

July 16, 2009. Updated with disclosure information

EXPERT STATEMENT

Four retrospective epidemiological studies recently published in *Diabetologia* have drawn attention to the known association between obesity, diabetes, and cancer. These studies arose from concern that insulin glargine might pose particular risks for patients using it for treatment. However, the studies have serious methodologic limitations, as well as inconsistencies within and between them, and so do not establish a link between the use of glargine and an increased risk of cancer or other safety issues for patients with diabetes.

Insulin – an essential agent for treating diabetes - has been shown, in experimental systems, to have mitogenic properties (which potentially might cause or promote the growth of tumors), but the clinical relevance of these findings has been controversial. Retrospective epidemiological studies have shown inconsistent associations of cancer with use of insulin in general, but interpretation has been difficult due to multiple confounding factors such as age, obesity, insulin resistance, and selective prescribing for particular populations. Firm answers will require appropriately designed and adequately powered studies to investigate the association between use of insulin in general, and of insulin analogues such as glargine in particular, and the risk of cancer.

Because the findings just published in *Diabetologia* are not conclusive, no change of current therapeutic recommendations is warranted. However, the important scientific and therapeutic questions raised call for further analyses of existing data and further basic and clinical investigations to guide future clinical recommendations.

<p style="text-align: center;">RATIONALE for the EXPERT STATEMENT and SPECIFIC RECOMMENDATIONS</p>

Following the publication of four papers in *Diabetologia* reporting on retrospective epidemiological studies using clinical databases, accompanied by a press release and an information pamphlet for patients, sanofi-aventis convened a group of experts in the fields of epidemiology, diabetology, and oncology on June 29, 2009 in Paris. The group was asked to review the new findings and offer the company scientific guidance on how to address this complex issue.

Acting as a panel of external consultants, the group has prepared this summary and report to sanofi-aventis.

We were asked to:

- A) Assess the merits of the published data**
- B) Review the evidence for or against the biological plausibility of a link between the use of insulin glargine and the risk of cancer**
- C) Define the best ways forward to bring clarity to the issue raised by the four articles on-line on 26 June 2009 in *Diabetologia*.**

Regarding the merits of the published data, we agreed that all four published manuscripts have significant methodological limitations and shortcomings. The nature of the biases and their potential magnitude are such that, individually or in aggregate, these studies provide inconsistent and inconclusive results which do not justify new clinical recommendations to patients.

We recommended the following:

- 1) Available randomized clinical trial data should be analyzed alone or in pooled analyses with appropriate statistical adjustments for cancer incidence, and published as soon as possible;**
- 2) A methodological critique of the four studies, authored by leading epidemiology, biostatistics and clinical experts, should be urgently prepared and submitted for publication in a top-tier medical journal. One aim of the critique should be to set standards for the methods used and level of evidence required to reach meaningful conclusions on this difficult issue.**

Regarding the biological plausibility of the association between the use of insulin glargine and risk of cancer, we agreed that this question is important and should not be dismissed. While the available animal toxicology data are reassuring, additional studies would be helpful.

We recommended consideration of studies:

- 1) In animals to further explore the safety of insulin glargine in additional experimental models;**
- 2) In humans, to confirm that plasma insulin concentrations achieved after large doses of insulin glargine remain below the concentration threshold needed in vitro to demonstrate greater affinity for binding to IGF-1R.**

Regarding the best ways forward, we agreed that while clarity needs to be brought to the questions posed by the publications, the formal statements from the EASD and the publicity resulting from them have led to an undue measure of alarm in the scientific community and among patients receiving insulin treatment. We were reassured to learn that several professional associations (American Diabetes Association, Endocrine Society, International Diabetes Federation) and international and local health authorities (FDA, EMEA, AFSSaPS) have not recommended any change of present therapeutic recommendations, but called for additional scientific information. Further thoughtful analyses and commentaries may provide a more balanced assessment of potential risks and benefits of treatments for diabetes, including the several kinds of insulin.

We recommended the following:

- 1) Conduct new studies using large databases, expertly designed and analyzed under the auspices of an independent professional association; and**
- 2) Consider the opportunities arising from the ongoing ORIGIN trial, which is studying randomized treatment of 12,612 patients over more than 5 years, to address the above questions.**

We appreciate the opportunity given us to discuss these issues, which cross the boundaries of our several scientific specialities, and we look forward to further cooperative efforts on this scientifically and medically important topic.

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Disclosure Information

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- *GB Bolli has received honoraria for consulting in advisory boards with sanofi-aventis, Mannkind, Novartis, Eli Lilly & Company. He has also received financial support for research from sanofi-aventis, Eli Lilly & Co., and Novartis.*

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- *Dr. B. Chabner has received consultancy fees from Johnson & Johnson, Pharmamar, Genzyme, Eli Lilly & Company, Epizyme, Aptium, sanofi-aventis and Thomas, McNermey & Partners. He is on the Board of Directors of Pharmamar and Epizyme. He holds options or shares in Johnson & Johnson, Pharmamar, Genzyme, Epizyme and Thomas, McNermey & Partners.*

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- *E. Eschwege reports receiving consulting fees from sanofi-aventis and Novo-Nordisk.*

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- *Professor Grimaldi has no duality of interest relevant to the content of this Expert Statement. He has, in the past, received speaking and consultancy honoraria from sanofi-aventis, Novo Nordisk, Eli Lilly & Company, Merck Sharpe & Dohme, Serono, Takeda and AstraZeneca.*

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- *Professor Hortobagyi has no relevant disclosures to make.*

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- *Dr Michael Pollak has consulted for Pfizer and served on advisory boards for Astra Zeneca, Novartis, Amgen, Bristol-Myers Squibb, OSI, and sanofi-aventis.*

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- *Dr Le Roith is an advisory board member for Bristol-Myers Squibb, Astrazeneca, sanofi-aventis and Merck. He has been a speaker at events sponsored by Bristol-Myers Squibb, Astrazeneca, Takeda, sanofi-aventis and Merck.*

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- *Dr Riddle has received grants or research support from Amylin, Eli Lilly Company and sanofi-aventis. He is a consultant to Amylin, Eli Lilly Company, Pfizer, sanofi-aventis and Valeritas. He has received honoraria for lectures from Amylin, Eli Lilly Company and sanofi-aventis. He does not hold stock or options for any of these companies.*

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- *Dr Rosenstock has served on advisory boards and received honorarium or consulting fees from Pfizer, Roche, Sanofi-Aventis, Novo Nordisk, Eli Lilly, MannKind, GlaxoSmithKline, Takeda, Daiichi Sankyo, Forest, Johnson & Johnson, Novartis and Amylin. He has received research grants from Merck, Pfizer, Sanofi-Aventis, Novo Nordisk, Roche, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Takeda, Novartis, AstraZeneca, Amylin, Johnson & Johnson, Daiichi Sankyo and MannKind.*

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- *Regarding insulin products, J.S.Skyler reports receiving consulting fees from MannKind Corporation, Novo-Nordisk, and sanofi-aventis, being a grant recipient from Halozyme Therapeutics, Inc., and being a shareholder of MannKind Corporation. He has previously received consulting fees from CPEX Pharmaceuticals, Halozyme Therapeutics, Inc., Eli Lilly & Co., and Pfizer Pharmaceuticals.*