A Double-Masked Placebo-Controlled Trial Assessing Effects of Various Doses of BTS 67 582, a Novel Insulinotropic Agent, on Fasting Hyperglycemia in NIDDM Patients

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OBJECTIVE — To determine the effect over a 4-week period of varying doses of BTS 67 582, a novel nonsulfonylurea insulinotropic agent, on fasting plasma glucose (FPG) levels in sulfonylurea-responsive NIDDM patients.

RESEARCH DESIGN AND METHODS — This was a 12-week multicenter, double-masked, placebo-controlled trial. Patients entered a 4-week stabilization period during which they received their previously prescribed sulfonylurea. Qualified patients (FPG ≤10 mmol/l) then entered a 4-week sulfonylurea withdrawal single-masked placebo run-in period. Qualified patients (FPG 8.9–16.7 mmol/l) were randomized to either placebo (n = 14), 50 mg b.i.d. BTS 67 582 (n = 18), 250 mg b.i.d. BTS 67 582 (n = 18), 500 mg b.i.d. BTS 67 582 (n = 15), 100 mg q.d. BTS 67 582 (n = 17), or 500 mg q.d. BTS 67 582 (n = 16). The primary efficacy variables were mean changes from baseline in FPG and fructosamine (FRUC). Additional variables included mean changes from baseline in HbA_{1c}, fasting serum insulin (FSI), and fasting serum C-peptide.

RESULTS — After 4 weeks of treatment, all BTS 67 582 dose groups showed a decrease from baseline in FPG and FRUC compared with the placebo group. The treatment groups of 250 mg b.i.d. (−3.1 ± 0.7 mmol/l), 500 mg b.i.d. (−2.3 ± 0.6 mmol/l), and 500 mg q.d. (−1.2 ± 0.7 mmol/l) had statistically significant ($P < 0.05$) decreases in FPG compared with placebo (0.7 ± 0.6 mmol/l). Similarly, there were statistically significant ($P < 0.05$) decreases from baseline in FRUC for the 250 mg b.i.d (−55 ± 10 μmol/l), 500 mg b.i.d. (−40 ± 12 μmol/l), and 500 mg q.d. (−13 ± 9 μmol/l) treatment groups compared with placebo (15 ± 11 μmol/l). Although the treatment period was only 4 weeks in duration, there were also significant differences ($P < 0.05$) in the HbA_{1c} changes from baseline for the 250 mg b.i.d (0.0 ± 0.1%) and 500 mg b.i.d. (−0.2 ± 0.1%) treatment groups compared with placebo (0.6 ± 0.2%). There were no significant differences among the treatment groups in the changes from baseline for FSI or C-peptide levels. The most frequently reported side effects were headache, asthenia, infection, and thirst, and the incidence of these events as well as the incidence of study drug discontinuation was comparable in all treatment groups including placebo.

CONCLUSIONS — Four weeks of treatment with BTS 67 582 at doses of 250 mg b.i.d. and 500 mg b.i.d. in NIDDM patients was effective in reducing FPG and FRUC, with significant results also seen for HbA_{1c}. The drug was well tolerated with an incidence of discontinuations and laboratory side-effect safety profiles comparable to placebo. BTS 67 582 is a safe and effective oral treatment for NIDDM patients.

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AUC, area under the curve; CV, coefficient of variation; FPG, fasting plasma glucose; FRUC, fructosamine; FSI, fasting serum insulin.

Nonpharmacological therapy (diet and exercise) remains the initial treatment strategy for NIDDM (1). This includes a discussion of appropriate food types and calorie limits with a dietitian with frequent follow-up and reinforcement as well as discussion of increasing physical activity based on individual assessment. For patients with symptomatic hyperglycemia or when patients are inadequately controlled by nonpharmacological intervention, pharmacological therapy is added to the regimen.

With the recent approval of two new classes of agents in the U.S. (biguanide-metformin and α-glucosidase inhibitor-acarbose), there are now additional choices to sulfonylureas and insulin for the management of patients. Health care providers can choose a single compound or use a combination of compounds as needed. Sulfonylureas increase insulin secretion from the pancreas (2,3). The biguanides reduce fasting plasma glucose (FPG) by inhibiting hepatic glucose production (4,5) through decreased gluconeogenesis (6) and by increasing peripheral insulin sensitivity (5). The α-glucosidase inhibitors help to reduce the postprandial blood glucose levels (7). The choice of agent or combination of agents can now be based on individual patient characteristics and side-effect profiles of the agents.

