Table 2. Comparison of BET and BBT Arms

Measure	BET	BBT	BET vs BBT	95% CI
IG at randomization, IU/kg/day	0.7 (0.3)	0.7 (0.3)	—	—
IG at 30 weeks	0.6 (0.3)	0.6 (0.3)	—	—
HbA1C at randomization, %	8.3 (1.0)	8.2 (0.9)	—	—
HbA1C at 30 weeks, %	7.2 (0.9)	7.1 (0.8)	0.03 (0.07)	−0.11, 0.18
Change (Δ) in HbA1C	−1.1 (0.05)[a]	−1.1 (0.05)[a]	−0.04 (0.07)[a]	−0.18, 0.11
Fasting glucose at randomization, mmol/L	7.1 (2.3)	7.0 (2.5)	—	—
Fasting glucose at 30 weeks	6.5 (2.0)	7.2 (2.8)	—	—
Δ Fasting glucose	−0.46 (0.16)[a]	0.18 (0.15)[a]	−0.64 (0.20)[a*]	−1.05, −0.24
Δ Postprandial glucose, mmol/L				
Δ Morning 2 hours post meal[b]	−2.6 (0.14)[a]	−2.3 (0.14)[a]	−0.27 (0.18)[a]	−0.63, 0.09
Δ Mid-day 2 hours post meal[b]	−2.2 (0.16)[a]	−3.1 (0.16)[a]	0.93 (0.21)[a**]	0.52, 1.34
Δ Evening 2 hours post meal[b]	−2.9 (0.17)[a]	−3.2 (0.17)[a]	0.28 (0.22)[a]	−0.16, 0.72

BBT=basal insulin glargine and bolus insulin lispro therapy; BET=basal insulin glargine and exenatide therapy; IG=insulin glargine. Values are mean (standard deviation) except as indicated. Shaded: Least squares mean change by mixed-effect model repeated measure. [a](SE) *p=0.002 for BET versus BBT; **p<0.0001 for BET versus BBT. [b]From self-monitored blood glucose profiles. Endpoint data is 30 weeks, per-protocol population.

Wolfenbuttel BHR et al. EASD 2013 (abstr 1).

Once-Weekly Exenatide Allows Sustained HbA1C Control

Written by **Brian Hoyle**

Jaret Malloy, PhD, Bristol-Myers Squibb, San Diego, California, USA, reported on the 3-year results of the Efficacy of Exenatide Once-Weekly and Once-Daily Insulin Glargine in Patients With Type 2 Diabetes Treated With Metformin Alone or in Combination With Sulfonylurea [DURATION-3; NCT00641056] open-label, randomized, controlled trial. Sustained HbA1C, greater weight reduction, and less frequent hypoglycemia were evident up to 3 years in subjects with type 2 diabetes mellitus (T2DM) compared with insulin glargine [Malloy J et al. EASD 2013 (abstr 2)].

Sustained control of glucose levels becomes increasingly difficult in T2DM because of the temporally progressive decline in insulin secretion. Typically, more intensive therapy is needed. The present study compared the abilities of the glucagon-like peptide-1 receptor agonist exenatide and insulin glargine to sustain HbA1C control, defined as achieving and maintaining HbA1C ≤7% (53 mmol/L) after 26 weeks of treatment. Loss of HbA1C control, or failure to achieve control, was evident as HbA1C >7% at two consecutive visits 10 to 12 weeks apart or HbA1C >9% at a single visit after 26 weeks of treatment. Insulin

glargine dose was established using the Initiate Insulin by Aggressive Titration and Education (INITIATE) algorithm.

