysed (for primary endpoint): 298 Metformin alone twice daily (met bid): entered: 345 treated: 345 analysed (for primary endpoint): 341

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Diagnosis and main criteria for inclusion:	Treatment-naïve patients (absence of any oral or injectable antidiabetic therapy for at least 12 weeks before randomisation) with type 2 diabetes mellitus; age ≥18 to ≤80 years; BMI ≤45 kg/m^2; HbA_{1c} 7.0% to 10.0% after global amendment 1 (6.5% to 10.0% in the original protocol)
Test product:	Linagliptin, tablet
dose:	5 mg, once daily
mode of admin.:	Oral
batch no.:	4000427
Reference therapy 1:	Placebo matching linagliptin 5 mg, tablet
dose:	Not applicable, once daily
mode of admin.:	Oral
batch no.:	4000428
Reference therapy 2:	Metformin, tablet
dose:	Starting from 500 mg daily, to be up-titrated to the maximal tolerated dose (maximum daily dose of 1000 mg for the once daily arm and 2000 mg for the twice daily arm) within 2 weeks; once daily in linagliptin+metformin arm or twice daily in metformin alone arm
mode of admin.:	Oral
batch no.:	251180, X2034, X2042
Reference therapy 3:	Placebo matching metformin 500 mg, tablet
dose:	Not applicable; once daily in linagliptin + metformin arm or twice daily in metformin alone arm
mode of admin.:	Oral
batch no.:	88058, 88059, 96921
Duration of treatment:	After 2 weeks of placebo run-in period, eligible patients were randomised to the two treatment arms and treated for 14 weeks in a double-blinded fashion, followed by a 1-week follow-up period.

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Criteria for evaluation:

Efficacy:

Primary endpoint: the change from baseline in HbA_{1c} after 14 weeks of treatment

Key secondary endpoints:

- The proportion of patients who achieved all the targets in a composite endpoint (HbA_{1c} below 7.0% after 14 weeks of treatment; no occurrence of pre-specified moderate or severe gastrointestinal (GI) side effects of metformin, as assessed by the investigators during 14 weeks of treatment)
- The occurrence of pre-specified moderate or severe GI side effects of metformin, as assessed by the investigators during 14 weeks of treatment

Other exploratory secondary endpoints:

- The change from baseline in fasting plasma glucose (FPG) after 14 weeks of treatment
- The intensity (mild, moderate, or severe) of pre-specified GI side effects of metformin, as assessed by the investigators during 14 weeks of treatment
- The intensity scores (based on visual analogue scale (VAS)) of pre-specified GI side effects of metformin, as assessed by the patients during 14 weeks of treatment
- The proportion of patients who achieved all the targets in a composite endpoint (HbA_{1c} below 6.5% after 14 weeks of treatment; no occurrence of pre-specified moderate or severe GI side effects of metformin, as assessed by the investigators during 14 weeks of treatment)
- The occurrence of a relative efficacy response (HbA_{1c} lowered by at least 0.5% after 14 weeks of treatment)
- The occurrence of a relative efficacy response (HbA_{1c} lowered by at least 0.8% after 14 weeks of treatment)
- The proportion of patients who achieved all the targets in a composite endpoint (HbA_{1c} lowered by at least 0.5% after 14 weeks of treatment; no occurrence of pre-specified moderate or severe GI side effects of metformin, as assessed by the investigators during 14 weeks of treatment)
- The proportion of patients who achieved all the targets in a composite endpoint (HbA_{1c} lowered by at least 0.8% after 14 weeks of treatment; no occurrence of pre-specified moderate or severe GI side effects of metformin, as assessed by the investigators during 14 weeks of treatment)

