Mean ± standard deviation (SD) baseline characteristics were similar in the linagliptin versus placebo groups: age, 59.7±9.9 versus 60.4±10.0 years; BMI, 30.8±5.4 versus 31.2±4.9 kg/m^2; HbA1C, 8.3%±0.9% in both groups; and basal insulin dose, 41.5±31.9 versus 40.1±27.3 IU/day. Mean exposure to study medication was comparable in both groups: 435 days for linagliptin versus 422 days for placebo.

Overall safety and tolerability of linagliptin was similar to placebo. The proportion of patients with ≥1 adverse event (AE) was slightly lower with linagliptin (78.4%) compared with placebo (81.4%); most AEs were of mild or moderate intensity. Despite better glycemic control with linagliptin, the incidence of hypoglycemia was similar in both groups (linagliptin 31.4%; placebo 32.9%), and the number of severe hypoglycemic events was low (linagliptin 1.7%; placebo 1.1%; Table 1). Mean ± SD change in body weight was minimal and comparable between the treatment groups (linagliptin –0.30±3.70 kg; placebo –0.04±3.10 kg).

Table 1. Incidence of Hypoglycemia in Linagliptin and Placebo Groups.

	Week 24		End of Treatment	
	Linagliptin 5 mg QD	Placebo	Linagliptin 5 mg QD	Placebo
Number of patients[a]	631	630	631	630
Hypoglycema (%)	22.0	23.2	31.4	32.9
Any confirmed symptomatic hypoglycemia[1] **with plasma glucose ≤3.9 mmol/L (70 mg/dL)**	17.0	18.7	23.9	25.1
Any confirmed symptomatic hypoglycemia[2] **with plasma glucose ≤3 mmol/L (54 mg/dL)**	8.6	8.7	14.3	14.1
Any severe hypoglycemic episode[3]	0.3	0.6	1.7	1.1

a Treated set: all patients who were treated with at least one dose of the study medication.

1 Accompanied by typical symptoms of hypoglycemia.

2 Accompanied by typical symptoms of hypoglycemia, but no need for external assistance.

3 Requiring the assistance of another person to actively administer carbohydrate, glucagon, or other actions.

The placebo-adjusted mean ± standard error (SE) change in HbA1C from baseline to Week 52 was –0.53%±0.05% ($p<0.0001$). This was accompanied by a mean ± SE change in basal insulin dose up to Week 52 of +2.6±0.8 IU/day for linagliptin versus +4.2±0.8 IU/day for placebo ($p<0.003$).

This trial demonstrated that linagliptin as add-on therapy to basal insulin significantly improved glycemic control after 24 weeks and did so independently of renal function and type of basal insulin. It was not associated with an increased risk of hypoglycemia or weight gain. Adding a DPP-4 inhibitor instead of a sulfonylurea to further improve glucose control might avoid hypoglycemia and weight gain.

12-Week Treatment with LY2409021 Significantly Lowers HbA1C and Is Well Tolerated in Patients with Type 2 Diabetes Mellitus

Written by ***Maria Vinall***

The glucagon receptor antagonist LY2409021 (LY) substantially lowers HbA1C without severe hypoglycemia or weight gain in type 2 diabetes mellitus (T2DM) patients. In a double-blind, randomized, placebo-controlled, Phase 2 study presented by Christof M. Kazda, MD, Eli Lilly and Company, Suresnes, France, researchers examined the margin between LY efficacy and safety by comparing mean changes in HbA1C and liver aminotransferases at 3 dose levels.

T2DM pathophysiology is characterized by greater postprandial glucose release, impaired insulin secretion, and abnormal glucagon plasma levels [Woerle HJ et al. *Am J Physiol Endocrinol Metab* 2006]. LY is a potent, selective glucagon receptor antagonist that inhibits hepatic glucose output and has significant glucose-lowering effects [Kelly RP et al. ADA 2011 Abstract 1004-P; Tham LS et al. ADA 2011 Abstract 416-PP]. In a Phase 1 study [NCT01606397], LY improved glycemic parameters and showed reversible dose-dependent increases in serum aminotransferase levels. The incidence of hypoglycemia was infrequent and was considered to be of mild to moderate intensity [Kelly RP et al. ADA 2011 Abstract 305-OR].

The primary endpoint of the current Phase 2a study [NCT00871572] was mean change in HbA1C and liver aminotransferases. Secondary objectives included the evaluation of LY effects on blood glucose, insulin, glucagon, glucagon-like peptide-1 (GLP-1), and blood lipids, as well as safety and tolerability.

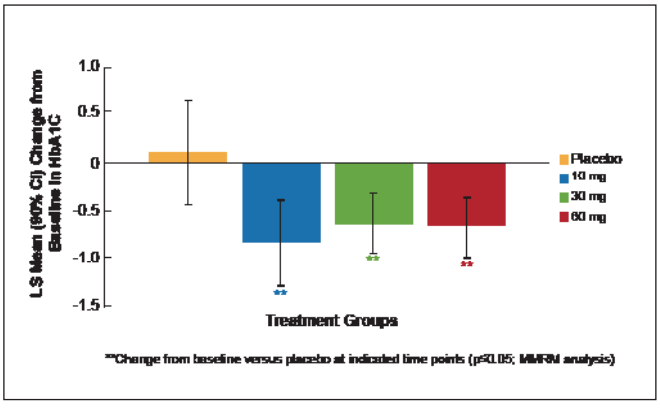
Patients aged 18 to 70 years with T2DM (HbA1C 6.5% to 10%) and a body mass index of 25 to 40 kg/m^2 who were

treated with diet and exercise alone, or with a stable dose of metformin (≥1000 mg/day for ≥3 months prior to screening) were eligible. Key exclusion criteria were related to hepatic diseases. Subjects (mean age 50 years, mean diabetes duration between 3 and 5 years) were randomly assigned to LY 10 mg (n=17), 30 mg (n=34), 60 mg (n=26), or placebo (n=10) QD for 12 weeks. There were 52.9% to 58.8% of the LY patients taking metformin versus 70% of placebo subjects. Mean baseline HbA1C was highest in the LY 10-mg group (8%) and 7.5%, 7.6%, and 7.8% in the 30-mg, 60-mg, and placebo groups, respectively.

At Week 12, HbA1C change from baseline showed that LY was associated with significant ($p \leq 0.05$) dose-dependent improvements in glycemic control in contrast to placebo (Figure 1). LY also produced dose-dependent increases in fasting glucagon, alanine aminotransferase, aspartate aminotransferase, and total GLP-1 that returned to baseline after LY washout.

The proportions of patients who experienced any treatment-emergent adverse event (TEAE) were similar in all treatment groups. No severe TEAEs were reported. Two non-drug-related serious adverse events occurred. There were no severe hypoglycemia events and 4 confirmed (blood glucose measurements) hypoglycemia events. Incidence of hypoglycemia was not dose dependent. There were no significant changes from baseline observed in any of the 3 LY treatment groups compared with placebo for body weight, blood pressure, triglycerides, low-density lipoprotein and high-density lipoprotein cholesterol, bilirubin, fasting insulin, or active GLP-1.

Figure 1. miTT Population: Mean Change from Baseline in HbA1C at Week 12.



LS=least squares; miTT=modified intention-to-treat; MMRM=Mixed Model Repeated Measures.

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Treatment with LY resulted in dose-dependent transient increases in mean aminotransferase, fasting glucagon, and total GLP-1 levels without elevated bilirubin or other signs/symptoms of liver injury. There were no increases in body weight, lipids, or blood pressure. The efficacy, safety, and tolerability profile of LY in patients with T2DM supports further clinical development.