Effect on Glycemic Control of Exenatide (Synthetic Exendin-4) Additive to Existing Metformin and/or Sulfonylurea Treatment in Patients With Type 2 Diabetes

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OBJECTIVE — AC2993 (synthetic exendin-4; exenatide) is a peptide that enhances glucose-dependent insulin secretion, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying. AC2993 also promotes β-cell proliferation and neogenesis in vitro and in animal models. This study examines the activity and safety of subcutaneously injected AC2993 in patients with type 2 diabetes currently treated with diet and/or oral antidiabetic agents (OADs).

RESEARCH DESIGN AND METHODS — A total of 109 patients treated with diet and a sulfonylurea and/or metformin were enrolled in a blinded study. Patients were randomly assigned to one of three subcutaneously (SC) injected regimens of AC2993 (0.08 μg/kg) or placebo for 28 days.

RESULTS — All three AC2993 regimens led to significant reductions in serum fructosamine relative to placebo (P ≤ 0.004). Mean reductions ranged from 39 to 46 μmol/l. All AC2993 groups had reductions in HbA1c ranging from 0.7 to 1.1% (P ≤ 0.006). An end-of-study HbA1c <7% was achieved by 15% of AC2993 patients versus 4% of placebo patients, confirming AC2993 effects on fasting and postprandial glycemia. On days 14 and 28, the β-cell index (homeostasis model assessment) for patients treated with AC2993 was 50–100% higher than baseline, contrasting with unchanged levels for placebo. The most common adverse event was transient mild-to-moderate nausea.

CONCLUSIONS — AC2993 is a promising therapeutic for patients with type 2 diabetes. In this study, it had significant effects on HbA1c levels in patients not currently achieving optimal glucose control with diet and/or OADs.

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Abbreviations: AUC, area under the concentration–time curve; BID, twice daily; DPP-IV, dipeptidyl peptidase-IV; GLP-1, glucagon-like peptide-1; HOMA, homeostasis model assessment; HPLC, high-performance liquid chromatography; SC, subcutaneous; TID, thrice daily.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Demographic and baseline characteristics of patients treated with AC2993 or placebo

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AC2993 BID (bd)</th>
<th>AC2993 BID (bs)</th>
<th>AC2993 TID (bds)</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>n</td>
<td>26</td>
<td>27</td>
<td>28</td>
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</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>62 (16)</td>
<td>63 (17)</td>
<td>57 (16)</td>
<td>75 (21)</td>
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<td>Women</td>
<td>38 (10)</td>
<td>37 (10)</td>
<td>43 (12)</td>
<td>25 (7)</td>
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<td>Race</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>54 (14)</td>
<td>44 (12)</td>
<td>54 (15)</td>
<td>68 (19)</td>
</tr>
<tr>
<td>Hispanic</td>
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<td>30 (8)</td>
<td>21 (6)</td>
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</tr>
<tr>
<td>Black</td>
<td>15 (15)</td>
<td>22 (6)</td>
<td>18 (5)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (1)</td>
<td>4 (1)</td>
<td>7 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Age (years)</td>
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<td>51 ± 9</td>
<td>50 ± 9</td>
<td>53 ± 9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>97.0 ± 16.7</td>
<td>98.2 ± 16.0</td>
<td>96.8 ± 17.5</td>
<td>97.6 ± 16.7</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>32.8 ± 3.8</td>
<td>33.5 ± 4.7</td>
<td>33.2 ± 4.8</td>
<td>32.8 ± 4.1</td>
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<tr>
<td>Fasting plasma glucose (mmol/l)</td>
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<tr>
<td>Day –1</td>
<td>11.2 ± 2.8</td>
<td>11.6 ± 3.3</td>
<td>10.9 ± 2.4</td>
<td>12.3 ± 3.6</td>
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<tr>
<td>Day 1</td>
<td>11.1 ± 3.4</td>
<td>11.7 ± 3.6</td>
<td>10.7 ± 2.5</td>
<td>12.0 ± 3.4</td>
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<tr>
<td>Serum fructosamine (µmol/l)*</td>
<td>344 ± 74</td>
<td>340 ± 71</td>
<td>331 ± 59</td>
<td>346 ± 56</td>
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<tr>
<td>Hba1c (%)</td>
<td>9.1 ± 1.2</td>
<td>9.3 ± 1.0</td>
<td>9.2 ± 1.1</td>
<td>9.4 ± 1.3</td>
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<tr>
<td>(Range)</td>
<td>(7.7–12.0)</td>
<td>(7.6–12.6)</td>
<td>(7.7–11.7)</td>
<td>(7.7–11.60)</td>
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<td>Oral agent use</td>
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<tr>
<td>Sulfonylurea alone</td>
<td>12 (3)</td>
<td>15 (4)</td>
<td>36 (10)</td>
<td>18 (3)</td>
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<tr>
<td>Metformin alone</td>
<td>23 (6)</td>
<td>22 (6)</td>
<td>21 (6)</td>
<td>21 (6)</td>
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<td>Sulfonylurea plus metformin</td>
<td>65 (17)</td>
<td>63 (17)</td>
<td>43 (12)</td>
<td>61 (17)</td>
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<tr>
<td>Antihypertensive agent</td>
<td>42 (11)</td>
<td>63 (17)</td>
<td>54 (15)</td>
<td>46 (13)</td>
</tr>
</tbody>
</table>

