The fixed-ratio combination is delivered in a once-daily single-injection device, consisting of insulin degludec 1 U and liraglutide 0.036 mg. It was compared with its individual components, liraglutide or insulin degludec alone, in a 26-week study of insulin-naïve patients with T2DM (n=1663) who were inadequately controlled on metformin plus/minus pioglitazone. Patients were randomized to the fixed-dose combination insulin degludec/liraglutide once daily (n=834), insulin degludec (n=414), or liraglutide 1.8 mg (n=415). The dosages of the fixed-dose combination and insulin degludec were titrated to achieve a mean fasting plasma glucose (FPG) of 72 to 90 mg/dL.

The primary endpoint was the change in HbA1C level over 26 weeks. HbA1C decreased by a mean of 1.91% (from 8.3% to 6.4%) in the patients randomized to fixed-dose insulin degludec/liraglutide, which was superior to liraglutide (1.28% reduction in HbA1C) and noninferior to insulin degludec (1.44% reduction in HbA1C).

Some 80.6% of patients treated with the fixed-dose combination reached the HbA1C goal of <7%, and 69.7% reached <6.5%, compared with 60.4% and 41.4%, respectively, with liraglutide alone, and 65.1% and 47.5%, respectively, with insulin degludec alone.

The fixed-dose insulin degludec/liraglutide combination also resulted in a mean weight reduction of 0.5 kg compared with a 2.2-kg increase with insulin degludec alone. The rate of confirmed hypoglycemia was 32% lower with fixed-dose insulin degludec/liraglutide than with insulin degludec. As expected, liraglutide was associated with less hypoglycemia and greater weight reduction than either basal insulin formulation.

At 26 weeks, change in FPG was similar for fixed-dose insulin degludec/liraglutide (5.6 mmol/L) and insulin degludec (5.8 mmol/L), compared with 7.3 mmol/L with liraglutide ($p<0.0001$ vs fixed-dose insulin degludec/liraglutide). An identical reduction in FPG level from baseline (65 mg/dL) in each insulin group occurred even though the final mean daily dose of insulin degludec in the group randomized to the fixed-dose combination was 15 U/day lower than in the group randomized to insulin degludec alone, said Prof. Gough.

Nine-point glucose profiles showed significantly lower mean prandial increments with fixed-dose insulin degludec/liraglutide and liraglutide compared with insulin degludec following all three main meals.

Gastrointestinal side effects with fixed-dose insulin degludec/liraglutide occurred less frequently than with liraglutide.

Fixed-dose insulin degludec/liraglutide combines the effects of insulin degludec and liraglutide in one injection, resulting in a substantial overall improvement in glycemic control with a low risk of hypoglycemia and weight gain, concluded Prof. Gough.

Glycemic Improvement With Canagliflozin Is Durable in T2DM Patients on Metformin

Written by **Wayne Kuznar**

The sodium glucose cotransporter 2 inhibitor canagliflozin is associated with durable glycemic improvement over 104 weeks compared with glimepiride in patients with type 2 diabetes mellitus (T2DM) on background metformin therapy. Such was the primary finding of a Phase 3 randomized, double-blind efficacy and safety study presented by Gisle Langslet, MD, Lipid Clinic, Oslo University Hospital, Oslo, Norway.

A previous Phase 3 study had demonstrated that canagliflozin 100 mg/day was noninferior to glimepiride (mean maximum dose 5.6 mg) and canagliflozin 300 mg/day was superior to glimepiride in lowering levels of HbA1C in patients with T2DM on background metformin over 52 weeks; both doses of canagliflozin were associated with reductions in body weight compared with glimepiride [Cefalu WT et al. *Lancet* 2013].

The 104-week study represents the longest follow-up of canagliflozin treatment to date, said Prof. Langslet. It compared canagliflozin with glimepiride in patients with T2DM inadequately controlled on metformin monotherapy. Patients with HbA1C ≥7.0% and ≤9.5% were randomized after a 2-week placebo run-in to canagliflozin 100 or 300 mg/day, or glimepiride up to 8 mg/day during the 52-week core period (n=1450), followed by a 52-week extension (n=1050). The mean duration of diabetes was 6.6 years. At baseline, patients' mean age was 56.2 years, their mean HbA1C was 7.8%, their mean fasting plasma glucose (FPG) was 9.2 mmol/L, and their mean body mass index was 31.0 kg/m^2.

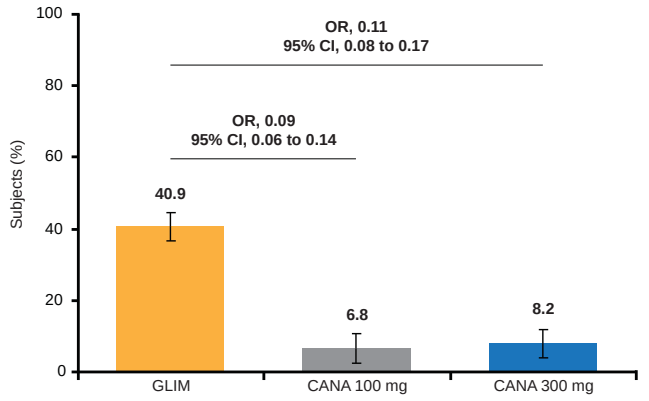
The rate of rise per year in HbA1C from Week 26 to Week 104 was lower with canagliflozin 100 and 300 mg than with glimepiride (0.16%, 0.16%, and 0.37%, respectively). The mean change in FPG from baseline to Week 104 was –0.6 mmol/L with glimepiride compared with –1.1 mmol/L with canagliflozin 100 mg, and –1.3 mmol/L with canagliflozin 300 mg. Body weight increased from baseline to Week 104 by 0.9% in the glimepiride group and decreased by 4.1% and 4.2% in the groups randomized to canagliflozin 100 mg and 300 mg, respectively. The weight changes were maintained over the 52-week extension period.

