AC2993 (Synthetic Exendin-4) Improved Glycemic Control in Patients With Type 2 Diabetes During 28 Days of Treatment in a Multicenter, Randomized, Triple-Blind, Placebo-Controlled Study

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Abstract

Background and Aims: The present study was undertaken to evaluate the effectiveness of AC2993 in improving glycemic control among patients with type 2 diabetes mellitus who were inadequately controlled ($HbA_{1c} \geq 8\%$) with sulfonylureas or metformin alone or in combination (specified oral hypoglycemic agents; SOHAs).

Materials and Methods: 109 patients [36% female; mean (±SD) age ± 52 ± 9 years; mean BMI (33 ± 4 kg/m^2)] with type 2 diabetes who were currently being treated with diet and SOHAs were studied at 24 centers. Baseline values were as follows: HbA_{1c} (range of means: 9.1 - 9.4%); fructosamine (331 - 346 µmol/L; ULN 285); fasting glucose (197 - 222 mg/dL). Patients continued their SOHA regimen throughout the study. After a 2-week single-blind placebo lead-in period subjects were randomized in a triple-blind manner to one of three AC2993 (0.08 µg/kg) treatment groups: BID [breakfast (b), dinner (d)]; BID [b, bedtime (s)]; TID [bds]; or placebo TID [bds]. To maintain the study blind, patients treated BID received a third injection consisting of placebo. Study assessments included changes from baseline (Day –1) to Day 28 in serum fructosamine, fasting and postprandial plasma glucose, HbA_{1c}, and body weight.

Results: AC2993 treatment led to significant ($p \leq 0.010$) reductions in mean ± SE serum fructosamine at Day 28 (-45 ± 8, -39 ± 9, and -46 ± 9 µmol/L for BID (bd), BID (bs), and TID, respectively) relative to placebo (5 ± 7 µmol/L). Similarly, significant ($p \leq 0.006$) reductions in mean ± SE HbA_{1c} were observed after AC2993 treatment (-1.1 ± 0.1, -0.7 ± 0.1, and -1.2 ± 0.1% for BID (bd), BID (bs), and TID, respectively) compared with placebo (-0.3 ± 0.1%) during the same treatment period. Reductions in HbA_{1c} of $\geq 0.5\%$ were achieved by 90% of AC2993 subjects compared with 33% of placebo subjects. Statistically significant reductions ($p < 0.007$) from baseline to Day 28 in mean ± SE postprandial plasma glucose concentration (time weighted) were observed with AC2993 treatment (-79 ± 16, -57 ± 12, and -60 ± 11 mg/dL for BID (bd), BID (bs), and TID, respectively) compared with placebo (-10 ± 10 mg/dL). Mean changes in fasting plasma glucose concentrations after AC2993 treatment at Day 28 (range of means: -22 to -30 mg/dL) were not significantly different from placebo (-19 mg/dL). AC2993 treatment was not associated with a significant increase in body weight (range of means: -0.5 to +0.2 kg) compared with placebo patients (+0.9 kg). The most common treatment-emergent adverse event reported in AC2993 treated subjects was nausea (26.4% mild or moderate intensity, 2.5% severe). Four subjects (3.7%) withdrew due to nausea.

Summary: 28 days of treatment with AC2993 resulted in significantly improved glycemic control as assessed by reductions in serum fructosamine, HbA_{1c}, and postprandial plasma glucose concentrations. This improvement was not accompanied by mean weight gain and was associated with few adverse events, the most common of which was nausea.

Conclusion: Given that changes in HbA_{1c} reflect average glycemia over the prior 3-month period, an approximately 1% reduction in HbA_{1c} over a 28-day period is highly clinically meaningful. These data support the continued clinical evaluation of AC2993 as a potent anti-hyperglycemic agent for the treatment of patients with type 2 diabetes not achieving glycemic control on metformin and/or sulfonylureas.

