



**Boehringer  
Ingelheim**

125 years more health

## Press Release

For non-US healthcare media

**Embargoed until: 22 September 2010, 13:00 CET**

**Boehringer Ingelheim GmbH**  
Corporate Communications  
Binger Straße 173  
D-55216 Ingelheim am Rhein

[www.boehringer-ingelheim.com](http://www.boehringer-ingelheim.com)

Phone +49/61 32/77-2622

Fax +49/61 32/72-2622

### **New phase III data further support the safety and efficacy profile of Boehringer Ingelheim's investigational drug linagliptin**

*Linagliptin continues to differentiate itself as potential future option for patients with type 2 diabetes, regardless of stage of the condition or kidney function*

**Ingelheim, Germany, 22<sup>nd</sup> September 2010** – New data from the linagliptin late stage clinical trial programme were presented this week at the 46<sup>th</sup> Annual Meeting of the European Association for the Study of Diabetes (EASD). The studies included two phase III trials: one investigating linagliptin monotherapy in type 2 diabetes patients for whom metformin therapy is inappropriate,<sup>1</sup> and the other studying linagliptin as add-on therapy to a sulphonylurea in patients with inadequately controlled type 2 diabetes.<sup>2</sup> In addition, a pharmacokinetic study was presented at the congress which investigated linagliptin in a special patient population with different degrees of renal impairment.<sup>3</sup>

Linagliptin belongs to the novel class of DPP-4 inhibitors and is currently in late stage development as a once-daily, single-dose oral tablet. The new data add to the large body of clinical evidence demonstrating that linagliptin cannot only achieve significant and sustainable reductions in blood glucose, but that based on its unique pharmacokinetic profile, linagliptin may not require dose adjustment even in patients with type 2 diabetes with any degree of renal impairment. Boehringer Ingelheim is filing linagliptin for market authorisation in key countries across the globe in 2010 and is looking forward to making this novel treatment available to people with type 2 diabetes as soon as possible.

### **Linagliptin's profile goes beyond the established favourable characteristics of this novel class of anti-diabetic treatments**

One of the unique characteristics of linagliptin among the DPP-4 inhibitors is its primarily non-renal route of excretion.<sup>4</sup> The pharmacokinetic study<sup>3</sup> was performed to support the assumption that linagliptin exposure would not show a clinically relevant increase when administered in patients with



**Boehringer  
Ingelheim**

125 years more health

any degree of renal impairment. Notably, results from this study confirmed that decreases in renal function had only little effect on the elimination of linagliptin and only minor changes were observed in linagliptin exposure in patients with renal impairment (1.4-fold increase in exposure in type 2 diabetes patients with severe renal impairment compared with type 2 diabetes patients with normal renal function). This, along with the large safety window of linagliptin,<sup>4</sup> supports the assumption that no dose adjustment of linagliptin may be required in type 2 diabetes patients with any degree of renal impairment.

“Treating type 2 diabetes demands a holistic approach if we want to be successful in helping patients not only achieve but also maintain good blood glucose levels. Kidney function is an important consideration when prescribing an anti-diabetes therapy. Many type 2 diabetes patients either have, or are at significant risk of developing kidney impairment,” said Professor Anthony Barnett, Professor of Medicine and Clinical Director of the Department of Diabetes and Endocrinology, Heart of England NHS Foundation Trust, Birmingham, UK. “Currently available DPP-4 inhibitors are mainly eliminated via the kidney and therefore not recommended in patients with advanced renal impairment in many countries. Others either require dose adjustment or are contraindicated for such patients. The clinical data for linagliptin seen to date suggest an advantage in this respect due to its primarily non-renal route of excretion. The convenience of a drug not needing additional monitoring of kidney function or not needing dose adjustment as kidney function declines, could improve patient compliance as well as making life easier for the health professional.”