BTS 67 582 (1,1-dimethyl-2-[2-morpholinophenyl] guanidine monofumarate) represents a nonsulfonylurea insulinotropic compound with a morpholinoguanidine chemical structure. Studies in animals have shown greater efficacy when administered to animal models in which sulfonylureas are not effective (i.e., A^{vy}/a mice, *ob/ob* mice, *db/db* mice, KK-Y mice, streptozotocin rats [8]). The efficacy in these animal models is related to enhanced insulin release compared with glyburide. BTS 67 582 affects the K^+ATP channel in the islet cell but at a different binding site than the sulfonylureas, and it has additional activity at the

K^+maxi channel, which is Ca^{2+} and voltage dependent (9,10).

This study was designed to assess the safety and efficacy of BTS 67 582 in individuals with "sulfonylurea responsive" NIDDM. BTS 67 582 was administered for 4 weeks at five different dosage levels (50 mg b.i.d., 250 mg b.i.d., 500 mg b.i.d., 100 mg q.d., 500 mg q.d.) to NIDDM patients on diet therapy (who were responsive to their prescribed sulfonylurea) to assess an effective dose range and evaluate its safety. The primary measures of drug efficacy were the changes from baseline in FPG and fructosamine (FRUC) compared with placebo. Secondary measures of efficacy included the changes from baseline in HbA_{1c}, fasting serum insulin (FSI), and fasting serum C-peptide. Postprandial (post-Sustacal) plasma glucose and serum insulin levels were also obtained and evaluated.

RESEARCH DESIGN AND METHODS

— This was a multicenter (nine), randomized, double-masked, placebo-controlled, parallel-group, dose-ranging study in obese (120–180% of ideal body weight, inclusive) patients with "sulfonylurea-responsive" NIDDM. Women (eligible only if 2 years postmenopausal or if they had a prior hysterectomy) and men, 18–75 years inclusive, with a diagnosis of NIDDM and receiving a sulfonylurea with an FPG 10 mmol/l were eligible for screening. Patients were excluded from the study for the following reasons: history or presence of significant diabetic complications or other diseases or conditions that could potentially create risk for the patient or affect the absorption, metabolism, elimination, or obscure the effects of treatment; concomitant therapy with insulin, heparin, warfarin, or other anticoagulants; concomitant administration of drugs that affect glucose tolerance unless receiving constant doses for at least 30 days; elevated creatinine (>2.0 mg/dl); elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (>2 times the upper limit of reference range); hemoglobin <11.0 g/dl. All patients gave their written informed consent before any screening procedures for the study.

After an initial screening visit consisting of medical history, physical examination, electrocardiogram, and laboratory analyses, qualified patients received weight-maintaining diet, exercise, and nutritional counseling and were maintained on their oral sulfonylurea for 4 to 6 weeks. Patients with an FPG value of ≤10 mmol/l after at least 4 weeks of sulfonylurea treatment had their sulfonylurea therapy withdrawn and received single-masked placebo medication twice daily until randomization. After 4 weeks, patients with an FPG of 8.9–16.7 mmol/l (inclusive) and an increase of at least 1.7 mmol/l from the last visit while on sulfonylurea therapy were eligible for randomization. Patients were seen every 2 weeks during the sulfonylurea maintenance and sulfonylurea withdrawal periods.

Before randomization and ingestion of the first dose of double-masked study medication, patients received a baseline Sustacal meal, a liquid nutritional supplement consisting of 360 calories (55% of calories derived from carbohydrates, 24% from protein, and 21% from lipids). Blood samples for analyses of glucose and insulin were collected before the meal, and at 30, 60, 90, 120, and 180 min after the meal. Within 7 days, patients were scheduled for another challenge meal, which was ingested with the first dose of double-masked study medication. Blood samples for lactate were also collected before the meal and at 60 and 120 min after the meal. Patients were instructed to take the study medications twice daily, with the first meal and with the evening meal. For safety monitoring in the event of hypoglycemic episodes, patients were instructed on the use of and provided with a glucose monitor and supplies. Patients were seen weekly. At the week 4 visit, the patients received another challenge meal with the last dose of study medication including the collection of blood samples for lactate analysis. Patients received single-masked placebo medication for a 1-week washout period, and a final visit was then completed.