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	• The change from baseline in HbA_{1c} by visit over time • The change from baseline in body weight by visit over time Other exploratory efficacy endpoints: • The occurrences of a treat-to-target response (HbA_{1c} below 7.0% after 14 weeks of treatment) • The occurrences of a treat-to-target response (HbA_{1c} below 6.5% after 14 weeks of treatment) • The use of rescue therapy
Safety:	All adverse events (AEs), hypoglycaemic events, changes from baseline in vital signs (blood pressure and pulse rate; to be recorded as adverse events if considered to be clinically relevant by the investigators), changes from baseline in ECG and clinical laboratory values (to be recorded as adverse events if considered to be clinically relevant by the investigators), withdrawal due to adverse events, and adverse events of special interest
Statistical methods:	Non-inferiority followed by superiority for the primary endpoint in a hierarchical sequence was tested for the treatment effect of linagliptin in combination with metformin once daily compared with the treatment effect of metformin alone twice daily. Key secondary endpoints were tested subsequently in the hierarchical sequence. The overall significance level was 5% (2-sided). Primary analysis: analysis of covariance (ANCOVA) based on the full analysis set (FAS_{1000mg}; excluding patients who did not tolerate a minimum daily dose of metformin 1000 mg at the end of the titration phase); the model included treatment as a fixed effect and baseline HbA_{1c} as a linear covariate Key secondary analyses: logistic regression models with treatment as a fixed effect and baseline HbA_{1c} as a covariate Explorative and descriptive statistics were provided for the other efficacy endpoints and safety parameters.

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SUMMARY – CONCLUSIONS:

Efficacy results:

Of the 1149 patients enrolled in this study, 689 were randomised, with 344 patients to the linagliptin+metformin once daily arm and 345 to the metformin alone twice daily arm. Of the 689 randomised patients, 51.1% were from Asia (Bangladesh, China, Hong Kong, India, Lebanon, the Philippines, Taiwan), 26.0% from South America (Guatemala, Mexico, Peru), the rest from North America (12.8%; Canada only) and Europe (10.2%; Belgium, Germany, Spain).

All randomised patients were treated with at least 1 dose of study medication. Of the 689 treated patients, 661 patients (95.9%) completed 14 weeks of treatment, whereas 28 patients (4.1%; 14 patients in either treatment arm) prematurely discontinued study medication. The most common reason for premature discontinuation was lost to follow-up and refusal to continue trial medication in the linagliptin+metformin once daily arm (4 patients, 1.2% for both reasons) and other reasons in the metformin alone twice daily arm (4 patients, 1.2%).

Among the treated patients, 47.5% were men. Almost half of the patients were Asian (47.6%); about a quarter of the patients were American Indian or Alaska Native (26.7%) and the other quarter White (25.3%); 3 patients (0.4%) were Black or African American. Almost all patients had either normal renal function (47.5%) or mild renal impairment (50.1%) at baseline, based on eGFR MDRD. Mean (standard deviation) age was 53.0 (10.7) years, baseline BMI 29.0 (5.6) kg/m^2, baseline HbA_{1c} 7.97% (0.88%; based on FAS_{1000mg}), and baseline FPG 156.5 (39.3) mg/dL (based on FAS_{1000mg}). In the FAS_{1000mg}, most of the patients (80.9%) had been diagnosed with diabetes for up to 5 years. The demographic and baseline characteristic parameters were in general balanced among the 2 treatment arms.

Treatment compliance was assessed at each visit, based on tablet count of dispensed and returned medication, and based on the FAS_{1000mg}. The accepted compliance window was 80 to 120%. For all visits, more than 97% of the patients in either treatment arm were compliant.

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Efficacy results (continued):

Efficacy analyses were mainly based on the FAS_{1000mg}, which is comprised of all patients in the full analysis set who tolerated a daily metformin dose of at least 1000 mg at the end of the titration phase. The main results for the primary and the 2 key secondary endpoints are summarised in the table below.

With regards to HbA_{1c} lowering after 14 weeks of treatment (the primary endpoint), the linagliptin+metformin once daily treatment was non-inferior to metformin alone twice daily, with a non-inferiority margin of 0.35%; the linagliptin+metformin once daily was not superior to metformin alone twice daily in this regard.

No treatment difference was seen in the 2 key secondary endpoints, which evaluated the proportion of patients with an HbA_{1c} of below 7.0% after 14 weeks combined with the absence of pre-specified moderate or severe GI side effects, as well as the proportion of patients with these moderate or severe GI events.

