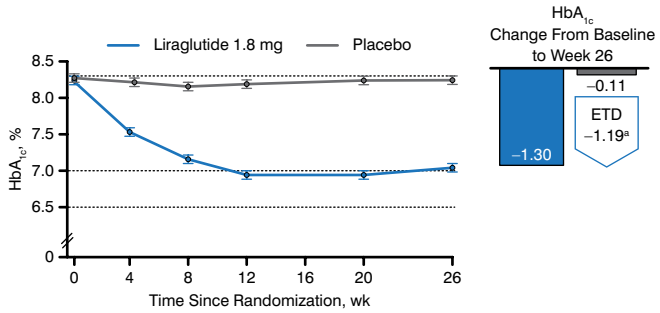
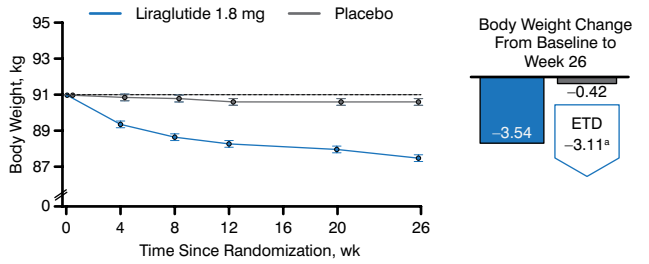
Figure 2. Change in HbA_{1c} in Patients Taking Liraglutide Versus Placebo Added to Basal Insulin Analogs



Estimated means ± standard errors, from mixed model for repeated measurements.
ETD, estimated treatment difference.
Reproduced with permission from J Lahtela, MD.
[a]95% CI, –1.39 to –0.99 (P<.0001).

Figure 3. Change in Weight in Patients Taking Liraglutide Versus Placebo Added to Basal Insulin Analogs



Estimated mean change from baseline to week 26, from mixed model for repeated measurements.
ETD, estimated treatment difference.
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[a]95% CI, –3.85 to –2.37 (P<.0001).

Three hundred sixty-five patients completed the trial. The primary end point was the change in HbA_{1c} from baseline to week 26. Patients taking liraglutide had a greater decrease in HbA_{1c} from baseline than those taking placebo (–1.3 and –0.11, respectively; Figure 2), and more liraglutide recipients reached HbA_{1c} < 7.0% (59.2% vs 14.0%) and HbA_{1c} ≤ 6.5% (42.9% vs 3.6%) (P<.0001 for both) despite using a lower mean estimated daily dose of basal insulin analog compared with placebo (35.8 vs 40.0 U).

Patients taking liraglutide also achieved greater decreases from baseline in fasting plasma glucose (FPG; –26 and –3 mg/dL, respectively), incremental postprandial self-measured plasma glucose (–17 and –7 mg/dL, respectively), body weight (Figure 3), systolic blood pressure (SBP) (–6 and –1 mm Hg, respectively), and lipids.

Nausea and vomiting occurred more frequently with liraglutide than placebo (22% vs 3% and 9% vs 1%, respectively). Minor hypoglycemia (plasma glucose < 56 mg/dL) occurred in 18% and 12% of liraglutide and placebo recipients, respectively. No severe hypoglycemic events (requiring assistance of another person) were reported during this trial.

In summary, the addition of liraglutide to insulin detemir or insulin glargine with or without metformin significantly improved glycemic control, which was attributed to the effect of liraglutide on both FPG and postprandial glucose levels. Additionally, liraglutide induced greater weight loss and reductions in SBP and selected lipids compared with placebo. Adverse effects were similar to those seen in other trials of liraglutide.

Dulaglutide Noninferior to Liraglutide for Glycemic Control in Patients With T2DM

Written by Maria Vinall

Results from the Assessment of Weekly Administration of LY2189265 in Diabetes-6 [AWARD-6; NCT01624259] trial, presented by Santiago Tofé Provedano, MD, Clinica Juaneda, Endocrinologia, Palma de Mallorca, Spain, show that once-weekly dulaglutide provides glycemic control that is noninferior to once-daily liraglutide with a similar safety and tolerability profile [Dungan KM et al. *Lancet*. 2014].

AWARD-6 was a phase 3 randomized, open-label, parallel-arm, 26-week study comparing the efficacy and safety of once-weekly dulaglutide 1.5 mg (n = 299), a long-acting glucagon-like peptide-1 receptor agonist, with once-daily liraglutide 1.8 mg (n = 300). Liraglutide was initiated at a dose of 0.6 mg/d and was titrated to 1.2 mg/d in week 2 and 1.8 mg/d in week 3. The study comprised type 2 diabetes (T2D) patients with an HbA_{1c} ≥ 7% and ≤ 10% who were on a stable dose of metformin (≥ 1500 mg) for ≥ 3 months.

Participants (~ 50% women and mostly white [86%]) had a mean age of 57 years and a mean HbA_{1c} of 8.1%. Most were obese (mean body mass index [BMI] 34 kg/m^2). The mean duration of diabetes was 7 years; mean daily metformin dose was more than 2000 mg. The primary study endpoint was the noninferiority of the change in HbA_{1c} from baseline to 26 weeks using a noninferiority margin of 0.4%. Superiority at week 26 (controlled for Type 1 error) was a key secondary endpoint and was to be tested if the noninferiority endpoint was met.

