

Combined randomised controlled trial experience of malignancies in studies using insulin glargine

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Abstract

Aims/hypothesis Recent publications of data extracted from population registries have suggested a possible relationship between treatment with insulin glargine and increased incidence of cancer/breast cancer. The aim of the present study was investigate this possible relationship using data from the manufacturer's (sanofi-aventis) pharmacovigilance database.

Methods We analysed the manufacturer's (sanofi-aventis) pharmacovigilance database for all randomised clinical trials (RCTs; Phase 2–4) comparing insulin glargine with any comparator in type 1 or type 2 diabetes. We identified all serious adverse events coded under the System Organ Class of 'neoplasms, benign, malignant and unspecified'. Treatment-emergent neoplasms judged to be malignant were included in this analysis.

Results The database included 31 studies, 12 in type 1 diabetes and 19 in type 2 diabetes. Twenty compared insulin glargine with NPH insulin, 29 were parallel-group studies and two had a crossover design. Studies were generally of 6 months' duration, except for trial reference number 4016 ($n=1,017$), which had a duration of 5 years. Overall, 10,880 people were included in the analysis (insulin glargine, 5,657; comparator, 5,223). Forty-five people (0.8%) vs 46 people (0.9%) reported 52 and 48 cases of malignant cancer in the insulin glargine and comparator groups, respectively (RR 0.90, 95% CI 0.60–1.36). Skin (12 people with 16 events vs

six people with seven events, RR 1.85, 95% CI 0.69–4.92), colon and rectum (six vs ten people, RR 0.55, 95% CI 0.20–1.52), breast (four vs six people, RR 0.62, 95% CI 0.17–2.18) and gastrointestinal tract (six vs four people, RR 1.38, 95% CI 0.39–4.90) were the most commonly reported sites.

Conclusions/interpretation In these 31 RCTs, insulin glargine was not associated with an increased incidence of cancer, including breast cancer, compared with the comparator group.

Keywords Cancer · Diabetes mellitus · Insulin analogues · Insulin glargine

Abbreviations

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
RCT randomised clinical trial
SEER Surveillance, Epidemiology and End Results

Introduction

Recent publications of data extracts from population registries have triggered debate about a potential relationship between treatment with insulin glargine (A21Gly,B31Arg, B32Arg human insulin) and an increased incidence of cancer or breast cancer [1–4]. Here, we fulfil an obligation to report the evidence from randomised clinical trials (RCTs) within the manufacturer's database.

All RCTs sponsored by sanofi-aventis that compared the use of insulin glargine with another active comparator in either type 1 or type 2 diabetes and had a treatment duration of at least 4 weeks were included in this analysis. These

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studies included people with either type 1 or type 2 diabetes, and were either part of the initial development plan for the registration of the product (Phase 2 and 3) or conducted after the commercial launch of insulin glargine (Phase 4 studies).

Methods

As it is obligatory for all sponsored trials routinely to report serious adverse events to the manufacturer, and as the manufacturer has a database of such studies, no literature search was performed. Only RCTs that compared insulin glargine with an active comparator and that had a final clinical study report available for review on 15 May 2009 were included in this analysis.

Studies and ascertainment of malignancy A thorough review of the sanofi-aventis safety database for the identified studies was performed to assess the incidence of any malignancies that led to reports of serious adverse events during the conduct of the trials. All RCTs of insulin glargine were included. All serious adverse events coded in the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class of neoplasms—benign, malignant and unspecified—were included in the evaluation [5]. An adverse event is classified as serious if it fulfils the criteria set down by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), that is if it: is life-threatening or results in death; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is another ‘medically important’ event that may jeopardise the study participant or may require intervention to prevent one of the other outcomes listed in the definition above [6]. The ICH recommends that cancers are characterised as ‘medically important’ adverse events and, therefore, are classified as serious adverse events [6].