All sensitivity analyses (based on different analysis sets, imputation methods, or models) for all primary and key secondary endpoints showed results consistent with the main analysis for the respective endpoint.

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Efficacy results (continued):

Primary and key secondary endpoints based on FAS_{1000mg}

	Lina+met qd	Met bid
Number of patients in FAS_{1000mg}	298	341
Primary endpoint: HbA_{1c} [%] change from baseline at Week 14		
Baseline mean (standard error (SE))	7.97 (0.06)	7.97 (0.04)
Adjusted mean change (SE)	-0.99 (0.05)	-0.98 (0.04)
Comparison vs. met bid adjusted mean (SE)	-0.01 (0.06)	--
95% confidence interval	-0.13, 0.12	
p-value non-inferiority (margin 0.35%)	<0.0001	
p-value superiority	0.8924	
First key secondary endpoint: the proportion of patients who achieved HbA_{1c} below 7.0% and without occurrence of pre-specified moderate or severe GI side effects of metformin (assessed by the investigators) after 14 weeks of treatment		
Number of responders overall	51.3%	51.3%
With baseline HbA_{1c} ≥7.0%	46.3%	48.4%
Odds ratio (95% CI) vs. met bid	0.96 (0.67, 1.37)	--
p-value	0.8201	
Second key secondary endpoint: the proportion of patients with pre-specified moderate or severe GI side effects of metformin (assessed by the investigators) during 14 weeks of treatment		
Number of patients with events	8.4%	8.2%
Odds ratio (95% CI) vs. met bid	1.02 (0.58, 1.80)	--
p-value (exploratory)	0.9397	

A total of 10 other exploratory secondary endpoints were assessed based on FAS_{1000mg}; they are described below.

The change from baseline in FPG was similar in the 2 treatment arms: adjusted mean (SE) was -24.5 (1.5) mg/dL for the linagliptin+metformin once daily arm and -26.6 (1.4) mg/dL for the metformin alone twice daily arm after 14 weeks of treatment.

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Efficacy results (continued):

The proportion of patients reported with pre-specified GI events was slightly lower in the linagliptin+metformin once daily arm (24.5%, 73 patients) than in the metformin alone twice daily arm (28.7%, 98 patients); the difference was mainly caused by a lower proportion of patients in the linagliptin+metformin arm having mild events (18.5%, 55 patients, vs. metformin alone arm: 24.3%, 83 patients). The total number of GI events was lower in the linagliptin+metformin once daily arm (157) than in the metformin alone twice daily arm (219), and there was an association between the severity of events and treatment (Chi-square test p=0.0314; Fishers exact p=0.0308).

Most of the patients had the first GI event during the titration period in the first 2 weeks in both arms, with numerically higher GI events in the metformin alone twice daily arm than in the linagliptin+metformin once daily arm.

A retrospective review of the types of pre-specified GI events showed that the most frequent event was diarrhoea, reported by a numerically lower proportion of patients in the linagliptin+metformin once daily arm (16.3%) than in the metformin alone twice daily arm (19.4%).

The intensity scores (based on VAS) of pre-specified GI side effects of metformin, as assessed by the patients during 14 weeks of treatment, were similar in the 2 treatment arms: adjusted mean (SE) was 4.9 (0.2) for the linagliptin+metformin once daily arm and 4.4 (0.2) for the metformin alone twice daily arm.

The proportion of patients who achieved HbA_{1c} below 6.5% and without occurrence of pre-specified moderate or severe GI side effects of metformin (assessed by the investigators) after 14 weeks of treatment was similar in the 2 treatment arms: overall 30.2% for the linagliptin+metformin once daily arm and 28.7% for the metformin alone twice daily arm.

The proportion of patients with HbA_{1c} lowered by at least 0.5% after 14 weeks of treatment was similar in the 2 treatment arms: overall 70.8% in the linagliptin+metformin once daily arm and 75.4% in the metformin alone twice daily arm.

The proportion of patients with HbA_{1c} lowered by at least 0.8% after 14 weeks of treatment was similar in the 2 treatment arms: overall 54.4% in the linagliptin+metformin once daily arm and 54.8% in the metformin alone twice daily arm.