Systolic blood pressure increased by 1.7 mm Hg from baseline to Week 104 in the glimepiride group but declined by 2.0 and 3.1 mm Hg with canagliflozin 100 and 300 mg, respectively. Both canagliflozin doses were associated with increases in high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) that were

stable from Week 26 to Week 104. Increases in LDL-C and HDL-C were smaller in patients randomized to glimepiride relative to canagliflozin, and these increases were also stable from Week 26.

Fewer subjects had hypoglycemic events with either dose of canagliflozin than with glimepiride (Figure 1).

Figure 1. Documented Hypoglycemic Episodes*



*Includes episodes that were biochemically documented (≤3.9 mmol/L) or severe (ie, requiring the assistance of another individual or resulting in seizure or loss of consciousness).

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The incidences of adverse events were 73.3%, 77.9%, and 78.4% with canagliflozin 100 mg and 300 mg and glimepiride, respectively. The incidences of serious adverse events were 9.7%, 9.7%, and 14.3% in the three groups, respectively. The rates of genital mycotic infection rates were higher in the canagliflozin groups than in the glimepiride group (Table 1). Higher rates of osmotic diuresis-related adverse events and urinary tract infections were observed with canagliflozin compared with glimepiride.

Table 1. Incidence of Selected Adverse Events

	Subjects, n (%)		
	GLIM (n=482)	CANA 100 mg (n=483)	CANA 300 mg (n=485)
Urniary tract infection	33 (6.8)	51 (10.6)	42 (8.7)
Genital mycotic infection			
Male	5 (1.9)	24 (9.5)	22 (9.1)
Female	6 (2.7)	32 (13.9)	38 (15.6)
Osmotic diuresis-related AEs*	10 (2.1)	28 (5.8)	32 (6.6)
Volume-related AEs†	11 (2.3)	8 (1.7)	12 (2.5)

*Includes dry mouth, micturition urgency, nocturia, pollakiuria (increased urine frequency), polydipsia, polyuria (increased urine volume), thirst, and urine output increased; †Includes blood pressure decreased, dehydration, dizziness postural, hypotension, orthostatic hypotension, presyncope, and syncope; AE=adverse event.

A larger decrease in estimated glomerular filtration rate was observed with glimepiride (6.2 mL/min/1.73 m^2) than with canagliflozin 100 and 300 mg (2.0 and 3.8 mL/min/1.73 m^2, respectively) at Week 104.

New Insulin Glargine Formulation Associated With Less Nocturnal Hypoglycemia

Written by Wayne Kuznar

A long-acting basal insulin glargine formulation, 300 U/mL (Gla-300), controlled glycemia as well as insulin glargine 100 U/mL (Gla-100) in patients with type 2 diabetes mellitus (T2DM) but with less nocturnal hypoglycemia. Matthew C. Riddle, MD, Oregon Health & Science University, Portland, Oregon, USA, presented findings from a Phase 3 multicenter, open-label study comparing the two insulin glargine formulations in patients with T2DM who were using basal plus mealtime insulin.

Gla-100 is a widely used basal insulin with no pronounced peak of action and a duration of action of ~24 hours; it causes less hypoglycemia than human neutral protamine Hagedorn (NPH) insulin [Riddle MC et al. *Diabetes Care* 2003]. The investigational insulin glargine (Gla-300) contains the same molecule as Gla-100 but in a lower volume. It has a flatter and more prolonged pharmacokinetic and pharmacodynamics profile than Gla-100 [Jax T et al. EASD 2013 (abstr 1029)]. Whether or not the differences in pharmacokinetics between Gla-100 and Gla-300 translate into a clinical benefit is being tested in a worldwide series of Phase 3 studies in several populations of patients with type 1 diabetes mellitus and T2DM. The data presented here from the Comparison of a New Formulation of Insulin Glargine With Lantus in Patients With Type 2 Diabetes Mellitus on Basal Plus Mealtime Insulin [EDITION I; NCT01499082] were the first from this series of Phase 3 trials.

Adults (n=807) with T2DM on a basal-bolus insulin regimen that included at least 42 U/day of basal glargine or NPH insulin were randomized to 6 months of open-label treatment with either Gla-300 or Gla-100 once daily in the evening while continuing mealtime insulin. The basal insulin was titrated weekly to achieve a fasting plasma glucose of 80 to 100 mg/dL. Mealtime insulin dosage was not systematically titrated, with adjustments made at investigators' discretion only for safety reasons.

Subjects' mean age was 60 years, their mean duration of diabetes was 15.8 years, and their mean body mass index was 36.6 kg/m^2. More than half of the patients were using metformin. On entry, the mean basal insulin dose was 0.67 U/kg/day and the mean total insulin dose was 1kg/day. The mean baseline HbA1C level was 8.16%.

The primary endpoint, the change in HbA1C from baseline to Month 6, was –0.83% in both the Gla-100 and Gla-300 groups, the 0.0% difference met the criterion for noninferiority of Gla-300. There were no differences