Conclusion: Exenatide QW elicited a robust and sustained improvement in glycaemic control in patients with type 2 diabetes who were on an array of background treatments. Importantly, this effect was associated with improvements in broader cardiometabolic measures, including body weight and lipids.
Clinical Trial Registration Number: NCT00308139

PS 063 GLP-1 receptor agonists: new drugs and new formulations

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Efficacy and safety of lixisenatide once-daily versus placebo in patients with type 2 diabetes mellitus insufficiently controlled on metformin (GetGoal-F1)

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Background and aims: This randomised, double-blind, placebo-controlled, parallel-group, multicentre study compared the efficacy and safety of lixisenatide QD in two dose-increase regimens vs placebo as add-on therapy in T2DM inadequately controlled by metformin.
Materials and methods: Patients with T2DM (n=482) treated with metformin (mean age 56.1 yr, diabetes duration 6.0 yr, BMI 32.5 kg/m^2, HbA_{1c} 8.0%) were randomised to one of 4 QD regimens: lixisenatide 2-step dose increase (10 μg for 1 wk, 15 μg for 1 wk then 20 μg; n=161), lixisenatide 1-step dose increase (10 μg for 2 wk then 20 μg; n=161), placebo 2-step (n=79) or placebo 1-step (n=81) (placebo groups were combined). After screening of up to 3 wk, patients entered a 24-wk main treatment period, followed by a variable extension of at least 52 wk, with lifestyle advice every 3 mo. The primary objective was to assess the efficacy of lixisenatide (2-step regimen) vs placebo in terms of HbA_{1c} reduction at Wk 24. Efficacy of the 1-step regimen was the next test in a step-down testing procedure.
Results: The 24-wk main treatment period data are presented. There were significant improvements in HbA_{1c} from baseline to Wk 24 in both lixisenatide groups vs placebo ($p<0.0001$) (Table). Significantly more patients in the lixisenatide groups achieved HbA_{1c} ≤6.5% (20.4% 2-step, 25.6% 1-step) and <7.0% (42.1% 2-step, 47.4% 1-step) vs placebo (7.6% and 24.1%, respectively; $p<0.001$). There were also significant improvements in FPG and body weight with lixisenatide vs placebo (Table). Rates of premature treatment discontinuation at Wk 24 were 10.6% in the lixisenatide 2-step, 8.7% in the 1-step and 5.6% in the placebo groups. Fewer patients required rescue therapy in both lixisenatide groups than in the placebo group (3.1% [2-step] and 1.3% [1-step] vs 4.4%). The incidence of patients with serious AEs was comparable in the lixisenatide groups (4.3% [2-step]; 3.1% [1-step]) and the placebo group (2.5%). The overall incidence of patients with AEs was 70.8% for lixisenatide 2-step, 67.7% for 1-step and 65.6% for placebo. The most frequently reported AEs were nausea (35.4% [2-step] and 26.1% [1-step] vs 4.4% with placebo) and vomiting (15.5% [2-step] and 11.8% [1-step] vs 0% with placebo). No significant difference was seen in the % of patients with symptomatic hypoglycaemia between the lixisenatide groups (2.5% [2-step]; 1.9% [1-step]) and placebo (0.6%; $p>0.1$). There were no cases of severe hypoglycaemia.
Conclusion: Lixisenatide QD administered in a 1- or 2- dose increase regimen significantly improved glycaemic control and decreased weight over 24 wks with no increased risk of hypoglycaemia in T2DM patients insufficiently controlled on metformin.