Data are % (n) or means ± SD. *The upper limit of the normal range for serum fructosamine is 285 µmol/l. The upper limit of the normal range for Hba1c is 6.0%.

**RESEARCH DESIGN AND METHODS**

**Study subjects**

A total of 116 patients with type 2 diabetes were recruited from 24 sites throughout the U.S. Males, or females who were surgically sterile or postmenopausal, aged 18–65 years were eligible for enrollment. Patients were to be treated with diet and a regimen of sulfonylurea or metformin (alone or in combination) that was stable for at least the prior 6 months. The entry oral antidiabetic agent regimen was continued throughout the study. Planned entry Hba1c was between 8.0 and 11.0%. Actual enrolled Hba1c ranges are given in Table 1. The target BMI at enrollment was 27–40 kg/m², inclusive. The following institutional review boards approved this study: The Western IRB, Olympia, Washington; University of North Carolina, Chapel Hill, North Carolina; Henry Ford Hospital, Detroit, Michigan; Washington Hospital, Freemont, California; Medstar Research Institute, Washington, D.C.; and Scripps Clinic, San Diego, California. All patients provided written informed consent.

**Study design**

This was a randomized, triple-blind (with respect to subject, investigator, and sponsor), parallel-group, placebo-controlled study designed to assess glucose control and evaluate safety in patients receiving subcutaneously (SC) injected AC2993 (0.08 µg·kg⁻¹·injection⁻¹) or placebo for 28 days. After a 2-week, single-blind, placebo lead-in, patients were randomly assigned to one of three AC2993 treatment groups: twice daily (BID) [breakfast (b) and dinner (d)]; BID [b and bedtime (s)]; thrice daily (TID) [bds]; or placebo TID [bds]. To maintain the study blind, patients treated BID received a third injection of placebo. Appropriate volumes of study medication [0.1 mg/ml AC2993 (Star Biochemicals, now Mallinckrodt, Inc., Torrance, CA)] or placebo, both manufactured according to current good manufacturing practices, were administered using an insulin syringe.

Activity assessments included changes from baseline to day 28 in serum fructosamine and postprandial plasma glucose, Hba1c, fasting plasma glucose, body weight, and fasting and postprandial lipids. Baseline was defined as day –1 for glucose and lipid measures and as day 1 for all other measures. Subjects were required to fast each day after midnight. After at least 14 days of single-blind placebo lead-in, subjects returned for a standardized meal tolerance test (day –1). The test was performed in the morning after the all-night fast, 15 min after injection of placebo. Blood samples were collected at 15 and 5 min before the injection, and at 0.5, 1, 1.5, 2, 3, 4, and 6 h after the injection. The 6-h sample was only assayed for AC2993. The following morning (day 1), after another all-night fast, subjects were randomized to placebo or one of three AC2993 treatments. Subjects also underwent identical standardized meal tolerance tests with timed blood sampling on days 1, 14, and 28. The standardized meal had a composition of 55% carbohydrate, 15% protein, and 30% fat. Patients consumed one bagel, one cheese slice, orange juice, soft corn margarine, and 2% milk. The quantity of liquids and margarine were adjusted based on body weight to maintain equal caloric intake per kilogram and activity level across the patient cohort.
Exendin-4 (AC2993) and glycemic control