All such identified records in the sanofi-aventis pharmacovigilance database were reviewed, by treatment, by the manufacturer’s drug safety personnel with experience of adverse event reporting, and only treatment-emergent neoplasms judged to be malignant were included, independent of treatment group. Each person was counted only once, although separate counts for people and cases are provided if more than one malignancy was reported in the same person. Relative risks and 95% confidence intervals were calculated for insulin glargine relative to the comparator for the total incidence of malignancies and for individual classifications using all identified RCTs in type 1 and type 2 diabetes combined.

Results

The Clintrace sanofi-aventis safety database contains 31 eligible studies. Twelve studies were performed in people with type 1 diabetes and 19 studies in people with type 2 diabetes; most of the studies compared insulin glargine with NPH insulin (20 studies). Nearly all (29) were parallel-group trials (two had a crossover design). Details of these studies are summarised in Table 1. Most studies were open label, 19 were of around 6 months in duration, with six of longer duration, notably the retinopathy study 4016, which had a duration of 5 years [7].

Overall, 10,880 people were included in the analysis, with 5,657 people randomised to insulin glargine and 5,223 people randomised to the comparator, representing a total follow-up time of 4,711 and 4,524 person-years, respectively. Baseline characteristics of the participants were comparable between treatment groups (Table 2).

Overall, there was no difference in the incidence of malignancies between insulin glargine-treated people and the comparator group (Table 3), with 52 cases of malignant cancer documented as a serious treatment-emergent event in 45 people in the insulin glargine group (0.8%) and 48 cases in 46 people in the comparator group (0.9%). Among such malignancies, most occurred in people with type 2 diabetes, with 45 cases in 39 people in the insulin glargine group (1.0%) and 46 cases in 44 people in the comparator group (1.2%).

The corresponding RR for malignant cancer with insulin glargine compared with the comparator is 0.90 (95% CI 0.60–1.36).

Four cases of malignant breast cancer were reported in the insulin glargine group (0.1%) and six cases in the control group (0.1%). The RR for breast cancer is 0.62 (95% CI 0.17–2.18).

These data were primarily driven by the findings in the 5 year RCT (study 4016) that compared insulin glargine ($n=514$) with NPH insulin ($n=503$) in people with type 2 diabetes who were randomised and received treatment [7, 8]. In that study, the overall number of people with neoplasms was similar in the insulin glargine and NPH insulin groups (57 [11.1%] and 62 [12.3%] people, respectively) [8]. When considering only the number of people in the retinopathy study with malignant neoplasms reported as serious treatment-emergent events, the rate was also similar in both groups (insulin glargine vs NPH insulin, 23 cases in 20 people [3.9%] vs 32 cases in 31 people [6.2%]). Finally, the number of people with breast cancer reported as a serious adverse event in that study was similar between the two treatment groups (three [0.6%] vs four [0.8%] cases – there was also an additional fifth case in the NPH insulin group, although this was reported as a non-serious adverse event).

Table 4 summarises the sites of all malignancies in the pooled studies comparing insulin glargine with comparator.

Table 1 Details of the studies included in the analysis

Trial number (reference)	Comparator	Study duration (weeks)	Participants randomised and treated (insulin glargine/control arm)
Type 1 diabetes			
2002 [15]	NPH	4	168/88
2003 [16]	NPH	4	223/110
3001 [17]	NPH	28	292/293
3003 [18]	NPH	28	174/175
3004 [19]	NPH	28	264/270
3005 [20]	NPH	16	310/309
4003 ^a	Ultralente	6–7	29/27
4005 [21]	NPH	32	26/25
4006 [22]	NPH	32	53/52
4010 [23]	NPH	30	62/63
4030 [24]	NPH or lente	24	85/90
4036 [25]	Insulin lispro as CSII	24	26/24
Type 2 diabetes			
2004 [26]	NPH	4	136/68
2006 ^a	‘Conventional insulin’	4	57/57
3002 [27]	NPH	52	289/281
3006 [28]	NPH	28	259/259
3102 ^a	NPH	28	158/159
3502 [29]	OGLDs	24	203/197
4001 [30]	NPH	28	464/233
4002 [31]	NPH	24	367/389
4012 [32]	NPH	24	221/223
4013 [33]	NPH	28	231/250
4014 [34]	Rosiglitazone	24	105/112
4016 [7, 8]	NPH	5 years	514/503
4020 ^a	Pioglitazone	48	164/181
4021 ^a	Insulin lispro 25%, insulin lispro protamine 75%, mix	24	113/99
4022 ^a	OGLDs	48	118/130
4027 [35]	NPH 30/70	28	177/187
4040 [36]	Insulin lispro	44	205/212
4042 [37]	OGLDs and dietary measures	40	103/108
6001 [38]	NPH	36	61/49

