
Press Release

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Boehringer Ingelheim announces results of phase III data showing that linagliptin significantly lowered blood glucose with an excellent safety and tolerability profile

New phase III data demonstrate clinically meaningful improvements in blood glucose control with linagliptin mono- and combination therapy

Ingelheim, Germany, 26th June 2010 - Linagliptin phase III data were presented for the first time this week at the 70th Scientific Sessions of the American Diabetes Association (ADA), showing that this investigational compound, a dipeptidyl peptidase (DPP)-4 inhibitor, achieved significant, sustained and clinically meaningful reductions in blood glucose as measured by haemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG), and postprandial glucose (PPG) concentrations.¹⁻⁶ Linagliptin is being investigated by Boehringer Ingelheim as a once-daily oral treatment in type 2 diabetes.

In the pivotal phase III studies, linagliptin was shown to have a very favourable safety profile, with an overall rate of adverse events similar to placebo. In addition, linagliptin showed an excellent tolerability, was weight neutral, showed no increased risk of drug-drug interactions and, importantly, there was no increased risk of hypoglycaemia attributed to linagliptin use in monotherapy, or combination therapy with metformin or pioglitazone.¹⁻⁶

Notably, in diabetes patients with mild and moderate renal impairment, linagliptin blood plasma levels were comparable to those seen in diabetes patients with normal renal function,¹ suggesting that linagliptin, which has a primarily non-renal route of excretion, may have distinct pharmacological features not yet seen in this novel class of drugs.⁸ The data suggest that linagliptin would not need dose adjustment in patients with type 2 diabetes regardless of the stage of renal impairment.

In four multi-centre, 24 weeks, randomised, double-blind, controlled trials, statistically significant reductions in blood glucose were observed with linagliptin monotherapy versus placebo¹ and when used in combination with other commonly used oral anti-diabetes drugs.²⁻⁴ This was accompanied by significant improvements in beta-cell function.^{1,3} Declining beta-cell function is a key factor driving the progression of type 2 diabetes.⁷

In a further study, linagliptin monotherapy showed superiority in glucose lowering versus placebo and versus voglibose, the most commonly used alpha glucosidase inhibitor in Japan.⁵⁻⁶

“Many type 2 diabetes patients treated with traditional anti-diabetes agents fail to achieve their glycaemic targets or maintain them over time, which can leave them at a higher likelihood of developing diabetic complications, including renal disease. Although renal impairment is very common in patients with type 2 diabetes, early stage renal dysfunction often goes undiagnosed. It is important to identify those patients as they will require effective and safer drugs with low risk of hypoglycaemia”, commented Julio Rosenstock, M.D., Director of Dallas Diabetes and Endocrine Center at Medical City and also a Clinical Professor of Medicine, University of Texas Southwestern Medical School, Dallas, Texas, USA. “For linagliptin, we see from studies that only approximately five percent of the orally administered drug is excreted via the kidneys. Data to date appear to indicate that linagliptin would not require dose adjustment, which could translate into an important benefit for physicians when choosing a treatment, not only for the type 2 diabetes patient population with diagnosed renal impairment, but also for those patients at risk of developing renal complications”, he added.

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Notes to Editor:

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About Diabetes and Type 2 Diabetes

There are approximately 285 million people with diabetes in the adult population worldwide.⁹ The International Diabetes Federation estimates that the number of people with diabetes will increase to 438 million people worldwide by 2030. Nearly four million people within the 20-79 age group are predicted to die from diabetes and its complications in 2010.⁹ Approximately 50% of people with diabetes die of cardiovascular disease,⁹ and more than 8% die of renal causes.¹⁰

For more information about type 2 diabetes, please also visit:

- Media webcast hosted by Boehringer Ingelheim at <http://www.boehringer-ingelheim-webcast.com/diabetes>
- Diabetes Health Lounge website at <http://www.DiabetesHealthLounge.com>
- DPP-4 mode of action video at <http://www.youtube.com/user/diabetismatters>