Quantitation of plasma glucose, fructosamine, insulin, HbA1c, lipids, and cortisol was performed by Esoterix Laboratory (Calabasas Hills, CA) according to well-established methods. Quantitation of AC2993 and anti-AC2993 antibodies was done by Amylin Pharmaceuticals, Inc. (San Diego, CA). Glucose was measured using the Roche Glucose/HK Reagent Set (Roche Diagnostics, Indianapolis, IN) for glucose analysis. Fructosamine was measured using a colorimetric assay (21). Insulin was measured using a two-site immunoenzymometric assay. Total hemoglobin and HbA1c were measured using high-performance liquid chromatography (HPLC), with a normal reference range of 4.2–5.9%. The assay provides values comparable to those obtained in the Diabetes Control and Complications Trial (22). Cortisol was measured by radioimmunoassay. Plasma AC2993 concentrations were measured using an immunoenzymometric assay. Briefly, microtiter plates were coated with an anti-AC2993 monoclonal antibody (Amylin Pharmaceuticals) at 4°C for 1–3 days. Nonspecific binding sites were blocked using 1% nonfat dried milk diluted in 0.05 mol/l carbonate buffer (pH 9.5). Samples were added to wells and incubated for 1–2 h at room temperature. A biotinylated secondary monoclonal antibody (Amylin Pharmaceuticals) pre-incubated with streptavidin-alkaline phosphatase was added to each well and incubated at room temperature for 1–2 h. Wells were washed with Tris-buffered saline/Tween (0.05 mol/l Tris, 0.15 mol/l sodium chloride, 0.02% sodium azide, and 0.1% Tween-20) between incubation steps. The assay was developed using 50 µl of 0.1 mg/ml 4-methylumbelliferyl phosphate solution. The reaction was stopped using 0.1 mol/l sodium phosphate/1.5 mol/l sodium chloride.

Measurement of anti-AC2993 antibodies was performed using a solid-phase enzyme-linked immunosorbent assay. Briefly, AC2993 (5 µg/ml in 0.05 mol/l carbonate buffer, pH 9.5) was added to wells of microtiter plates, except for control wells coated with anti-human Ig (10 µg/ml in the same buffer). The plates were incubated for 1–3 days at 4°C, then incubated with MegaBloc3 (1:500; Cell Associates, The Sea Ranch, CA) for 1 h at room temperature. Samples were added and incubated for 1 h. Between incubation steps, wells were washed with PBS/0.1% Tween-20. Anti-human IgG horseradish peroxidase was added and the mixture was incubated for 1 h. The assay was then developed using O-phenylenediamine (Sigma, St. Louis, MO) in citrate buffer (0.055 mol/l phosphate/0.024 mol/l citrate, pH 5.0). The reaction was stopped by 4N sulfuric acid. Absorbance was read at 490 nm.

Homeostasis model assessment (HOMA) (23) was conducted to assess β-cell function at baseline and at days 14 and 28. The HOMA scores (24) were calculated as follows:

\[
\text{HOMA β-cell index} = \frac{20 \times \text{fasting insulin (µU/ml)}}{\text{fasting glucose (mmol/l)}} - 3.5
\]

Safety was evaluated using spontaneous adverse event reporting and monitoring of clinical laboratory measures and vital signs. Nausea was assessed as part of the routine adverse event–gathering process.

Statistical analysis

All summaries and analyses were based on the intent-to-treat population. A total of 109 patients were randomized and received at least one dose of study medication. Twelve subjects withdrew from the study [three in placebo, four in AC2993 BID (bd), two in AC2993 BID (bs), and three in AC2993 TID], but were included in the statistical analyses up until the time of their withdrawal. Efficacy end points were analyzed using one-way ANOVA to test the null hypothesis of no difference among treatment groups versus the alternative hypothesis of a difference among treatment groups. No data imputation was employed. Pairwise comparisons were also conducted between the AC2993 arms and placebo. P values ≤0.05 were considered significant. Specific P values are given in the text.

