

## **5-year Study Published in *Diabetologia* Demonstrated Long-Term Safety of Lantus® Compared to NPH**

**- Long-term study found no increased progression of retinopathy in Lantus® over NPH treatment regimen -**

**Bridgewater, NJ July 6, 2009** - Sanofi-aventis (EURONEXT: SAN and NYSE: SNY) announced today that the results of the long-term, 5-year study of Lantus® (insulin glargine [rDNA] injection) versus NPH insulin on progression of retinopathy in patients with type 2 diabetes, published on-line in *Diabetologia* (DOI 10.1007/s00125-009-1415-7) showed similar effects on retinopathy and overall safety in the two treatment groups. This is the longest controlled study ever reported using insulin glargine.

Diabetic retinopathy is a major cause of blindness in patients with diabetes. It is a progressive disease that results from cellular proliferation within the eye. The stimulation of IGF1 receptors is involved in this process. In the study of patients with retinopathy, the progression of diabetic retinopathy was similar in the two treatment groups over the long-term course of treatment.

This indicates that Lantus does not have mitogenic effects different from the human NPH insulin within the eye.

*“This 5-year study is the longest randomized controlled study with insulin glargine versus NPH human insulin,”* said lead investigator Julio Rosenstock, MD, Director of the Dallas Diabetes and Endocrine Center at Medical City and also Clinical Professor of Medicine, University of Texas Southwestern Medical School. *“This study demonstrated no evidence of a greater risk of progression of retinopathy with insulin glargine.”*

The 5-year open-label study was specifically designed to further characterize the retinal safety profile of Lantus® versus NPH in 1024 patients (Lantus® once daily: 515 patients; NPH twice daily: 509 patients). Retinopathy progression was assessed using serial fundus photography.

Progression was evaluated using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale; the scores at study end were similar in both treatment groups (Lantus®: 14.2%, NPH: 15.7%; 95% CI: -7.02, 3.06). As per protocol, the study aimed to achieve similar levels of glycemic control in both groups, in order to avoid introducing bias on the primary retinopathy end-point that could be related to differences in blood glucose control. Both groups had comparable HbA1c at study end (mean HbA1c improved from a baseline of 8.4% and 8.3% to 7.8% and 7.6% for all patients in the insuline glargine and NPH insulin groups respectively). NPH insulin was associated with a significantly greater incidence of severe hypoglycemia than was insulin glargine (11.1% vs 7.6% respectively,

p=0.0439) and mean yearly rates of symptomatic hypoglycemia (7.08+/-16.49 vs 5.13+/-12.79, p=0.0017).

There was no observable trend for a difference in the incidence of serious adverse events including cancer, as well as adverse events leading to study withdrawal. The most common adverse events in the study were: upper respiratory tract infection (glargine 149 [29%], NPH 169 [33.6%]), peripheral edema (glargine 103 [20%], NPH 114 [22.7%]), and arthralgia (glargine 73 [14.2%], NPH 81 [16.1%]).

### About the study

This long-term study was designed to further characterize the retinal safety profile of insulin glargine (glargine) and human neutral protamine Hagedorn insulin (NPH) in patients with type 2 diabetes mellitus.

This was an open-label, 5-year, randomized (1:1), multicentre, stratified, parallel-group study comparing patients treated with either twice-daily NPH (n=509) or once-daily basal glargine (n=515).

The main objective of this study was to compare the progression of diabetic retinopathy between treatment groups by analyzing the percentage of patients with  $\geq 3$ -step progression in the Early Treatment Diabetic Retinopathy Study (ETDRS) retinopathy patient-level severity scale after treatment with either insulin. Masked, centralized grading of seven-field stereoscopic fundus photographs was used.

Main characteristics of the population were the following and well balanced between groups: : mean age 55, 54% males, mean baseline HbA1c 8.4 vs 8.3% (glargine vs NPH) diabetes duration 11 years, and about 70% of the population was already treated with insulin prior to study entry.

Similarly sustained glycaemic control was observed in both the glargine and NPH treatment groups. Despite a slightly greater severity of diabetic retinopathy for the glargine-treated group at baseline,  $\geq 3$ -step progression in ETDRS score from baseline to end-of-study was similar between treatment groups (14.2% [53/374] of glargine-treated patients vs 15.7% [57/363] of NPH-treated patients). Other measures of retinopathy – the development of proliferative diabetic retinopathy and progression to clinically significant macular oedema – occurred to a similar degree in both treatment groups. Rates of symptomatic and clinically important hypoglycaemia were significantly lower in the glargine group: NPH insulin was associated with a significantly greater incidence of severe hypoglycemia than was insulin glargine (11.1% vs 7.6% respectively, p=0.0439) and mean yearly rates of symptomatic hypoglycemia (7.08+/-16.49 vs 5.13+/-12.79, p=0.0017). Body weight gain tended to be greater with NPH insulin compared with insulin glargine treatment, with a baseline to endpoint increase in mean body weight of 3.7 kg for insulin glargine and 4.8 kg for NPH insulin (ITT population; p=0.0505). No other safety issues for either insulin emerged during the 5-year study.

### About sanofi-aventis

Sanofi-aventis, a leading global pharmaceutical company, discovers, develops and distributes therapeutic solutions to improve the lives of everyone. Sanofi-aventis is listed in Paris (EURONEXT: SAN) and in New York (NYSE: SNY).

#### Forward Looking Statements

*This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts. These statements include product development, product potential projections and estimates and their underlying assumptions, statements regarding plans, objectives, intentions and expectations with respect to future events, operations, products and services, and statements regarding future performance. Forward-looking statements are generally identified by the words “expects,” “anticipates,” “believes,” “intends,” “estimates,” “plans” and similar expressions. Although sanofi-aventis’ management believes that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of sanofi-aventis, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include among other things, the uncertainties inherent in research and development, future clinical data and analysis, including post*

*marketing, decisions by regulatory authorities, such as the FDA or the EMEA, regarding whether and when to approve any drug, device or biological application that may be filed for any such product candidates as well as their decisions regarding labelling and other matters that could affect the availability or commercial potential of such products candidates, the absence of guarantee that the products candidates if approved will be commercially successful, the future approval and commercial success of therapeutic alternatives as well as those discussed or identified in the public filings with the SEC and the AMF made by sanofi-aventis, including those listed under "Risk Factors" and "Cautionary Statement Regarding Forward-Looking Statements" in sanofi-aventis' annual report on Form 20-F for the year ended December 31, 2008. Other than as required by applicable law, sanofi-aventis does not undertake any obligation to update or revise any forward-looking information or statements.*

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