Boehringer Ingelheim Diabetes Pipeline

Metabolism is one of Boehringer Ingelheim's core R&D areas and diabetes one of the indications at the centre of interest within the company's global research network. Boehringer Ingelheim is committed to researching and developing new diabetes compounds with novel modes of action to improve patients' health and increase overall quality of life. These include:

- The DPP-4 inhibitor linagliptin is the most advanced compound in the Boehringer Ingelheim diabetes portfolio. Linagliptin is being investigated as an oral once-daily tablet for the treatment of type 2 diabetes, as monotherapy and as combination therapy. Linagliptin has a primarily non-renal route of excretion (only approx. 5% excreted via the kidneys).
- The compound BI10773 is a sodium-dependent glucose transporter-2 (SGLT-2) inhibitor. The Phase II clinical trials have concluded. BI10773 blocks renal glucose absorption in the kidneys, thereby improving glycaemic control. The inhibition of SGLT-2 has been seen to have a positive effect on body weight loss and reduction in blood pressure.
- An 11 β -HSD1 inhibitor: Inhibition of 11 β -HSD1 offers a novel potential therapy for the management of diabetes by lowering intracellular cortisol concentrations resulting in improved insulin sensitivity, blood lipid levels and vascular function. The 11 β -HSD1 inhibitor compound currently being studied by Boehringer Ingelheim is in early stage of clinical development.

Linagliptin phase III pivotal trials description:¹⁻⁶

Four multi-centre, randomised, placebo-controlled, double-blind, phase III studies were conducted to investigate the efficacy, safety and tolerability of linagliptin (5 mg once daily) versus placebo, administered over 24 weeks in type 2 diabetes mellitus patients with insufficient glycaemic control. The overall HbA_{1c} range for these studies was $\geq 6.5\%$ and $\leq 11\%$, with the following background therapy: linagliptin monotherapy¹ (exercise and diet alone), as add-on to metformin², as add-on to metformin plus a sulfonylurea³, and as initial combination with pioglitazone.⁴ A multi-centre, 12 and 26 weeks, randomised, double-blind, controlled study comparing the efficacy and safety and tolerability of linagliptin versus placebo and the alpha glucosidase inhibitor voglibose in drug-naïve or previously treated Japanese patients with type 2 diabetes (baseline HbA_{1c} 7-10% if drug-naïve, 7.0-9.0% if previously treated with an oral hypoglycaemic agent).⁵⁻⁶

Summary of key efficacy results from these trials:

- Linagliptin as monotherapy provided significant, clinically meaningful and sustained improvements in glycaemic control accompanied by improvements in beta-cell function.¹ Among other results, data from this trial showed that:
 - Linagliptin showed a mean placebo-adjusted change in HbA_{1c} from baseline of -0.69% (p<0.0001).