Introduction

- AC2993 is synthetic exendin-4, a 39-amino acid peptide that shares 53% homology with human glucagon-like peptide-1 (GLP-1).[1, 2]
- In clinical studies, AC2993 has been shown to have multiple mechanisms of action that lower both fasting and postprandial glycemia and improve metabolic control.[3] These mechanisms of action include:
  - Stimulation of insulin secretion in a glucose-dependent manner
  - Suppression of postprandial glucagon secretion
  - Coordination of the rate of delivery of food from the stomach to the small intestine
  - Reduction of appetite
- In this study, we explored the safety and efficacy of 28 days of subcutaneous (SC) administration of AC2993 (BID or TID) as adjunctive therapy to metformin and/or sulfonylureas in patients with type 2 diabetes who failed to achieve HbA_{1c} levels less than 8% while stably treated with metformin, sulfonylurea, or both.

Study Objectives

1. To examine the effect on glucose control of subcutaneously injected AC2993 (0.08 µg/kg) administered two or three times a day for 28 days in subjects with type 2 diabetes mellitus treated with sulfonylureas and/or metformin, as measured by:
   - serum fructosamine concentrations
   - HbA_{1c}
   - plasma glucose profiles during a standard meal tolerance test
2. To assess the safety and tolerability of 28 days of subcutaneously injected AC2993 (0.08 µg/kg BID or TID) in subjects with type 2 diabetes mellitus treated with sulfonylureas and/or metformin

Study Design/Methods

- Four-arm, multicenter, randomized, triple-blind, placebo-controlled, parallel-group study
- Two-week placebo lead-in followed by 28 days of randomized treatment
- 109 patients with type 2 diabetes inadequately controlled ($HbA_{1c} \geq 8$) with either:
  - Metformin
  - Sulfonylurea
  - Combination of metformin and sulfonylurea
- All patients continued on their current regimen of oral hypoglycemic agents
- Patients were randomized to one of four treatment regimens:
  - Placebo TID
  - BID 0.08 µg/kg AC2993 given at breakfast and dinner (BD)
  - BID 0.08 µg/kg AC2993 given at breakfast and bedtime (BS)
  - TID 0.08 µg/kg AC2993 given at breakfast, dinner, and bedtime (BDS)
- BID treatment arms received placebo as a third injection to maintain study blind
- Serum fructosamine and HbA_{1c} were measured at baseline and day 28
- Plasma glucose was measured in response to a standardized breakfast meal (solid food) at baseline and day 28 (55% carbohydrate, 15% protein, and 30% fat at 20% of total daily maintenance calories)
- Safety and tolerability were assessed by collection of adverse events, 12-lead ECG, physical exam, and safety lab monitoring
- Statistical comparisons were computed using one-way ANOVA for overall comparisons. Dunnett's adjustment for multiple comparisons was used to test pairwise comparisons of active treatment arms to placebo.

Patient Population

Table 1: Baseline Demographics Were Comparable Across Treatment Groups

Mean ± SD	Placebo N=28	AC2993 BID (BD) N=26	AC2993 BID (BS) N=27	AC2993 TID N=28
Age (years)	52.6 ± 9.1	53.9 ± 7.5	50.6 ± 9.1	50.3 ± 8.9
BMI (kg/m^2)	32.8 ± 4.1	32.8 ± 3.8	33.5 ± 4.7	33.2 ± 4.8
% Male	75%	62%	63%	57%
Race (%): Caucasian	68%	54%	44%	54%
Black	7%	15%	22%	18%
Hispanic	25%	27%	26%	21%
Other	0%	4%	4%	7%

Table 2: Majority of Patients on Combination Metformin and Sulfonylurea

Number (%) Patients	Placebo N=28	AC2993 BID (BD) N=26	AC2993 BID (BS) N=27	AC2993 TID N=28	Total N=109
Metformin Alone	8 (28.6%)	6 (23.1%)	7 (25.9%)	7 (25.0%)	28 (25.6%)
Sulfonylurea Agents Alone	5 (17.9%)	4 (15.4%)	4 (14.8%)	9 (32.1%)	22 (20.2%)
Metformin + Sulfonylurea Agents	15 (53.6%)	16 (61.5%)	16 (59.3%)	12 (42.9%)	59 (54.1%)

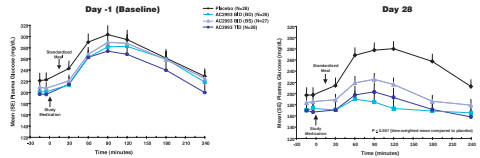
Table 3: Baseline Metabolic Characteristics Were Comparable Across Treatment Groups