^aData available from sanofi-aventis on request
CSII, continuous subcutaneous insulin infusion (of insulin lispro [B28Lys,B29Pro human insulin]); OGLDs, oral glucose-lowering drugs

The most frequently reported site (insulin glargine vs comparator) included the skin (16 events in 12 people [0.2%] vs seven events in six [0.1%] people, RR 1.85, 95% CI 0.69–4.92), colon and rectum (six [0.1%] vs ten [0.2%], RR 0.55, 95% CI 0.20–1.52), breast (four [0.1%] vs six [0.1%], RR 0.62, 95% CI 0.17–2.18) and gastrointestinal tract (six [0.1%] vs four [0.1%], RR 1.38; 95% CI 0.39–4.90).

With respect to the type of malignancy, at least two more tumours were reported in the comparator group vs the insulin glargine group for the following classifications: colon and rectum (ten [0.2%] vs six [0.1%]), prostate (three [0.1%] vs one [0.0%]), neurological (two [0.0%] vs zero [0.0%]) and bladder (two [0.0%] vs zero [0.0%]). Con-

versely, there were nine more cases of skin cancer in the insulin glargine group compared with the comparator group (16 cases in 12 people [0.2%] vs seven cases in six people [0.1%]), including an imbalance of six (0.1%) to one (0.0%) for malignant melanoma. However, in the 5 year Study 4016, the incidence of all melanomas (documented as serious and non-serious adverse events) was not different between treatment groups (three each, with one case in the comparator [NPH insulin] group and two in the insulin glargine group reported as serious adverse events).

Within the sanofi-aventis safety database, in addition to the RCTs, there are 26 completed uncontrolled studies with insulin glargine, involving a total of 68,201 participants with type 1 or type 2 diabetes treated for up to 3 years. The data

Table 2 Participant characteristics in the studies identified for inclusion in the analysis