Parameter		Lixisenatide 2-step dose increase	Lixisenatide 1-step dose increase	Placebo
Mean baseline and 24-week changes in efficacy parameters (mITT population)		**N=160**	**N=158**	**N=159**
HbA_{1c} (%)	Baseline±SD	8.12±0.89	7.99±0.88	8.03±0.83
	LS mean±SE change from baseline	-0.83±0.10	-0.92±0.10	-0.42±0.10
	LS mean difference *vs* placebo [95% CI]; p-value	-0.41 [-0.58 to -0.23]; p<0.0001	-0.49 [-0.67 to -0.32]; p<0.0001	—
Fasting plasma glucose (mmol/L)	Baseline±SD	9.52±2.50	9.55±2.04	9.46±1.95
	LS mean±SE change from baseline	-0.56±0.21	-0.53±0.21	+0.11±0.21
	LS mean difference *vs* placebo [95% CI]; p-value	-0.67 [-1.04 to -0.30]; p=0.0004	-0.65 [-1.02 to -0.28]; p=0.0007	—
Body weight (kg)	Baseline±SD	88.1±16.8	90.3±19.0	87.9±17.3
	LS mean±SE change from baseline	-2.68±0.39	-2.63±0.39	-1.63±0.39
	LS mean difference *vs* placebo [95% CI]; p-value	-1.05 [-1.73 to -0.37]; p=0.0025	-1.00 [-1.69 to -0.32]; p=0.0042	—
Safety parameters (safety population)		**N=161**	**N=161**	**N=160**
N (%) of patients with symptomatic hypoglycaemia *		4 (2.5%)	3 (1.9%)	1 (0.6%) p>0.1

*event with clinical symptoms with either plasma glucose <3.3 mmoL or prompt recovery after oral carbohydrate administration if no plasma glucose measurement was available.

Clinical Trial Registration Number: NCT00763451
Supported by: sanofi aventis

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Efficacy and safety of lixisenatide once-daily versus placebo in patients with type 2 diabetes mellitus insufficiently controlled on sulfonylurea ± metformin (GetGoal-S)

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Background and aims: This randomised, double-blind, placebo-controlled, two-arm, parallel-group, multicentre study compared the efficacy and safety of once-daily (QD) lixisenatide vs placebo as add-on therapy in people with T2DM inadequately controlled by sulfonylurea ± metformin.
Materials and methods: A total of 859 patients with T2DM treated with a sulfonylurea ± metformin (16% on sulfonylurea alone, mean age 57.2 yrs, diabetes duration 9.4 yrs, BMI 30.2 kg/m^2, baseline HbA_{1c} 8.3%) were randomised to lixisenatide 20 µg QD (n=573) or placebo (n=286) in a 2-step dose increase regimen. After a screening period of up to 3 weeks, patients entered a 24-week main treatment period, followed by a variable extension of at least 52 weeks. The primary objective was to assess the efficacy of lixisenatide vs placebo in terms of HbA_{1c} reduction at Week 24.
Results: The 24-week main treatment period data are presented. Lixisenatide QD significantly reduced HbA_{1c} compared to placebo (-0.85 vs -0.10%; p<0.0001). Lixisenatide QD vs placebo also significantly improved 2-hour PPG (after a standardised meal test) (-6.19 vs -0.21 mmol/L), FPG (-0.99 vs -0.36 mmol/L) and body weight (-1.76 vs -0.93 kg) and increased the proportion of patients achieving HbA_{1c} <7.0% (36.4 vs 13.5%) (p<0.0001 for all; see Table). The percentage of patients requiring rescue therapy was significantly lower in the lixisenatide group than in the placebo group (3.5% and 12.0% respectively, p<0.0001). Rates of premature treatment discontinuation at Week 24 were 12.9% in the lixisenatide group and 10.8% in the placebo group. The overall incidence of patients with adverse events (AEs) was 68.3% in the lixisenatide group and 61.1% in the placebo group. The difference between groups was mainly attributable to GI events, mainly nausea (25.3% with lixisenatide vs 7.0% with placebo) and vomiting (8.7% vs 3.5%). No difference was seen in the incidence of patients with serious AEs between lixisenatide (3.5%) and placebo (5.6%). Lixisenatide QD did not significantly increase symptomatic hypoglycaemia vs placebo (Table). There was 1 case (0.2%) of severe hypoglycaemia in the lixisenatide group and none in the placebo group.
Conclusion: Add-on treatment with lixisenatide once-daily significantly improved glycaemic control with weight loss, without increasing the risk of hypoglycaemia, over 24 weeks in T2DM patients insufficiently controlled on sulfonylurea ± metformin.