The study was powered to detect a statistically significant difference (α = 0.05) of 30 µmol/l in the change in fructosamine from baseline to one of the AC2993 treatment groups and placebo. The sample size also provided ~80% power to detect a statistically significant difference (α = 0.05) of a 1.7 mmol/l change in average postprandial plasma glucose from baseline between one of the AC2993 groups and placebo.

Time-weighted averages over all post-meal time points were computed for days −1, 1, and 28 postprandial glucose concentration values. The time-weighted average was computed as the area under the concentration–time curve (AUC) value obtained using the trapezoidal rule divided by the sampling duration. Time-weighted averages were also calculated for postprandial lipids.

RESULTS

Study subjects

A total of 116 patients with type 2 diabetes were recruited from 24 sites throughout the U.S., resulting in 109 subjects randomized to the intent-to-treat population. Of the seven excluded subjects, four did not meet the inclusion/exclusion criteria after screening, two withdrew consent, and one had an adverse event before randomization (motor vehicle accident). Baseline and demographic characteristics were well balanced across the four treatment groups (Table 1).

Serum fructosamine and HbA1c

AC2993 treatment led to statistically significant (P ≤ 0.004) reductions in serum fructosamine at day 28 [45, 39, and 46 µmol/l for BID (bd), BID (bs), and TID (bds), respectively] relative to placebo (5 µmol/l, Fig. 1A). Similarly, statistically significant (P ≤ 0.006) reductions in HbA1c were observed after all AC2993 regimens [1.1, 0.7, and 1.0% for BID (bd), BID (bs), and TID, respectively] compared with placebo (0.3%) during the same treatment period (Fig. 1B). The overall reduction for the three AC2993 groups combined was ~0.9%. End-of-study HbA1c of ≤7% was achieved by 15% of all AC2993 patients compared with 4% of placebo. The proportion of patients with entry HbA1c ≥8% achieving HbA1c <8% was 43% and 5% for AC2993 and placebo patients, respectively.

β-Cell function

AC2993 treatment appeared to enhance β-cell function, as assessed by HOMA analysis (Fig. 1C). The β-cell index for all regimens ranged from 50 to 100% greater at days 14 and 28 of AC2993 treatment compared with baseline (day −1) and day 1. The β-cell index for placebo-treated patients remained unchanged.
Plasma glucose
Statistically significant reductions ($P \leq 0.004$) from baseline to day 28 in mean postprandial plasma glucose concentration were observed with AC2993 treatment [4.4, 3.2, and 3.4 mmol/l for BID (bd), BID (bs), and TID, respectively] compared with placebo (0.6 mmol/l). These results were similar to the reductions seen on the first day of treatment (Fig. 2). Mean reductions in fasting plasma glucose after AC2993 treatment at day 28 (range of means 1.2–1.7 mmol/l) were not significantly different from placebo (1.1 mmol/l), although there was a trend toward reduced fasting glucose throughout the study. Compared with day 1, the AC2993 plasma glucose profile on day 28 showed reduced fasting glucose concentrations. On day 28, there was a modest rise in postprandial glycemia after AC2993 treatment; however, this change was markedly lower than in the placebo treatment arm on day 28.

Body weight
There was no significant effect of AC2993 treatment on change in body weight from day 1 to day 28 (range of means −0.8 to +0.1 kg) compared with placebo treatment arm (+0.9 kg). There was no detectable influence of baseline HbA$_{1c}$, baseline body weight, or concomitant anti-diabetic therapy on weight loss; however, the overall size of the cohort and the duration of the trial were insufficient to definitively state that these were not covariates.

Lipids
There were no notable differences among the treatment groups in fasting concentrations of triglycerides, HDL cholesterol, LDL cholesterol, or apolipoprotein B at day 28. While not statistically significant, incremental (baseline-adjusted) time-weighted average postprandial triglyceride concentrations tended to be decreased at day 28 compared with day −1 in the AC2993 treatment groups (change from day −1 to day 28, range −0.25 to −0.35 mmol/l) compared with placebo (change from day −1 to day 28, 0.14 mmol/l).