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Efficacy results (continued):

The proportion of patients who achieved HbA_{1c} lowering by at least 0.5% and without occurrence of pre-specified moderate or severe GI side effects of metformin (assessed by the investigators) after 14 weeks of treatment was similar in the 2 treatment arms: 65.1% for the linagliptin+metformin once daily arm and 69.2% for the metformin alone twice daily arm.

The proportion of patients who achieved HbA_{1c} lowering by at least 0.8% and without occurrence of pre-specified moderate or severe GI side effects of metformin (assessed by the investigators) after 14 weeks of treatment was similar in the 2 treatment arms: 50.0% for the linagliptin+metformin once daily arm and 51.3% for the metformin alone twice daily arm.

The change from baseline in HbA_{1c} over time showed very similar profiles in the 2 treatment arms. For both treatment arms, there was a steep decrease in HbA_{1c} in the first 8 weeks and a less steep decrease between Week 8 and 14.

Small decreases in body weight from baseline over time were seen in both treatments. The decrease was slightly more prominent in the metformin alone twice daily arm (adjusted mean=-1.05 kg, SE=0.13 kg) than in the linagliptin+metformin once daily arm (adjusted mean=-0.44 kg, SE=0.14 kg) after 14 weeks of treatment.

Three other exploratory efficacy endpoints were evaluated based on FAS_{1000mg} and are described below.

The proportion of patients achieving HbA_{1c} below 7.0% after 14 weeks of treatment was similar in the 2 treatment arms: overall 56.7% for the linagliptin+metformin once daily arm and 56.3% for the metformin alone twice daily arm.

The proportion of patients achieving HbA_{1c} below 6.5% after 14 weeks of treatment was similar in the 2 treatment arms: overall 32.9% for the linagliptin+metformin once daily arm and 31.7% for the metformin alone twice daily arm.

Fewer patients used rescue therapy in the linagliptin+metformin once daily arm (1 patient, 0.3%) than in the metformin alone twice daily arm (6 patients, 1.8%).

The mean (SD) metformin dose at Week 14 was 939.9 (162.8) mg/day in the linagliptin+metformin once daily arm (N=333) and 1798.5 (348.9) mg/day in the metformin alone twice daily arm (N=335).

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Safety results:

Exposure to study medication was balanced between treatment arms, with mean exposures (SD) of 97.3 (14.1) days in the linagliptin+metformin once daily arm and 97.5 (13.0) days in the metformin alone twice daily arm. The mean (SD) metformin dose after the titration period (at Day 14) was 940.8 (161.7) mg/day in the linagliptin+metformin once daily arm and 1798.5 (347.6) mg/day in the metformin alone twice daily arm; thereafter, no patient was recorded to have changed metformin daily dose.

An overview of the adverse events is summarised below based on the treated set; the frequency for each AE type was comparable in both arms (except investigator-defined hypoglycaemic AEs and serious AEs, which were more common in the metformin alone twice daily arm).

	Lina+met qd		Met bid	
	N	(%)	N	(%)
Number of patients	344	(100.0)	345	(100.0)
Patients with any AE	219	(63.7)	229	(66.4)
Patients with severe AEs	12	(3.5)	9	(2.6)
Patients with investigator defined drug-related AEs	71	(20.6)	80	(23.2)
Patients with other significant AEs (according to ICH E3)	7	(2.0)	6	(1.7)
Patients with AEs leading to discontinuation of study medication	3	(0.9)	3	(0.9)
Investigator-defined hypoglycaemic AE	2	(0.6)	6	(1.7)
Patients with AEs of special interest (pre-specified events)	6	(1.7)	5	(1.4)
Hypersensitivity reactions	1	(0.3)	1	(0.3)
Cutaneous skin lesions	0		0	
Hepatic adverse events	5	(1.5)	9	(2.6)
Renal adverse events	0		0	
Pancreatitis	1	(0.3)	0	
Patients with serious AEs	2	(0.6)	7	(2.0)
Requiring hospitalisation	1	(0.3)	7	(2.0)
Other SAEs	1	(0.3)	0	