### **Linagliptin improves glycaemic control in type 2 diabetes patients for whom metformin therapy is inappropriate**

The phase III study assessing the efficacy, safety and tolerability of linagliptin patients with inadequately controlled type 2 diabetes for whom metformin therapy is inappropriate due to intolerability or contraindication,<sup>1</sup> confirmed earlier efficacy and safety findings. Importantly, the incidence of hypoglycaemia was very low and the observed episodes of mild intensity (1.3% in the linagliptin group). No significant difference in change in body weight was observed between the groups. The overall incidence of reported adverse events was similar for both groups (48.7% placebo versus 40.4% linagliptin). An earlier phase III study investigating linagliptin monotherapy versus placebo had already shown that a once-daily 5 mg single dose for 24 weeks produced significant, clinically meaningful and sustained improvements in glycaemic control compared to placebo (–0.7% placebo-adjusted reduction in HbA<sub>1c</sub>).<sup>5</sup> This new 18-week interim analysis in patients for whom metformin is inappropriate further supports linagliptin’s favourable efficacy profile. Linagliptin 5 mg showed a clinically relevant and statistically significant mean difference in HbA<sub>1c</sub> reduction (primary outcome) compared to placebo. Statistically significant differences between linagliptin and placebo could already be seen at week 6, and at week 18 the



**Boehringer  
Ingelheim**

125 years more health

placebo adjusted mean difference was  $-0.6\%$  ( $p < 0.0001$ ). Linagliptin was also superior to placebo in reducing fasting plasma glucose (FPG) levels (adjusted mean change from baseline  $-1.1$  mmol/l ( $-20.5$  mg/dl);  $p = 0.0002$ ).

Metformin is currently the standard first-line treatment for patients with type 2 diabetes. However, it is known that metformin is not tolerated at high doses in all patients<sup>6</sup> (metformin is associated with dose-related side effects such as diarrhoea, nausea and abdominal bloating, and a potential risk for lactic acidosis), thus limiting metformin use across the range of patients with type 2 diabetes. This study suggests that linagliptin would be a valuable treatment also in this type 2 diabetes population for whom metformin therapy is inappropriate due to contraindications and intolerability, including patients with renal impairment.

### **Safety and efficacy of linagliptin as add-on therapy to an SU in inadequately controlled type 2 diabetes patients**

In the other phase III study presented at the EASD Annual Meeting, linagliptin 5 mg was assessed in an 18-week, multi-centre, randomised, double-blind, placebo-controlled, parallel-group design to determine the efficacy, safety and tolerability of linagliptin as add-on therapy to sulphonylurea (SU) in patients with type 2 diabetes and insufficient glycaemic control.<sup>2</sup>

An earlier phase III study in over 1,000 patients had demonstrated significant improvements in glycaemic control when linagliptin was added to the combination of metformin and an SU (mean placebo adjusted HbA<sub>1c</sub> reduction was  $-0.6\%$ ;  $p < 0.0001$ ).<sup>7</sup> The new study, although conducted in a smaller patient group ( $n = 245$  randomised), shows a statistically significant and clinically relevant reduction in HbA<sub>1c</sub> from baseline (mean placebo adjusted HbA<sub>1c</sub> reduction  $-0.5\%$ ;  $p < 0.0001$ ), thus further supporting the efficacy of linagliptin as add-on therapy.<sup>2</sup>

Further, the trial results showed an overall incidence of adverse events similar to placebo (42.2% versus 42.9% respectively) and, importantly, there was no significantly increased risk for hypoglycaemia when linagliptin was added to SU background therapy (5.6% in the linagliptin group versus 4.8% in the placebo group). The percentage of participants requiring rescue therapy in the linagliptin group was only half the proportion of those requiring rescue therapy in the placebo group (7.6% versus 15.9%). No significant difference in change in body weight was observed between the groups. The safety results from this study are an important finding as sulphonylureas are associated with side effects such as weight gain and risk of hypoglycaemia which could be exacerbated with uptitration of the SU agent. The study concluded that linagliptin has the potential to be used safely as add-on therapy in type 2 diabetes patients with insufficient glycaemic control on sulphonylurea alone.

- end -

### Notes to Editor:

**Please be advised:** This release is from Boehringer Ingelheim Corporate Headquarters in Germany. Please be aware that there may be national differences between countries regarding specific medical information, including licensed uses. Please take account of this when referring to the information provided in this document. This press release is not intended for distribution within the U.S.A.