Patients in the intention-to-treat (ITT) group (n=466) who received exenatide (n=233) or insulin glargine (n=223) were followed through a 26-week core phase with an option for continued treatment for up to 156 weeks. At baseline, the exenatide and insulin glargine arms were similar in mean age (57 and 58 years), proportion of males (52% and 55%), mean duration of diabetes (both ~8 years), and mean HbA1C (both 8.3%). Metformin alone and metformin along with a sulfonylurea was taken by 70% and 30% of patients, respectively, in both study arms. Of the ITT group, 140 exenatide patients and 147 insulin glargine patients continued treatment for the full 3 years.

HbA1C control was achieved and sustained at the last visit by 50% of exenatide patients and 43% of insulin glargine patients in the ITT population. Of the patients treated with exenatide and insulin glargine for 3 years, the rate of HbA1C control was 43% and 33%, respectively. HbA1C control was maintained longer for those receiving exenatide (median 25.0 months) than for insulin glargine patients (median 16.7 months). Of those who displayed HbA1C control until the last visit, a more pronounced reduction of the level of HbA1C was evident in patients receiving exenatide (least squares [LS] mean −1.32%) than in insulin glargine patients (LS mean −1.17%; 95% CI difference, −0.34 to 0.04; p=0.12). Exenatide patients displayed less reduction in fasting serum glucose and greater weight loss (LS mean −2.28 mmol/L and −3.44 kg, respectively) than insulin glargine patients (LS mean −3.07; 95% CI difference, 0.03 to 1.54; p=0.04; and LS mean +0.70 kg; 95% CI difference, 5.71 to −2.56; p<0.0001, respectively). Exenatide patients displayed less hypoglycemia than insulin glargine patients (event rate per year 1.1 vs 3.1), but the rates of nausea (16% and 2%) and diarrhea (14% and 7%) were more common in exenatide patients than insulin glargine patients.

Despite continued uptitration of insulin, patients with T2DM treated with exenatide displayed better HbA1C control, greater weight reduction, and less frequent hypoglycemia than patients treated with insulin glargine.

Liraglutide Is a Safe and Beneficial Adjunct to Insulin in Glycemic Control in Type 1 Diabetes

Written by **Brian Hoyle**

Simon Heller, University of Sheffield Medical School, Sheffield, United Kingdom, reported on the short-term findings of a randomized, double-blind, placebo-controlled crossover trial that demonstrated the prowess of the glucagon-like peptide-1 analogue liraglutide, used

as an adjunct to insulin, in promoting glycemic control in type 1 diabetes (T1D) [Heller SR et al. EASD 2013 (abstr 3); NCT01536665].

The objective in this segment of the study, which is actually the secondary objective in the overall study, was to look at the safety and tolerability, as well as the pharmacodynamics of three different doses of liraglutide over 4 weeks of treatment. Liraglutide is not currently approved for treatment of T1D.

The study involved 45 adults with T1D. They were randomly allocated to receive a liraglutide dose of 0.6, 1.2, or 1.8 mg/day, administered initially as 0.6 mg/day with a weekly escalation of 0.6 mg until the target dose was reached. Each target dose was then maintained for at least 2 weeks. A fourth group received placebo. All groups were included as add-on to a 4-week regimen of insulin. A crossover design was used with a 2- to 3-week wash-out period.

Efficacy of the doses was ascertained by measuring daily insulin dose, change in HbA1C, and the mean of a 9-point self-measured plasma glucose (SMPG) determination. Safety was assessed by the number of episodes of hypoglycemia, number and type of adverse events (AEs), vital signs including pulse and blood pressure, and body weight.

Similar baseline characteristics were evident for subjects in all four groups in terms of age (mean, 34.6 years), body mass index (~23.9 kg/m^2), HbA1C (~7.6%), and duration of T1D (mean, 16.7 years). Also, the groups were similar in the daily insulin dose. At the end of the 4-week treatment, the liraglutide dose of 1.2 and 1.8 mg significantly lowered the

daily insulin dose compared with placebo by 27% and 24%, respectively (p<0.001; Figure 1). The mean SMPG profile, change in HbA1C, and hypoglycemic events were similar in all groups (Table 1). Systolic and diastolic blood pressures did not differ appreciably. AEs were not serious, and the gastrointestinal maladies (mainly nausea, with some cases of diarrhea, vomiting, or other symptoms) observed more frequently with liraglutide use were expected. Of the five withdrawals, one was related to liraglutide-associated vomiting. The weight loss of up to 3.3 kg associated with liraglutide was not of concern, and could be beneficial.