Trial number	Age (years)		Sex ratio M/F		BMI (kg/m ²)		Duration of diabetes (years)		Baseline HbA _{1c} (%)	
	Insulin glargine	Comparator	Insulin glargine	Comparator	Insulin glargine	Comparator	Insulin glargine	Comparator	Insulin glargine	Comparator
Type 1 diabetes										
2002 ^a	37.3	37.9	51.2/48.8	53.4/46.6	24.2	24.5	16.3	16.3	7.9	7.9
2003 ^a	36.6	35.7	60.5/39.5	61.8/38.2	24.0	24.0	9.5	11.0	8.0	7.8
3001	39.4 (12.8)	39.0 (11.7)	54.8/45.2	56.7/43.3	24.6 (3.2)	25.1 (3.3)	15.9 (11.5)	15.2 (9.4)	7.9 (1.2)	8.0 (1.2)
3003	11.8 (2.5)	11.5 (2.4)	55.7/44.3	48.0/52.0	18.8 (2.8)	18.9 (2.9)	5.0 (3.0)	4.7 (3.1)	8.5 (1.3)	8.9 (1.6)
3004	38.2 (12.2)	38.9 (11.9)	53.4/46.6	47.8/52.2	25.6 (4.0)	25.9 (4.6)	17.9 (11.7)	16.9 (10.0)	7.7 (1.2)	7.7 (1.1)
3005	38.9 (12.2)	39.5 (12.2)	48.7/51.3	52.4/47.6	25.5 (3.4)	25.7 (3.9)	18.7 (11.5)	18.4 (11.8)	7.6 (1.2)	7.7 (1.2)
4003	36.4 (9.2)	37.4 (9.2)	45.0/55.0	26.0/74.0	26.3 (3.5)	25.2 (3.1)	N/A	N/A	N/A	N/A
4005	15.1 (1.7)	14.5 (1.6)	46.2/53.8	38.5/61.5	23.3 (4.1)	23.0 (3.8)	6.1 (3.6)	8.0 (3.3)	9.4 (1.1)	9.1 (1.4)
4006	41.1 (13.9)	41.1 (10.7)	32.0/68.0	41.4/58.6	26.5 (2.8)	25.4 (3.0)	22.4 (15.1)	20.8 (11.3)	8.1 (0.8)	7.9 (0.8)
4010	41.7 (12.9)	39.3 (13.9)	38.7/61.3	39.7/60.3	27.0 (3.6)	26.0 (3.9)	17.9 (10.5)	17.1 (9.7)	9.2 (1.1)	9.7 (1.3)
4030	13.1 (2.4)	13.3 (2.5)	45.9/54.1	45.6/54.4	22.7 (3.8)	22.7 (5.0)	5.1 (3.4)	5.4 (3.7)	7.8 (0.8)	8.0 (0.8)
4036	42.4 (9.9)	37.6 (12.3)	53.8/46.2	54.2/45.8	24.3 (1.9)	23.8 (2.7)	20.9 (10.6)	18.5 (8.4)	7.8 (0.6)	7.7 (0.7)
Type 2 diabetes										
2006	60.9 (10.8)	60.5 (9.8)	59.6/40.4	59.6/40.4	27.0 (2.9)	26.3 (3.3)	13.4 (8.2)	13.8 (8.6)	9.3 (1.1)	9.6 (1.2)
2004 ^a	59.5	59.2	61/39	57.4/42.6	27.2	27.7	9.7	9.1	9.7 (1.3)	9.5 (1.4)
3002	59.6 (9.3)	59.4 (9.1)	53.3/46.7	54.1/45.9	29.3 (4.3)	28.8 (4.3)	10.2 (6.2)	10.5 (6.0)	9.0 (1.2)	8.9 (1.1)
3006	59.5 (9.7)	59.2 (9.9)	57.9/42.1	62.2/37.8	30.7 (5.0)	30.4 (5.1)	13.4 (8.3)	14.1 (9.0)	8.6 (1.2)	8.5 (1.2)
3102 ^b	—	—	—	—	—	—	—	—	9.1 (1.1)	9.1 (1.0)
3502	56.2 (9.3)	56.8 (10.0)	66.5/33.5	63.7/36.3	31.2 (4.5)	31.4 (4.6)	7.7 (5.5)	8.2 (6.5)	8.6 (1.1)	8.5 (1.0)
4001	60.3 (9.2)	61.8 (8.5)	54.9/45.1	51.3/48.7	28.7 (4.2)	28.9 (3.9)	10.2 (7.0)	9.9 (6.0)	8.9 (0.8)	8.9 (0.8)
4002	54.7 (9.5)	55.6 (8.9)	55/45	56.3/43.7	32.5 (4.6)	32.2 (4.8)	8.4 (5.6)	9.0 (5.6)	8.6 (0.9)	8.6 (0.9)
4012	55.4 (8.4)	56.3 (8.4)	39.4/60.6	43.8/56.2	24.8 (3.0)	25.1 (3.1)	10.3 (6.2)	10.0 (5.2)	9.0 (0.9)	9.1 (0.9)
4013	56.1 (9.9)	57.1 (9.6)	42.9/57.1	38.0/62.0	27.3 (3.7)	27.2 (4.0)	10.3 (6.4)	10.8 (6.4)	9.0 (1.0)	9.2 (0.9)
4014	55.9 (10.5)	55.3 (11.4)	45.2/54.8	58/42	34.6 (7.0)	33.6 (6.3)	8.5 (5.8)	8.1 (5.1)	8.8 (1.0)	8.7 (1.0)
4016	54.9 (8.8)	55.3 (8.5)	54.2/45.8	53.6/46.4	34.5 (7.2)	34.1 (7.2)	10.7 (6.9)	10.8 (6.7)	8.4 (1.4)	8.3 (1.4)
4020	52.5 (11.0)	51.8 (10.3)	48/52	49.6/50.4	33.6 (7.0)	33.6 (7.3)	6.4 (4.9)	5.8 (4.2)	9.4 (1.2) ^c	9.4 (1.3) ^c
4021	54.2 (10.5)	52.8 (9.8)	47.8/52.2	45.5/54.5	33.4 (5.2)	33.5 (6.2)	10.1 (7.0)	8.9 (6.6)	9.1 (0.9)	9.0 (0.9)
4022	53.6 (9.7)	52.1 (10.3)	47.5/52.5	48.5/51.5	34.5 (7.0)	35.2 (7.4)	7.5 (4.5)	7.6 (6.0)	9.0 (1.2)	9.0 (1.2)
4027	60.9 (8.7)	60.4 (9.1)	61.0/39.0	57.0/43.0	29.5 (3.6)	29.6 (3.6)	9.9 (7.3)	9.9 (6.4)	8.9 (1.0)	8.9 (0.9)
4040	60.0 (9.0)	59.7 (9.0)	52.5/47.6	58.7/41.4	29.2 (3.7)	29.4 (3.5)	9.0 (6.8)	8.5 (6.1)	8.7 (1.0)	8.7 (1.0)
4042	60.6 (7.7)	60.7 (8.1)	55.3/44.7	50.0/50.0	30.1 (3.5)	29.8 (3.4)	10.0 (6.2)	10.1 (6.9)	7.6 (0.3)	7.5 (0.4)
6001	56.1 (9.4)	57.5 (8.5)	62/38	65/35	31.3 (5.3)	32.1 (5.4)	8.6 (4.3)	8.5 (4.8)	9.1 (1.2)	9.3 (1.1)