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Safety results (continued):

The highest frequency of AEs was reported for the MedDRA system organ class gastrointestinal disorders, with frequencies of 33.7% in the linagliptin+metformin once daily arm and 35.1% in the metformin alone twice daily arm. For adverse events with a frequency of above 2% in either treatment arm at preferred term level, the following were less frequent in the linagliptin+metformin once daily arm than in the metformin alone twice daily arm: diarrhoea (18.0% vs. 21.4%), abdominal pain (6.7% vs. 8.7%), urinary tract infection (4.9% vs. 9.9%), dyspepsia (1.7% vs. 3.5%), and decreased appetite (1.7% vs. 3.5%); on the other hand, the following AEs were more frequent in the linagliptin+metformin once daily arm than in the metformin alone twice daily arm: nasopharyngitis (4.9% vs. 2.9%; a recognised adverse drug reaction for linagliptin) and asymptomatic bacteriuria (2.3% vs. 0.9%).

Most of the adverse events were mild or moderate. Mild diarrhoea was reported less often in the linagliptin+metformin once daily arm (11.6%) than in the metformin alone twice daily arm (15.4%); on the other hand, severe diarrhoea was reported only in the linagliptin+metformin once daily arm (4 patients, 1.2%). Severe increased lipase was reported for 2 patients (0.6%) in the linagliptin+metformin once daily arm and 1 patient (0.3%) in the metformin alone twice daily arm. All other severe adverse events were reported for no more than 1 patient in either treatment arm.

The highest frequency of drug-related AEs was reported for the system organ class gastrointestinal disorders. At the preferred term level, the most common drug-related AEs were diarrhoea (9.3% vs. 12.8%), abdominal pain (4.9% vs. 5.5%), nausea (4.4% vs. 4.9%), and decreased appetite (1.5% vs. 2.6%), all with slightly lower frequencies reported in the linagliptin+metformin once daily arm than in the metformin alone twice daily arm.

Few patients had investigator-defined hypoglycaemic adverse events; none of these patients had a recorded plasma glucose level of <54 mg/dL and no patient had any severe hypoglycaemic event requiring external assistance.

No deaths occurred in this trial. Serious AEs at preferred term level were reported for no more than 2 patients in either treatment arm.

No patient had any cardiac or cerebrovascular event confirmed by the clinical event committee. No patient had any confirmed case of hospitalisation for heart failure.

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Safety results (continued):	Adverse events of special interest were infrequent in both treatment arms. One report in the linagliptin+metformin once daily arm of acute pancreatitis, based on only laboratory abnormalities (elevated amylase and lipase values), was received; however, the case did not meet the diagnostic criteria for acute pancreatitis. No patient was reported with pancreatic cancer. No relevant changes from baseline and no relevant differences between the 2 treatment arms were observed in safety laboratory parameters or vital signs. Particularly, no relevant differences were seen in amylase laboratory values between the 2 treatment arms.
Conclusions:	In this randomised double-blind study, treatment with linagliptin 5 mg in combination with metformin once daily was compared to metformin alone twice daily, in treatment-naïve patients with type 2 diabetes mellitus and insufficient glycaemic control. Both treatments showed clinically meaningful glycaemic control, with around half of the patients achieving a clinically relevant HbA_{1c} target of below 7.0% after 14 weeks. The linagliptin and metformin once daily treatment was non-inferior to the metformin alone twice daily treatment in lowering HbA_{1c} after 14 weeks. There were no obvious differences between the observed adverse events and the known safety profiles. Fewer serious adverse drug reactions and fewer investigator-defined hypoglycaemic events were observed with the linagliptin and metformin once daily treatment. Protocol-prespecified moderate and severe gastrointestinal side effects were similar for the 2 treatments; however, the once-daily treatment led to fewer patients with mild gastrointestinal side effects. The most frequent gastrointestinal event was diarrhoea, which was lower in patients treated with the once-daily therapy. Furthermore, the total number of gastrointestinal events was reduced with the once-daily treatment. The results of this study support the convenient once-daily dosing regimen of linagliptin 5 mg in combination with metformin.