AC2993 pharmacokinetics
Plasma AC2993 for all patients increased steadily until reaching peak concentrations 2–3 h after administration of 0.08 µg/kg SC and was still detectable 6 h postdose. For subjects with undetectable anti-AC2993 antibodies, $t_{1/2}$ was 202 ± 182 min on day 1 and 226 ± 170 min on day 28 with corresponding $C_{\text{max}}$ values of 163 ± 86 and 159 ± 81 pg/ml, respect-
For subjects with anti-AC2993 antibodies at any time during the study, $t_{1/2}$ was $125 \pm 42$ min on day 1 and $373 \pm 250$ min on day 28 with corresponding $C_{\text{max}}$ values of $172 \pm 57$ and $357 \pm 215$ pg/ml, respectively ($n = 18$ for all AC2993 arms combined).

**Vital signs and clinical laboratory assessments**

No notable differences were observed for the change in vital signs (blood pressure and heart rate) from day –1 to day 28 among any treatment groups, which included a substantial proportion of patients (~50%) receiving concomitant medications for preexisting hypertension. No patient withdrew prematurely from the study due to a vital sign abnormality.

There were no clinically relevant changes in hematology, clinical chemistry, or urinalysis analyte values from day –1 to day 28 in any of the treatment groups.

There were no statistically significant effects of AC2993 on postprandial plasma cortisol on days 1 and 28 (data not shown). The range of means was 246–480 nmol/l. There was a small, acute, transient increase in serum cortisol concentrations after dosing with AC2993 on day 1, as compared with placebo. There was no rise in postdose mean cortisol values in any of the treatment groups at day 28.

Fifteen (19%) of the 81 AC2993-treated patients developed low-titer anti-AC2993 antibodies during the study. There was no evidence that patients with an antibody response had a diminished glycemic response.

**Adverse events**

The most common treatment-emergent adverse events reported were nausea (31% overall incidence) and hypoglycemia (15% overall incidence). The normal range for plasma glucose is 3.9–5.8 mmol/l. Values <3.3 mmol/l were considered hypoglycemic. The majority (91%) of the reported nausea and all hypoglycemic cases were mild or moderate in intensity, with no reports of hypoglycemia requiring the assistance of another individual. Hypoglycemia only occurred in patients who were taking a sulfonylurea.

Nausea was only observed in the AC2993 arms and was most pronounced during the initial days of treatment. Thereafter, the incidence of nausea de-
declined to ~13% by the end of the 28-day treatment period. Four (3.7%) of the 109 patients withdrew due to nausea, all within the first 12 days of the study. There was no evidence of adverse events that could be associated with an allergic reaction to study medication for patients with anti-AC2993 antibodies.

CONCLUSIONS — Exendin-4 was originally isolated from the salivary secretions of the lizard Heloderma suspectum (Gila monster), in which it circulates after ingestion of a meal (25), and may have endocrine functions related to metabolic control. Exendin-4 has a 53% amino acid sequence overlap with mammalian GLP-1. However, exendin-4 is the product of a separate gene distinct from the proglucagon gene from which GLP-1 is expressed (26). Unlike GLP-1, which is degraded within 1–2 min by dipeptidyl peptidase-IV (DPP-IV) when administered SC, exendin-4 is resistant to DPP-IV degradation and, thus, is more readily available for exerting beneficial metabolic effects similar to those of GLP-1 (27). These properties confer upon AC2993 (synthetic exendin-4, exenatide) a very high (>1,000-fold) in vivo potency relative to GLP-1 (10,28). However, not all actions of exendin-4 are predictable based on the known pharmacology of GLP-1. For example, GLP-1, but not exendin-4, suppresses gastric acid secretion (29). Moreover, while intraportal GLP-1 infusion triggers the hepatic vagal afferents, exendin-4 does not (30).

The current study indicates that 28 days of AC2993 treatment reduces HbA1c by ~0.9% compared with baseline in patients with type 2 diabetes not attaining HbA1c goals with oral agent therapy or diet. In addition, the proportion of patients achieving the American Diabetes Association target HbA1c <7% (31) was fourfold greater in the AC2993 arms. Given that HbA1c only fully reflects a change in glycemia 3 months after a sustained change has occurred, this reduction in HbA1c and enhanced ability to achieve clinically relevant HbA1c target values over 1 month are highly clinically significant.