Dulaglutide was noninferior to liraglutide at 26 weeks (mean difference in HbA_{1c} –0.06%; 95% CI, –0.19

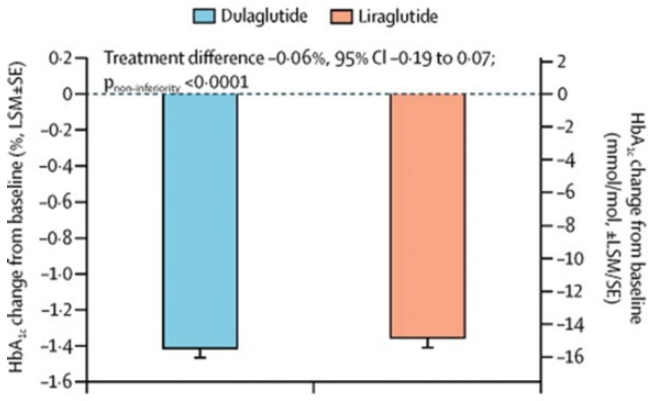
to 0.07; $P_{noninferiority} < .001$; Figure 1). The reductions in HbA_{1c} were similar throughout time and did not differ based on HbA_{1c} at baseline (ie, < 7.0% vs ≤ 6.5%). The effect on postprandial and fasting blood glucose was similar with both drugs. The mean difference in HbA_{1c} was not superior with dulaglutide as compared with liraglutide.

Both groups experienced significant weight reduction; however, patients treated with liraglutide had greater reductions in weight compared with dulaglutide-treated patients (0.7 kg, $P < .05$, Figure 2).

Similar numbers of patients reported adverse events (AEs). As expected, the most common AEs were gastrointestinal. These included nausea (20% and 18% for dulaglutide and liraglutide, respectively), diarrhea (both 12.0%), dyspepsia (8% and 6%), and vomiting (7% and 8%). The rate of study or study drug discontinuation due to any AE was similar (18 [6%] in each group). The rate of hypoglycemia (≤ 3.9 mmol/L ± symptoms) events was low: 0.3/patient/y with dulaglutide and 0.5 with liraglutide. No episodes of severe hypoglycemia were reported. There were no incidences of adjudicated pancreatitis or pancreatic cancer.

The once-weekly dosing regimen of dulaglutide allowed patients to administer substantially fewer injections while achieving similar glycemic benefits. In this study, the compliance rate (defined as patients achieving > 75% of prescribed doses) for dulaglutide was 98.5% compared with 97.8% for liraglutide [Dungan KM et al. *Lancet.* 2014]. An additional study is needed to determine whether long-term use of once-weekly drugs like dulaglutide might improve treatment compliance compared with more frequently administered regimens.

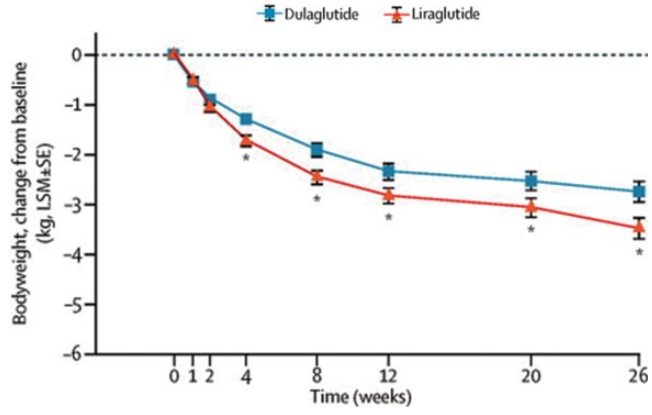
Figure 1. HbA_{1c} Change From Baseline at Week 26



LSM, least squares mean.

[a]Treatment difference (nominal 95%) CI, mixed-model repeated-measures analysis. Reprinted from *The Lancet*, 384, Dungan KM, Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial, 1349–1357, Copyright 2014, with permission from Elsevier.

Figure 2. Body Weight Change Throughout Time



LSM, least squares mean.

* $P < .05$.

Reprinted from *The Lancet*, 384, Dungan KM, Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial, 1349–1357, Copyright 2014, with permission from Elsevier.

Dulaglutide Reduces HbA_{1c} More Than Glargine When Used in Combination With Prandial Insulin

Written by Maria Vinall

Results from the Assessment of Weekly Administration of LY2189265 in Diabetes–4 trial [AWARD-4; NCT01191268], presented by Johan Jendle, MD, PhD, Endocrine and Diabetes Center, Karlstad and Faculty of Health Sciences and Medicine, Orebro University, Sweden, indicate that dulaglutide, in combination with insulin lispro, is an effective and safe option for treatment intensification in type 2 diabetes (T2D) patients who are inadequately controlled on 1 or 2 doses of insulin.

A basal-bolus insulin regimen is often recommended for patients with T2D who are unable to achieve target glycemic control with conventional therapy. However, many of these patients fail to achieve optimal HbA_{1c} levels, possibly because of the increased frequency of hypoglycemia and weight gain associated with this regimen. The combination of insulin and a glucagon-like peptide–1 (GLP-1) receptor agonist is being examined as an alternative regimen, but studies to date have included only basal insulin. AWARD-4 is the first randomized trial to explore the use of a GLP-1