Similar efficacy and safety with LY2963016 insulin glargine compared with insulin glargine in patients with type 2 diabetes mellitus: the ELEMENT 2 study

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Background and aims: LY2963016 (LY IGlar) and insulin glargine (Sanofi-Aventis; IGlar) are both insulin glargine products, with identical amino acid sequences. Even with identical primary structure, protein-based therapeutics manufactured by distinct processes must be shown to be clinically similar.
Materials and methods: This was a 24-week, Phase 3, randomized, double-blind, parallel study to compare the efficacy and safety of LY IGlar and IGlar. The primary objective was to test the non-inferiority (0.3% margin) of LY IGlar to IGlar as measured by change in HbA_{1c} from baseline to 24 weeks in patients with T2DM on ≥2 oral antihyperglycaemic medications (OAMs). Testing for non-inferiority of IGlar to LY IGlar was also performed and pre-specified as a complementary hypothesis, which if met along with the primary aim, would demonstrate equivalent efficacy between LY IGlar and IGlar. Patients were insulin-naïve (HbA_{1c} ≥7.0% to ≤11.0%) or previously on IGlar (HbA_{1c} ≤11.0%). Insulin-naïve patients started on 10 U/day while those previously on IGlar started at an equivalent dose to their prestudy IGlar dose. Both groups followed a patient-driven titration algorithm until fasting blood glucose reached ≤5.6 mmol/L. For blinding purposes, patients randomized to treatment were provided syringes and insulin vials contained in a partial cover that concealed distinguishing differences in vial appearance.
Results: Both treatment groups had within-group similarly significant (p<.001) decreases in mean HbA_{1c} values (~ -1.3% [Endpoint: LY IGlar, 7.04%; IGlar, 6.99%]). Change in HbA_{1c} from baseline with LY IGlar was non-inferior to IGlar (Table). Noninferiority of IGlar to LY IGlar was also demonstrated; thus, criteria for equivalence in clinical efficacy between LY IGlar and IGlar were met. There were no treatment differences in secondary efficacy or safety outcomes, including hypoglycaemia and treatment-emergent antibody response, in the total population and in the insulin-naïve/prestudy IGlar subgroups. The treatment groups had similar mean (SD) overall nocturnal hypoglycaemia rate (events/patient/year) (LY IGlar: 7.46 (11.73), IGlar: 8.08 (14.62), p=.686) and only 2 patients per group experienced severe hypoglycaemia. Adverse event frequencies (LY IGlar, 52%; IGlar, 48%; p=.31) were similar. No treatment differences were observed in mean (SD) weight change (kg) at endpoint, LY IGlar: 2.09 (3.80), IGlar: 2.33 (3.39), p=.334).
Conclusion: LY IGlar compared with IGlar in combination with OAMs provided equivalent efficacy and similar safety profiles in patients with T2DM.

Table

Outcome Measure LSM (SE) Unless Otherwise Indicated		Total LY IGlar N=376[a]	Total IGlar N=380[a]	p-value	Insulin Naïve LY IGlar N=220[a]	Insulin Naïve IGlar N=235[a]	p-value
HbA_{1c} (%)	Baseline	8.350 (0.06)	8.310 (0.06)	.611	8.502 (0.07)	8.425 (0.07)	.449
	Change from Baseline (LOCF)	-1.286 (0.06)	-1.338 (0.06)	.403	-1.475 (0.07)	-1.536 (0.07)	.432
	LSM Diff [95% CI] (LOCF)	0.052 [-0.070, 0.175]			0.061 [-0.091, 0.214]		
N (%) of Patients Reaching HbA_{1c} <7.0%		180 (49)	197 (53)	.340	117 (54)	139 (60)	.355
FBG (mmol/L) by SMBG	Baseline	8.8 (0.1)	8.9 (0.1)	.837	9.6 (0.2)	9.5 (0.2)	.528
	Change from Baseline (LOCF)	-2.6 (0.2)	-2.6 (0.2)	.685	-3.2 (0.2)	-3.1 (0.2)	.726
	LSM Diff [95% CI] (LOCF)	-0.07 [-0.40, 0.26]			-0.07 [-0.478, 0.334]		
Daily Mean Blood Glucose (LOCF), mmol/L		7.6 (0.1)	7.7 (0.1)	.401	7.4 (0.1)	7.4 (0.1)	.842
Insulin Dose, U/kg/day Mean (SD)		0.50 (0.03)	0.48 (0.03)	.393	0.45 (0.03)	0.46 (0.03)	.640
Total Hypoglycaemia[b] Rate (events/patient/year) Mean (SD), Overall		21.3 (24.4)	22.3 (28.2)	.995	21.6 (25.6)	22.9 (27.4)	.432
N (%) of Patients with TEAR, Overall		14 (3.8)	14 (3.8)	>.999	10 (4.7)	13 (5.8)	.612

[a]Full Analysis Set, N numbers reflect maximum sample size
[b]Including events with blood glucose ≤3.9 mmol/L, if blood glucose was available
LOCF = last observation carried forward (endpoint); LSM = least squares mean; TEAR = treatment emergent antibody response (including patients who were antibody negative at baseline and developed antibody binding values ≥1.26% postbaseline or patients with detectable antibody levels at baseline with at least a 1% increase in antibody binding value and which is 30% greater than baseline).

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