Data are means (SD) unless otherwise indicated

^a SDs for trials 2002, 2003 and 2004 are unavailable in source documents^b Data for trial number 3102 are unavailable^c Adjusted mean (SEM)

N/A, not applicable

Table 3 All malignant neoplasms reported in controlled clinical trials comparing insulin glargine with a comparator (participants evaluable for safety)

Trial duration	Insulin glargine			Comparator		
	No. of patients	All malignancies No. affected (%) [no. of events]	Breast cancer No. affected (%) [no. of events]	No. of patients	All malignancies No. affected (%) [no. of events]	Breast cancer No. affected (%) [no. of events]
Type 1 diabetes (12 trials): insulin glargine vs other basal insulin						
3001	292	2 (0.7) [2]	0	293	0	0
3004	264	3 (1.1) [3]	1 (0.4) [1]	270	0	0
3005	310	1 (0.3) [2]	0	309	2 (0.6) [2]	0
2002	168	0	0	88	0	0
2003	223	0	0	110	0	0
3003	174	0	0	175	0	0
4003	29	0	0	27	0	0
4005	26	0	0	25	0	0
4006	53	0	0	52	0	0
4010	62	0	0	63	0	0
4030	85	0	0	90	0	0
4036	26	0	0	24	0	0
Total type 1	1,712	6 (0.4) [7]	1 (0.1) [1]	1,526	2 (0.1) [2]	0
Type 2 diabetes: insulin glargine vs NPH insulin ≤1 year in duration (ten trials) ^a						
3002	289	3 (1.0) [3]	0	281	7 (2.5) [7]	1 (0.4) [1]
3006	259	6 (2.3) [8]	0	259	3 (1.2) [4]	0
3102	158	1 (0.6) [1]	0	159	1 (0.6) [1]	0
4001	464	3 (0.6) [3]	0	233	1 (0.4) [1]	0
4002	367	0	0	389	1 (0.3) [1]	1 (0.3) [1]
2004	136	0	0	68	0	0
4012	221	0	0	223	0	0
4013	231	0	0	250	0	0
4027	177	0	0	187	0	0
6001	61	0	0	49	0	0
Total	2,363	13 (0.6) [15]	0	2,098	13 (0.6) [14]	2 (0.1) [2]
Type 2 diabetes: insulin glargine vs NPH insulin >1 year in duration (one trial)						
4016	514	20 (3.9) [23]	3 (0.6) [3]	503	31 (6.2) [32]	4 (0.8) ^b
Type 2 diabetes: insulin glargine vs oral agents (five trials)						
3502	203	1 (0.5) [1]	0	197	0	0
4014	105	0	0	112	0	0
4020	164	0	0	181	0	0
4022	118	0	0	130	0	0
4042	103	2 (1.9) [2]	0	108	0	0
Total	693	3 (0.4) [3]	0	728	0	0
Type 2 diabetes: insulin glargine vs other insulin than NPH (three trials)						
2006	57	1 (1.8) [1]	0	57	0	0
4021	113	0	0	99	0	0
4040	205	2 (1.0) [3]	0	212	0	0
Total	375	3 (0.8) [4]	0	368	0	0
Total type 2 diabetes	3,945	39 (1.0) [45]	3 (0.1) [3]	3,697	44 (1.2) [46]	6 (0.2) [6]
Grand total	5,657	45 (0.8) [52]	4 (0.1) [4]	5,223	46 (0.9) [48]	6 (0.1) [6]