### About Diabetes and Type 2 Diabetes

There are approximately 285 million people with diabetes in the adult population worldwide.<sup>8</sup> The International Diabetes Federation estimates that the number of people with diabetes will increase to 438 million people worldwide by 2030.<sup>8</sup> Nearly four million people within the 20–79-year age group are predicted to die from diabetes and its complications in 2010.<sup>8</sup> Approximately 50 percent of people with diabetes die of cardiovascular disease.<sup>9</sup>

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

- Media webcast hosted by Boehringer Ingelheim at [www.boehringer-ingelheim-webcast.com/diabetes](http://www.boehringer-ingelheim-webcast.com/diabetes)
- Diabetes Health Lounge website at [www.DiabetesHealthLounge.com](http://www.DiabetesHealthLounge.com)
- DPP-4 inhibitors mode of action video at [www.youtube.com/diabetismatters](http://www.youtube.com/diabetismatters)

### Boehringer Ingelheim Diabetes Pipeline

Metabolism is one of Boehringer Ingelheim's core R&D areas and diabetes is 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 – the most advanced compound in the Boehringer Ingelheim diabetes portfolio. Linagliptin is being investigated as an oral once-daily, single dose tablet for the treatment of type 2 diabetes, as monotherapy and as combination therapy. Linagliptin has a primarily non-renal route of excretion (only 5% is excreted via the kidneys) and is mainly excreted unchanged via the enterohepatic system (linagliptin has no active metabolite).
- The compound BI10773 – a sodium-dependent glucose co-transporter-2 (SGLT-2) inhibitor. The Phase II clinical trials have concluded. BI10773 blocks renal glucose absorption in the kidneys, thereby increasing urinary excretion of glucose and consequently 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.



**Boehringer  
Ingelheim**

125 years more health

- An 11 $\beta$ -HSD1 inhibitor – inhibition of 11 $\beta$ -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 $\beta$ -HSD1 inhibitor compound currently being studied by Boehringer Ingelheim is in the early stages of clinical development.

### **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.

For more information, please visit [www.boehringer-ingelheim.com](http://www.boehringer-ingelheim.com)

### **Contact:**

Ursula Bardon

Corporate Communications

Boehringer Ingelheim GmbH

55216 Ingelheim/Germany

Phone: + 49-6132-77 2622

Fax: + 49-6132-72 2622

E-mail: [press@boehringer-ingelheim.com](mailto:press@boehringer-ingelheim.com)

### **References**

1. Barnett AH, Harper R, Toorawa R, *et al.* Linagliptin monotherapy improves glycaemic control in type 2 diabetes patients for whom metformin therapy is inappropriate. Poster no. 823-P, 46<sup>th</sup> European Association for the Study of Diabetes Annual Meeting, September 2010, Stockholm, Sweden.
2. Lewin AJ, Arvay L, Liu D, *et al.* Safety and efficacy of linagliptin as add-on therapy to a sulphonylurea in inadequately controlled type 2 diabetes. Poster no. 821-P, 46<sup>th</sup> European Association for the Study of Diabetes Annual Meeting, September 2010, Stockholm, Sweden.
3. Graefe-Mody U, Friedrich C, Port A, *et al.* Linagliptin, a novel DPP-4 inhibitor: no need for dose adjustment in patients with renal impairment. Poster no. 822-P, 46<sup>th</sup> European Association for the Study of Diabetes Annual Meeting, September 2010, Stockholm, Sweden.
4. Hüttner S, Graefe-Mody EU, Withopf B, *et al.* Safety, tolerability, pharmacokinetics, and pharmacodynamics of single oral doses of BI 1356, an inhibitor of dipeptidyl peptidase 4, in healthy male volunteers. *J Clin Pharmacol.* 2008;48:1171–1178.
5. Del Prato S, Barnett A, Huisman H, *et al.* Linagliptin monotherapy improves glycaemic control and measures of beta-cell function in Type 2 diabetes. Poster no 695-P, 70th American Diabetes Association Scientific Sessions, June 2010, Orlando, Florida, U.S.A.



**Boehringer  
Ingelheim**

125 years more health

6. Derosa G, Mereu R, Salvadeo SAT, *et al.* Pioglitazone Metabolic Effect in Metformin-Intolerant Obese Patients Treated with Sibutramine. *Intern Med* 2009; 48; 265-71.
7. Owens DR, Swallow R, Woerle HJ, *et al.* Linagliptin improves glycemic control in Type 2 diabetes patients inadequately controlled by metformin and sulfonylurea without weight gain and low risk of hypoglycaemia. Poster no 548-P, 70th American Diabetes Association Scientific Sessions, June 2010, Orlando, Florida U.S.A.
8. International Diabetes Federation (IDF). [www.idf.org](http://www.idf.org). Accessed: September 2010.
9. Morrish NJ, Wang SL, Stevens LK, *et al.* Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia*. 2001 Sep;44 Suppl 2:S14–21.