Parameter		Lixisenatide	Placebo	
Mean baseline and 24-week changes in efficacy parameters (mITT population)		**N=564**	**N=284**	**LS mean difference [95% CI]; p-value**
HbA_{1c} (%)	Baseline±SD	8.28±0.86	8.22±0.83	
	LS mean±SE change from baseline	-0.85±0.06	-0.10±0.07	-0.74 [-0.87 to -0.62]; p<0.0001
2-hour postprandial plasma glucose (mmol/L)*	Baseline±SD	16.61±4.09	16.55±3.74	
	LS mean±SE change from baseline	-6.19±0.41	-0.21±0.49	-5.98 [-6.91 to -5.04]; p<0.0001
Fasting plasma glucose (mmol/L)	Baseline±SD	9.67±2.24	9.29±2.37	
	LS mean±SE change from baseline	-0.99±0.14	-0.36±0.16	-0.63 [-0.92 to -0.35]; p<0.0001
Body weight (kg)	Baseline±SD	82.6±21.9	84.5±22.8	
	LS mean±SE change from baseline	-1.76±0.20	-0.93±0.23	-0.84 [-1.25 to -0.42]; p<0.0001
Proportion achieving HbA_{1c}<7.0%	n (%)	198 (36.4%)	37 (13.5%)	p<0.0001
Safety parameters (safety population)		**N=574**	**N=285**	**p-value**
N (%) of patients with symptomatic hypoglycaemia**		88 (15.3%)	35 (12.3%)	>0.1

*using a standardised meal-test in selected sites (lixisenatide: n=249, placebo: n=120)
**event with clinical symptoms with either plasma glucose <3.3 mmoL or prompt recovery after oral carbohydrate administration if no plasma glucose measurement was available.

Clinical Trial Registration Number: NCT00713830
Supported by: sanofi-aventis

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Efficacy and safety of lixisenatide once-daily versus exenatide twice-daily in patients with type 2 diabetes insufficiently controlled on metformin (GetGoal-X)

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Background and aims: This randomised, open-label, active-controlled, parallel-group, multicentre study compared the efficacy and safety of lixisenatide QD *vs* exenatide BID as add-on therapy in T2DM inadequately controlled on metformin monotherapy.
Materials and methods: Individuals with T2DM (n=634) treated with metformin ≥1.5 g/day (mean age 57.4 yr, diabetes duration 6.8 yr, BMI 33.6 kg/m^2, HbA_{1c} 8.0%) were randomised to lixisenatide 20 µg QD (n=318) or exenatide 10 µg BID (n=316). After a screening period of up to 2 wk, subjects entered a 24-wk main treatment period, followed by a variable extension of at least 52 wk. Both groups received a stepwise increase in dose up to a maximum 20 µg/day. The primary objective was to demonstrate non-inferiority of lixisenatide to exenatide in terms of HbA_{1c} reduction at Wk 24. Non-inferiority was demonstrated if the upper limit of the 2-sided 95% CI of the difference between lixisenatide and exenatide in adjusted mean change in HbA_{1c} from baseline to Wk 24 was ≤0.4%.
Results: The 24-wk main treatment period data are presented. Lixisenatide QD achieved its primary endpoint of non-inferiority in HbA_{1c} reduction from baseline [BL] at Wk 24 *vs* exenatide BID (Table). Improvements in mean FPG and the proportion of subjects achieving HbA_{1c} <7.0% were comparable between groups (Table). Mean body weight significantly decreased from BL in both groups: 94.5 to 91.7 kg with lixisenatide and 96.7 to 92.9 kg with exenatide. The incidence of subjects with adverse events (AEs) was similar for lixisenatide (69.5%) and exenatide (72.2%). Rates of premature treatment discontinuation were 12.9% and 14.2% for lixisenatide and exenatide, respectively, and discontinuations due to AEs (mainly GI events) were 33 (10.4%) in lixisenatide and 41 (13.0%) in exenatide subjects. Serious AEs occurred in 9 lixisenatide (2.8%) and 7 exenatide (2.2%) subjects. Significantly fewer subjects experienced symptomatic hypoglycaemia with lixisenatide, with 6-fold fewer hypoglycaemic events with lixisenatide (Table). There were no cases of severe hypoglycaemia. Overall GI tolerability appeared better for lixisenatide *vs* exenatide, with fewer experiencing nausea and vomiting (Table). More subjects in the lixisenatide group tolerated the targeted maintenance dose of 20 µg/day (93% *vs* 83% exenatide).
Conclusion: Add-on lixisenatide QD in T2DM insufficiently controlled on metformin demonstrated non-inferior improvements in HbA_{1c}, but with less