- Linagliptin patients were significantly more likely to achieve a reduction in HbA_{1c} $\geq 0.5\%$ at 24 weeks than placebo (47.1% versus 19.0%, $p < 0.0001$).
 - Greatest mean placebo-adjusted HbA_{1c} reductions (-1.01%) were seen in patients with elevated blood glucose levels at baseline, HbA_{1c} $\geq 9.0\%$.
 - Linagliptin showed a highly significant placebo-adjusted change in postprandial glucose (PPG) levels of -58.4 mg/dl ($p < 0.0001$).
 - Conclusion: Linagliptin monotherapy showed a significant, clinically meaningful and sustained improvement in glycaemic control reflected in changes in FPG, PPG, and HbA_{1c}. This is accompanied by beta-cell function improvements and a safety profile comparable to placebo.
- Linagliptin as an add-on to metformin resulted in a significant change in HbA_{1c}.² Among other results, data from this trial showed that:
 - Linagliptin showed a significant placebo-adjusted mean change in HbA_{1c} from baseline of -0.64% ($p < 0.0001$) after 24 weeks of treatment.
 - Linagliptin showed a highly significant placebo-adjusted change in postprandial glucose (PPG) levels of -67.1 mg/dl ($p < 0.0001$).
 - Conclusion: Linagliptin 5 mg as add-on therapy for type 2 diabetes patients inadequately controlled on metformin was well tolerated and produced significant and clinically meaningful improvements in glycaemic control.
- Linagliptin as an add-on to metformin plus a sulfonylurea was efficacious and safe in producing significant and clinically meaningful improvements in glycaemic control.³ Among other results, data from this trial showed that:
 - After 24 weeks of treatment, mean placebo-adjusted HbA_{1c} was -0.62% lower ($p < 0.0001$) with the addition of linagliptin versus placebo.
 - Patients with baseline HbA_{1c} $\geq 7.0\%$ were significantly more likely to achieve a target HbA_{1c} $< 7.0\%$ when treated with linagliptin (29.2%) compared to placebo (8.1%, $p < 0.0001$).
 - Conclusion: Therapy with linagliptin added to the combination of metformin and sulfonylurea was shown to be efficacious and safe in producing significant and clinically meaningful improvements in glycaemic control in type 2 diabetes patients. Thus, linagliptin may provide an additional option prior to insulin therapy in many patients failing on oral anti-diabetic combination therapy.
- Linagliptin in combination with pioglitazone showed significant and clinically meaningful improvements in FPG and HbA_{1c} levels.⁴
 - Linagliptin in combination with pioglitazone resulted in a mean placebo-adjusted HbA_{1c} change of -1.06% from baseline and a

difference of -0.51% in comparison with the pioglitazone and placebo group.

- Conclusion: Initial combination therapy with linagliptin and pioglitazone showed significant and clinically meaningful improvements in FPG and HbA_{1c} levels and was well tolerated. Combining these two drugs may be an important initial dual therapy for type 2 diabetes, targeting both, β -cell dysfunction and peripheral insulin resistance, known as the pathophysiological key factors of this disease. Initial combination therapy with linagliptin and pioglitazone may provide an important synergistic initial treatment option for type 2 diabetes patients with inadequate glycaemic control or those with renal impairment for whom metformin is contraindicated.
- Japanese study (week 12 and week 26): Linagliptin as monotherapy demonstrated greater efficacy than placebo and voglibose, respectively, for improving glycaemic control in Japanese patients with type 2 diabetes and was well tolerated in this population.⁵⁻⁶

At week 12:⁵

- The differences of placebo-adjusted mean changes from baseline in HbA_{1c} were -0.87% for linagliptin 5 mg vs. placebo ($p < 0.0001$) and -0.88% for linagliptin 10 mg versus placebo ($p < 0.0001$)
- The proportions of patients achieving HbA_{1c} $< 7.0\%$ after 12 wks were 26.4% for linagliptin 5 mg and 35.7% for linagliptin 10 mg versus 10.0% for placebo
- Conclusion: Linagliptin demonstrated a significant and clinically meaningful improvement in glycaemic control, reflected in changes in HbA_{1c} and FPG in Japanese patients with type 2 diabetes.

At week 26:⁶

- The differences of placebo-adjusted mean changes from baseline in HbA_{1c} were -0.32% for linagliptin 5mg versus voglibose ($p = 0.003$) and -0.39% for linagliptin 10mg versus voglibose ($p < 0.0001$)
- Drug-related gastrointestinal disorders were less frequently observed in the linagliptin groups than in the voglibose group (8.2% and 8.1% for linagliptin 5mg and 10mg, respectively; 14.2% for voglibose).
- Conclusion: Linagliptin monotherapy demonstrated greater efficacy than voglibose for improving glycaemic control in Japanese patients with type 2 diabetes and was well tolerated in this population.

About Boehringer Ingelheim

The Boehringer Ingelheim group is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, it operates globally with 142 affiliates in 50 countries and more than 41,500 employees. Since it was founded in 1885, the family-owned company has been committed to researching, developing, manufacturing and marketing novel products of high therapeutic value for human and veterinary medicine.

In 2009, Boehringer Ingelheim posted net sales of 12.7 billion euro while spending 21% of net sales in its largest business segment Prescription Medicines on research and development.

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