^a One study used NPH premixed insulin (4027)^b Includes one recurrent breast cancer; in addition, there was one case of breast cancer present at baseline that was not considered treatment emergent

Table 4 Location of malignancies in randomised controlled studies of insulin glargine

Classification	No. using insulin glargine (%) [no. of events]	No. in the control group (%) [no. of events]	Relative risk (95% CI)
Total number of people	5,657 (100) [52]	5,223 (100) [48]	–
Blood	2 (0.04) [2]	1 (0.02) [1]	1.85 (0.17–20.36)
Vertebral body	1 (0.02) [1]	0	–
Breast	4 (0.07) [4]	6 (0.11) [6]	0.62 (0.17–2.18)
Nasal	1 (0.02) [1]	0	–
Lung	3 (0.05) [3]	3 (0.06) [3]	0.92 (0.19–4.57)
Gastrointestinal (not otherwise stated)	6 (0.11) [6]	4 (0.08) [4]	1.38 (0.39–4.90)
Colon and rectum	6 (0.11) [6]	10 (0.19) [10]	0.55 (0.20–1.52)
Hepatic and biliary	2 (0.04) [2]	3 (0.06) [3]	0.62 (0.10–3.68)
Pancreas	3 (0.05) [3]	3 (0.06) [3] ^a	0.92 (0.19–4.57)
Renal	3 (0.05) [3]	0	–
Prostate	1 (0.02) [1]	3 (0.06) [3]	0.31 (0.03–2.96)
Bladder	0	2 (0.04) [2]	–
Genitourinary	3 (0.05) [3]	4 (0.08) [4]	0.69 (0.16–3.09)
Thyroid	2 (0.04) [2]	0	–
Endocrine	0	1 (0.02) [1]	–
Neurological	0	2 (0.04) [2]	–
Skin	12 (0.21) [16]	6 (0.11) [7]	1.85 (0.69–4.92)
Total number of people with malignancies ^b	45 (0.80) [52]	46 (0.88) [48]	0.90 (0.60–1.36)

^a Includes one pancreatic carcinoma from study 3005 that was erroneously reported as a non-serious adverse event

^b The sum of each location of malignancies differs slightly from the total number owing to the fact that individuals could have malignancies in more than one location or more than one preferred term may be associated with a malignancy

from these 26 uncontrolled studies represent a total follow-up time of 22,074 person-years for insulin glargine treatment.

In total, there were 111 cases of malignancy, including nine cases of breast cancer, reported in these studies. The overall cancer rate is estimated to be 5.0 cases per 1,000 person-years (111 out of 22,074 person-years) and the breast cancer rate is estimated to be 82 cases per 100,000 person-years (that is, nine out of 11,027 person-years—the denominator here being the exposure of women in the type 2 diabetes RCTs). In investigator-sponsored trials and product registries (intensified monitoring) for which no enrolment figures are available, the sanofi-aventis safety database contains an additional 75 individuals with malignancies, including nine cases of breast cancer.