Mean ± SD	Placebo N=28	AC2993 BID (BD) N=26	AC2993 BID (BS) N=27	AC2993 TID N=28
Mean Fasting Glucose (mg/dL)	222 ± 64	201 ± 50	208 ± 59	197 ± 44
Serum Fructosamine (µmol/L)*	346 ± 56	344 ± 74	340 ± 71	331 ± 59
HbA_{1c} (%)	9.4 ± 1.3	9.1 ± 1.2	9.3 ± 1.0	9.2 ± 1.1
Body weight (kg)	97.9 ± 17.0	97.0 ± 16.7	98.2 ± 16.0	96.8 ± 17.5

* Upper limit of normal =285 µmol/L

Results

Figure 1: AC2993 Significantly Lowered Postprandial Hyperglycemia Throughout the Treatment Period



- Mean changes in fasting plasma glucose concentrations after AC2993 treatment at day 28 (range of means: -22 to -30 mg/dL) were not significantly different from placebo (-19 mg/dL).

Figure 2: Fructosamine Concentrations Reduced to 283–332 µmol/L at Day 28 (Upper Limit of Normal = 285 µmol/L)

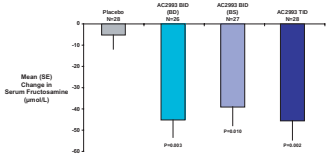


Figure 3: HbA_{1c} Levels Reduced to 8.1–8.5% At Day 28

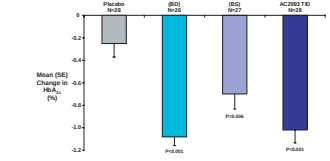
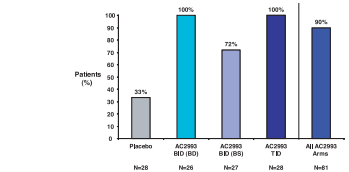


Figure 4: 90% of Patients Treated with AC2993 Achieved ≥ 0.5% Reduction in HbA_{1c} At Day 28



Weight:

- AC2993 treatment was not associated with a significant increase in body weight (range of means: -0.5 to +0.2 kg) compared with placebo patients (+0.9 kg; overall ANOVA P-value = 0.178)

Table 4: Most Common Treatment-Emergent Adverse Event Was Mild to Moderate Nausea
<4% of Patients Treated With AC2993 Withdrew Secondary to Nausea

Adverse Event N (%)	Placebo	AC2993 all doses	Severe* AC2993 AE
Nausea	0 (0)	25 (30.9)	2 (2.5)
Hypoglycemia	0 (0)	12 (14.8)	0 (0)
Vomiting	0 (0)	6 (7.4)	0 (0)
Dizziness	1 (4)	5 (6.2)	0 (0)
Diarrhea	0 (0)	5 (6.2)	0 (0)
Headache	0 (0)	4 (4.9)	0 (0)

* An event reported by the investigator. For hypoglycemia, a severe event was defined through one of the following criteria: 1) subject required the assistance of another person to obtain treatment for the event; 2) subject was treated for the event with intravenous glucose or intramuscular glucagon; or 3) subject was in a life-threatening situation as a result of the episode (e.g., seizure or loss of consciousness while driving a car).

- Assessments of physical exam, ECG, and laboratory tests showed no clinically relevant findings across treatment groups

Summary

Treatment with AC2993 for 28 days resulted in significantly improved glycemic control as assessed by reductions in serum fructosamine, HbA_{1c}, and postprandial plasma glucose concentrations. This glycemic improvement was not accompanied by mean weight gain and was associated with few adverse events, the most common of which was nausea.

Conclusions

Given that changes in HbA_{1c} reflect average glycemia over the prior 3-month period, an approximately 1% reduction in HbA_{1c} over a 28-day period is highly clinically meaningful. These data support the continued clinical evaluation of AC2993 as a potent anti-hyperglycemic agent for the treatment of patients with type 2 diabetes not achieving glycemic control on metformin and/or sulfonylureas.

References

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