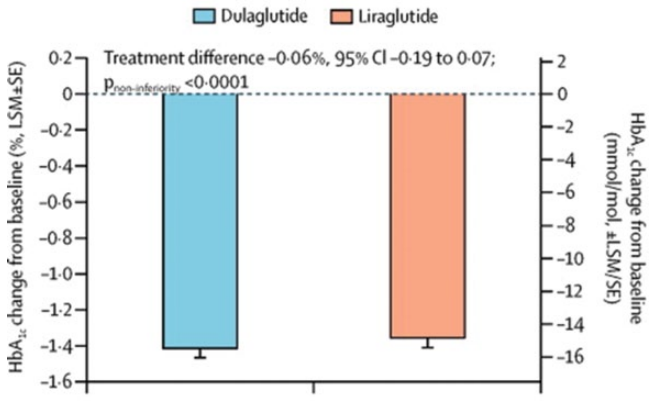
to 0.07; $P_{noninferiority} < .001$; Figure 1). The reductions in HbA_{1c} were similar throughout time and did not differ based on HbA_{1c} at baseline (ie, < 7.0% vs ≤ 6.5%). The effect on postprandial and fasting blood glucose was similar with both drugs. The mean difference in HbA_{1c} was not superior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

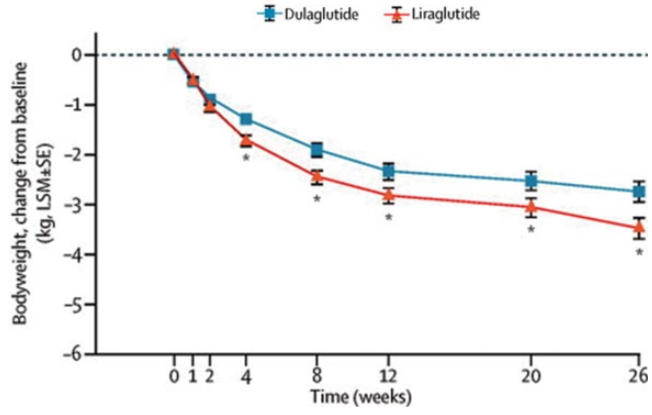
Figure 1. HbA_{1c} Change From Baseline at Week 26



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.

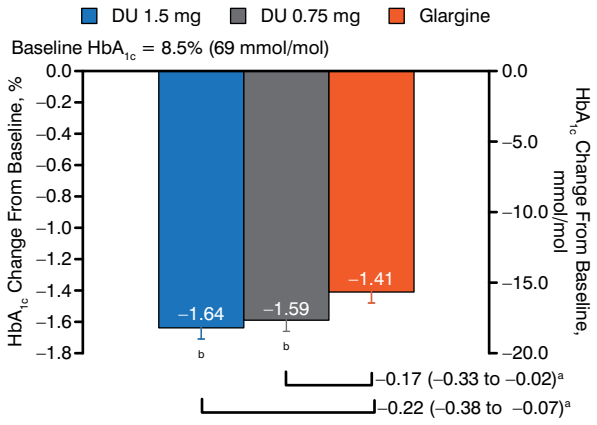
A basal-bolus insulin regimen is often recommended for patients with T2D who are unable to achieve target glycemic control with conventional therapy. However, many of these patients fail to achieve optimal HbA_{1c} levels, possibly because of the increased frequency of hypoglycemia and weight gain associated 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

receptor agonist with prandial insulin. The objective of this 52-week, parallel-arm, open-label, phase 3 study was to compare dulaglutide with basal glargine when used in combination with prandial insulin (lispro). Insulin glargine and insulin lispro were titrated in an attempt to reach glycemic targets.

The study enrolled patients with T2D who were inadequately controlled, with HbA_{1c} levels ≥ 7% and ≤ 11%. In addition, patients also were taking 1 or 2 stable insulin doses daily for 3 months and had body mass indexes (BMIs) ≥ 23 and ≤ 45 kg/m². Subjects were randomized (1:1:1) to once weekly dulaglutide 1.5 mg, once weekly dulaglutide 0.75 mg, or once daily glargine. All participants also received insulin lispro 3 times daily with meals. Both glargine and insulin lispro were titrated to target on the basis of the previous stable insulin dose. The primary objective was to assess the noninferiority of dulaglutide 1.5 mg to glargine on HbA_{1c} from baseline to week 26 using a 0.4% margin. If noninferiority was met, then the superiority of dulaglutide 1.5 mg and the noninferiority and superiority of dulaglutide 0.75 mg were tested.

Participants had a mean age of 59 years, a mean duration of disease of 13 years, a mean HbA_{1c} level of 8.5%, and a mean BMI of 32 kg/m². The majority (> 75%) were on metformin prior to randomization and/or basal insulin only. The mean total daily insulin dose was 56 U. At week 26, patients treated with dulaglutide doses had greater reductions in HbA_{1c} compared with those receiving glargine (Figure 1). This difference was maintained at 52 weeks.

Figure 1. HbA_{1c} Change From Baseline: 26 Weeks



[a]Treatment difference (nominal 95% CI).

[b]$P < .025$, superiority vs glargine (1-sided, adjusted to control for type I error).

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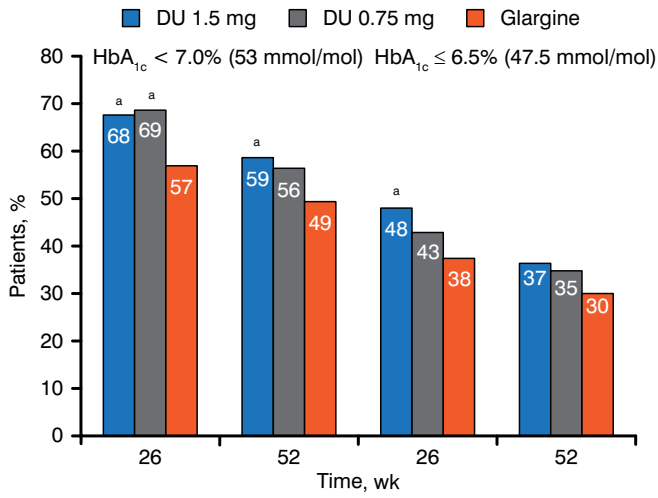
Figure 2. HbA_{1c} Targets at 26 and 52 Weeks



[a]$P < .05$ vs glargine.

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Table 1. Number of Hypoglycemic Events at 26 Weeks

Treatment	Total	Documented Symptomatic	Nocturnal
Dulaglutide 1.5 mg (n = xxx)	44[b]	32[a]	4[b]
Dulaglutide 0.75 mg (n = xxx)	52	39	5[b]
Glargine (n = xxx)	63	44	9

[a]$P < .05$ versus glargine.

[b]$P < .001$ versus glargine.

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At both weeks 26 and 52, a higher percentage of patients treated with either dose of dulaglutide reached HbA_{1c} target compared with patients treated with glargine (Figure 2).

Patients treated with glargine gained weight, whereas dulaglutide 1.5 mg was weight neutral over time. The weight difference between the dulaglutide 1.5-mg dose and glargine at week 52 was 3.3 kg ($P < .001$). The incidence of hypoglycemia was significantly lower with dulaglutide 1.5 mg compared with glargine at week 26 (Table 1).

There were no differences in overall adverse events. As expected, there were significantly ($P < .001$) more reports of gastrointestinal events (nausea, diarrhea, and vomiting) among patients treated with dulaglutide compared with glargine. Reports of severe hypoglycemia were low for all treatment groups, as were injection site reactions. There were no reports of pancreatic cancer.