Discussion

Based on our analysis of 31 RCTs, insulin glargine was not associated with an increased incidence of cancer, including breast cancer, when compared with the control/comparator group.

The overall incidence of cancer in the trials included in this analysis was lower in people with type 1 diabetes than

in those with type 2 diabetes, perhaps because the former were younger and less obese than the people with type 2 diabetes (Table 2), and were exposed for a shorter time. Obesity increases the risk of colon cancer by as much as 1.5- to 2-fold and accounts for up to 35% of the total incidence of colon cancer [9]. In terms of age, the prevalence of cancer increases with increasing age and peaks in people aged 75 years or older [10, 11]. People with type 2 diabetes in this analysis were typically in their mid to late fifties and, thus, the majority were at an age associated with greater risk for cancer compared with the people with type 1 diabetes.

The results presented are based on formal RCTs, which represent level 1—the highest level—of evidence-based study design. Another advantage of the present analysis is that the clinical trials database reviewed here included a large number of people ($n=10,880$), allowing the opportunity to identify rarer adverse events. Furthermore, the events were recorded reasonably accurately, as in any RCT, as the monitoring of adverse events followed the rules of good clinical practice and international pharmacovigilance regulations [12]. Finally, our analysis included one long-term 5 year controlled study that showed comparably reassuring findings, with no differences in the incidence of

cancers between patients treated with insulin glargine and patients treated with NPH insulin.

Nevertheless, this analysis must be considered in light of some limitations. The duration of most of the studies was relatively short (mostly 6 months) and does not reflect the lifetime risk for cancer, while only one study was longer than 1 year. Nevertheless, if growth promotion is postulated as the mechanism of any increased cancer risk, it would appear early in the use of any therapeutic entity. None of the RCTs was specifically designed to evaluate the risk of cancer with insulin glargine, although all had mandatory reporting of adverse events, including treatment-emergent neoplasms. Randomised controlled trials may not fully reflect real-life clinical practice; investigators may, for example, be less likely to include people with previous malignancies. People using thiazolidinediones, which have been suggested as protective against breast or pancreatic cancer [13, 14] and linked with increases in bladder cancer, [13] were often not included in the insulin studies, owing to the relative or absolute labelling restrictions in participating countries. Finally, the number of malignancies reported here may differ slightly from the published numbers for each study owing to differences in reporting methods; for example, only cases classified as serious treatment-emergent events were included in this analysis, whereas the original publications may have included cases classified as non-serious or serious. In addition, we only included treatment-emergent cases, whereas some of the publications may have included pre-existing cases.

However, analysis of the 26 uncontrolled trials with insulin glargine shows that the overall cancer rate is estimated to be 5.0 cases per 1,000 person-years. Compared with the age-adjusted incidence rate of 4.63 per 1,000 per year in the USA (based on cases diagnosed in 2002–2006 from 17 geographic areas included in the Surveillance, Epidemiology and End Results [SEER] programme), there was no indication of increased cancer risk in people with diabetes using insulin glargine. However, we acknowledge that under-reporting of cancer events can occur in uncontrolled observational studies, where follow-up with physicians is not always possible and, therefore, these results should be interpreted with caution.

For breast cancer, the incidence rate in women participating in non-interventional trials of insulin glargine may be estimated to be 82 cases per 100,000 person-years. Compared with the incidence rate of 124 per 100,000 women per year in the US SEER database, no safety signal for breast cancer was identified with the use of insulin glargine in these clinical trials.

In conclusion, these data suggest that insulin glargine is not associated with an increased risk of cancer compared with the different comparators (mainly NPH insulin). While the data provide useful reassuring and contributory infor-

mation regarding the safety of insulin glargine, they underscore the importance of continued long-term follow up of participants in clinical trials.

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