Figure 1. Reductions in Insulin Dose
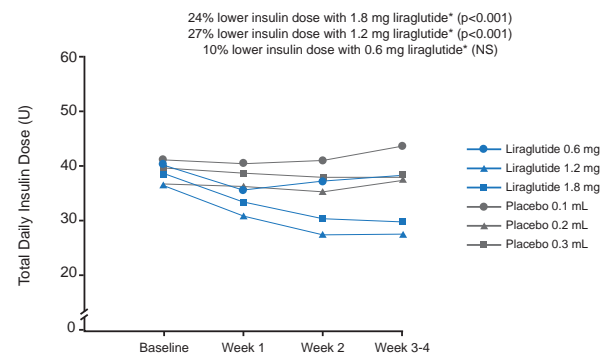
*Compared with the corresponding placebo group.

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The data support the use of liraglutide in glycemic control in T1D and pave the way for long-term, controlled trials.

Table 1. Summary of Data

	Liraglutide 0.6 mg/ Placebo	ETD or R (95% CI) p Value	Liraglutide 1.2 mg/ Placebo	ETD (95% CI) p Value	Liraglutide 1.8 mg/ Placebo	ETD (95% CI) p Value
Daily insulin dose (Units) at end of treatment[a]	42.1/47.0	R=0.90 (0.77, 1.04) p=0.138	32.6/44.8	R=0.73 (0.63, 0.85) p<0.001	31.8/41.7	R=0.76 (0.66, 0.88) p<0.001
Mean 9-point SMPG profile (mmol/L)	8.95/9.34	ETD=−0.39 (−1.30, 0.52) p=0.388	9.02/8.59	ETD=0.43 (−0.50, 1.35) p=0.351	9.76/8.85	ETD=0.91 (−0.01, 1.83) p=0.051
Change in HbA1C (%)[b]	−0.10/−0.01	ETD=−0.09 (−0.36, 0.18) p=0.504	−0.12/−0.12	ETD=0.01 (−0.27, 0.28) p=0.971	−0.04/−0.02	ETD=−0.02 (−0.29, 0.25) p=0.891
Hypoglycemic events n (%) Events[c]	14 (93.3) 289/ 14 (100) 313	N/A	13 (92.9) 263/ 13 (100) 326	N/A	14 (100) 316/ 15 (100) 295	N/A
GI AEs n (%) Events	10 (66.7) 12/ 2 (14.3) 2	N/A	12 (85.7) 24/ 1 (7.7) 2	N/A	13 (92.9) 31/ 3 (20.0) 5	N/A
GI AEs related to nausea n (%) Events	8 (53) 8/ 1 (7.1) 1	N/A	11 (78.6) 14/ 1 (7.7) 1	N/A	11 (78.6) 13/ 2 (13.3) 2	N/A
Change in body weight[b], kg	−1.2/0.8	ETD=−2.0 (−3.1, −0.9) p<0.001	−3.3/0.4	ETD=−3.7 (−4.9, −2.6) p<0.001	−2.9/0.4	ETD=−3.3 (−4.4, −2.2) p<0.001

AE=adverse event; ETD=estimated treatment difference; GI=gastrointestinal; N/A= not applicable; R=ratio; SMPG=self-measured plasma glucose.

Unless otherwise stated, data are presented as estimated means; [a]End of the 4-week treatment period; [b]Change from baseline to end of treatment; [c]Assessed according to ADA definition.

Heller SR et al. EASD 2013 (abstr 3).