Results of a post-hoc analysis of tumour development during the diabetic retinopathy study

We have reported [1] a randomized, long-term safety study comparing the effects of using the insulin analogue glargine versus human NPH insulin for five years in management of type 2 diabetes. The study, in which 1017 patients were randomised and treated, was designed to assess ocular complications of diabetes, and found no excess of such effects with glargine compared with NPH treatment and similar slow progression of diabetic retinopathy with both insulins. Because of recent concerns about postulated neoplastic effects of insulins, we report here additional information from this study which bears on this question.

In total, the mean cumulative exposure was more than 4 years (1524 days in the insulin glargine group and 1522 days NPH insulin group) with more than 70% of patients exposed to more than 4 years of treatment (76% and 71%, respectively) (Table 1).

The baseline demographics and diabetes status were similar among the two treatment groups (insulin glargine vs NPH insulin): diabetes duration (10.7 vs 10.8 years), BMI (34.5 vs. 34.1 kg/m^2), oral hypoglycaemic agent duration (9.0 vs 8.9 years), prior insulin use (67% vs 70%), HbA_{1c} (8.4% vs 8.3%) and FPG (10.5 vs 10.0 mmol/l).

Although the study was not designed to investigate the frequency of tumour development, the long duration of the trial enables a comparative assessment of the occurrence of benign or malignant tumours with insulin glargine and NPH insulin during more than 4 years of exposure. The number of patients with treatment-emergent adverse events (defined as events that first occurred or worsened after randomisation) of Neoplasm, summarised by System Organ Class and High-Level Group Term level using the standard MedDRA coding dictionary (version 10.0) are shown in Table 2. Benign and malignant tumors, along with those of unspecified pathology, reported by investigators are included. . A more detailed listing of MedDRA-coded neoplasms can be found in reference 2.

The overall number of patients with neoplasms (using the standard MedDRA coding dictionary) occurring during the trial was similar in the two treatment groups; 57 patients (11.1%) in the glargine-treated group vs 62 patients (12.3%) in the NPH insulin-treated group with a relative risk (RR) for glargine of 0.90 (95% CI 0.64-1.26). In addition, when only the number of patients with malignant neoplasms reported as serious treatment-emergent events are captured, the rate was also similar in both treatment groups: 20 patients (3.9%) with 23 events in the insulin glargine-treated group vs 31 patients (6.2%) with 32 events in the NPH insulin-treated group, with a RR for glargine of 0.63 (95% CI 0.36-1.09). The number of patients with malignant breast tumours reported was also similar between treatments: 3 patients in the insulin glargine group (all reported as serious) compared with 5 patients (4 reported as serious) in the NPH insulin group.

This study did not have sufficient power to detect significant changes of risk of breast cancer, for example a doubling of risk (for RR 2.0, power 16%). The relative risk estimate of all breast cancer cases including non-serious cases in this study (3 vs. 5) clearly favours glargine (RR=0.59 (CI 0.14-2.44), but the 95% confidence interval includes 2.0. However, for all malignancies the approximately 500 patients per treatment group provide sufficient power to detect an increase (RR=2.0) over a 5 year period (power =85%) The upper bound of the confidence interval is even less than1.30 (a 30 % increase of risk).

In summary, this study is the longest controlled treatment comparison of insulin glargine versus NPH insulin in patients with type 2 diabetes mellitus. No new safety issues emerged

for either insulin studied based on the data from this 5-year trial. . Additional data reported here also confirm that there was no evidence of any difference in the rate of benign or malignant tumour development with insulin glargine compared with NPH insulin.

References

1. Rosenstock J, Fonseca V, McGill JB, et al (2009). Similar progression of diabetic retinopathy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: a long-term, randomised, open-label study. Diabetologia Jun 13. [Epub ahead of print]:DOI: 10.1007/s00125-009-1415-7.

2. MedDRA® is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

3. Clinicalstudyresults.org website

Table 1: **Summary of extent of exposure (safety population)**

Variable	**Insulin glargine (*n* = 514)**	**NPH insulin (*n* = 503)**
Cumulative exposure (patient-years)	2144.0	2095.8
Extent of exposure (days)		
Mean	1523.55 ± 571.77	1521.82 ± 562.14
Median	1821.50	1823.00

Data are mean ± SD unless otherwise stated

Table 2: Patients with neoplasms reported as treatment-emergent adverse events[a]

All neoplasms	Insulin glargine (*n* = 514)	NPH insulin (*n* = 503)
Any event	**57 (11.1)**	**62 (12.3)**
Breast neoplasms, malignant	3 (0.6)	5 (1.0)
Cutaneous neoplasms, benign	13 (2.5)	12 (2.4)
Endocrine neoplasms, malignant	5 (1.0)	7 (1.4)
Gastrointestinal neoplasms, malignant	6 (1.2)	9 (1.8)
Haematopoietic neoplasms	1 (0.2)	0
Hepatobiliary neoplasms, malignant	0	1 (0.2)
Lymphomas, non-Hodgkin's B-cell	0	1 (0.2)
Metastases	0	1 (0.2)
Miscellaneous and site unspecified neoplasms, malignant	1 (0.2)	3 (0.6)
Nervous system neoplasms, benign	1 (0.2)	2 (0.4)
Ocular neoplasms	3 (0.6)	2 (0.4)
Plasma cell neoplasms	1 (0.2)	0
Renal and urinary tract neoplasms, malignant	2 (0.4)	1 (0.2)
Reproductive neoplasms female, benign	2 (0.4)	1 (0.2)
Reproductive neoplasms female, malignant	2 (0.4)	4 (0.8)
Reproductive neoplasms male, malignant	2 (0.4)	3 (0.6)
Respiratory and mediastinal neoplasms, malignant	6 (1.2)	2 (0.4)
Skin neoplasms, malignant	11 (2.1)	9 (1.8)
Soft tissue neoplasms, benign	3 (0.6)	4 (0.8)
Soft tissue sarcomas	0	1 (0.2)

[a]Includes MedDRA System Organ Class "Neoplasm benign, malignant and unspecified (including cysts and polyps) (version 10.0); Data are *n* (%), in alphabetical order. All patients with Neoplasm-coded adverse events (whether considered serious or non-serious) as reported by the investigator are included. Patients may have had more than one adverse event.