Glucose profiles during ingestion of a mixed meal demonstrated a marked acute effect of AC2993 to reduce postprandial glycemia that was sustained over the 28-day observation period. This postprandial effect is likely mediated via three key actions of AC2993 that have been observed in animal models of diabetes: 1) increased release of insulin and amylin from the β-cell (10); 2) suppression of the paradoxically high glucagon secretion observed in animals with diabetes (12); and 3) slowing of the rate of gastric emptying (13). While no statistically demonstrable effect on fasting plasma glucose was observed at day 28, day 14 fasting plasma glucose in the AC2993 group was significantly reduced compared with placebo (data not shown). The ability of AC2993 to reduce fasting plasma glucose has previously been reported to be secondary to enhanced insulin secretion (10) and suppression of inappropriately elevated glucagon secretion (12). In patients with type 2 diabetes, GLP-1 has also been shown in a 6-week study to lower both fasting and postprandial glucose (32). However, in contrast to AC2993, GLP-1 needed to be continuously infused (32).

The effects of AC2993 on postprandial and, to a lesser extent, fasting glycemia were the key factors leading to the changes in fructoseamine and HbA1c (indicators of average glycemic control over the prior 2 weeks and 3 months, respectively). It is important to note that the study was not designed to assess differences among the various treatment groups. Across the different regimens, 28 days of AC2993 resulted in fructoseamine concentrations approaching the upper limit of normal (285 μmol/l) and HbA1c reductions of ~0.9%. This clinically significant improvement in glycemic indexes over 28 days in patients not previously achieving glycemic control with metformin and/or sulfonylurea treatment is remarkable, as the magnitude of improvement is difficult to achieve with the simple addition of a second or third oral agent (33). Moreover, while insulin therapy can be used to achieve this outcome, a vast literature documents that this approach is generally associated with significant weight gain (4), increased hypoglycemia (4), and attendant morbidities (34). Interestingly, AC2993 treatment was associated with no weight gain in the face of improved glycemic control. Consistent with this observation, exendin-4 has been reported to acutely reduce food intake in healthy human subjects (35) and cause weight loss in animal models of obesity (9).

HOMA analysis revealed improved β-cell secretory function following AC2993 therapy. It is noteworthy that fasting values of plasma glucose and insulin, which were used to calculate HOMA, were obtained before the morning dose of AC2993 when plasma concentrations of AC2993 were negligible, suggesting a fundamental alteration in β-cell function following AC2993 exposure. These data are consistent with the extensive literature documenting enhanced β-cell function after treatment with exendin-4 in animal models of diabetes (16–18).

AC2993 treatment was also associated with a strong trend toward reduced postprandial serum triglyceride concentrations, as was also seen in previous, short-term clinical studies (36). While fasting lipid parameters tended to improve, there were no differences compared with placebo.

Safety was evaluated using spontaneous adverse event reporting and monitoring of clinical laboratory measures and vital signs. The most common adverse events encountered were mild-to-moderate nausea and hypoglycemia. Nausea tended to occur mainly upon initiation of therapy and subsided over the first week. Hypoglycemia was mostly undocumented, mild to moderate, and did not require assistance from another person. Importantly, there were no reports of hypoglycemia in AC2993-treated patients receiving metformin alone—consistent with the notion that sulfonylureas are inherently hypoglycemic independent of the prevailing glucose concentration. Although one mechanism of AC2993 action is to slow gastric emptying to better match the rate of nutrient inflow with the rate of glucose disposal, there was no clinical evidence from this study that AC2993 treatment resulted in the induction or exacerbation of conditions such as gastroparesis.

While a small, acute, and transient rise in serum cortisol was observed on the first day of AC2993 treatment, similar to that seen with GLP-1 (37), the assessment on day 28 revealed no such rise in any study patient. There were no clinically relevant effects of AC2993 on other clinical laboratory analytes, blood pressure, or heart rate.

In conclusion, these data demonstrate for the first time in a randomized, triple-blinded trial that AC2993 administered BID or TID for 28 days in patients...
Exendin-4 (AC2993) and glycemic control

with type 2 diabetes failing oral agent therapy causes a marked reduction in HbA1c.

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