Laboratory evaluations of hematology, serum chemistry, urinalysis, and pregnancy tests were obtained at screening, before randomization, after 4 weeks of double-masked treatment, and at follow-up. The analyses were performed at SciCor, Indianapolis, IN. Laboratory evaluations for FPG were obtained at every visit. Blood was collected in sodium fluoride–treated collection tubes, and the plasma was separated and analyzed at SciCor using the hexokinase enzymatic method. The intra-assay and interassay coefficients of variation (CVs) were 2%. The efficacy laboratory variables of FRUC and HbA_{1c} were collected before sulfonylurea withdrawal, before randomization, and after 4 weeks of double-masked treatment. The efficacy variables of insulin and C-peptide were collected on the challenge meal days, i.e., before randomization, with the first dose of double-masked study medication, and with the last dose of double-masked study medication. The efficacy variables of HbA_{1c}, FRUC, insulin, and C-peptide were analyzed at University of Missouri, Columbia, MO. HbA_{1c} was analyzed using the Biorad Diamat method (ion exchange HPLC) with an interassay CV <2%. Fructosamine was analyzed using a colorimetric test based on the nitroblue tetrazolium method by which ketoamines reduce nitroblue tetrazolium at alkaline pH (RoTag). Serum insulin was analyzed using a radioimmunoassay from Pharmacia Diagnostics. The low detection limit was 5 μU/ml. Blood for C-peptide was collected in serum separator tubes to which Trasylol was added to prevent degradation of the sample. Proinsulin was removed by PEG precipitation, and C-peptide was analyzed using NOVA radioimmunoassay (antibody K-6). Physical examinations and electrocardiograms were performed at screening, before randomization, and after 4 weeks of double-masked treatment. Blood pressure, pulse rate, and weight were measured at every visit.

Statistical analyses

All statistical analyses were performed as two-tailed tests at the $\alpha = 0.05$ level. All data are reported as the means ± SE, except for HbA_{1c}, which is reported as the means ± SD.

Treatment groups were assessed for comparability with respect to baseline demographic and efficacy variables using one-way analysis of variance or, in the case of categorical data, using χ^2 tests. Treatment-related differences in the change from baseline for FPG, FRUC, and HbA_{1c} were analyzed using two-way (factors for treatment group and site) analysis of covariance (rank baseline observation as the covariate). Change from baseline data were rank transformed before analysis. Dunnett's multiple comparison procedure was used to detect statistically significant differences among the five active BTS 67 582 treatments and the placebo control group. For FPG, analyses were performed (1) on the observed dataset at each time point and (2) on the dataset with missing values estimated by carry forward. Postchallenge meal profiles of plasma glucose and serum insulin were summarized by incremental area under the curve (AUC_i [0–3 h]) estimated by the linear trapezoidal rule. Safety was examined and assessed by comparing the incidence rates

Table 1—*Baseline demographic data*

	Placebo	BTS 67 582				
		100 mg q.d.	500 mg q.d.	50 mg b.i.d.	250 mg b.i.d.	500 mg b.i.d.
n	17	18	20	21	19	18
Age (years)	56 ± 1.9	57 ± 2.4	56 ± 1.5	58 ± 2.3	57 ± 1.8	59 ± 2.0
Weight (lbs)	217 ± 8.4	211 ± 6.7	206 ± 6.6	203 ± 8.1	216 ± 6.4	221 ± 10.0
BMI (kg/m^2)	34 ± 0.9	33 ± 0.8	31 ± 0.8	32 ± 0.9	32 ± 0.8	34 ± 1.0
Duration NIDDM (years)	4.2 ± 1.1	4.8 ± 1.1	3.9 ± 0.8	6.3 ± 1.2	5.3 ± 1.2	7.6 ± 1.5
Women	35	44	30	57	42	39
Men	65	56	70	43	58	61
White	71	78	80	71	74	67
African-American	18	11	10	14	16	17
Mexican-American	12	11	10	14	11	17

Data are means ± SE or %.

among the treatment groups of treatment-emergent adverse events and treatment-emergent abnormal laboratory values, vital signs, physical examination findings, and electrocardiogram changes.

RESULTS — There were 113 patients randomized in the study, and all are included in the safety analysis. There were 12 patients who did not complete the study and three patients who did not have efficacy laboratory data collected at the last visit. Therefore, 98 patients had efficacy data at the double-masked week 4 visit. These included 14 in the placebo group, 17 in the 100 mg q.d. group, 16 in the 500 mg q.d. group, 18 in the 50 mg b.i.d. group, 18 in the 250 mg b.i.d. group, and 15 in the 500 mg b.i.d. group. The six treatment groups were comparable with respect to demographic data (Table 1).

Efficacy

Table 2 presents the baseline efficacy variables. There was a >1.7 mmol/l difference between the means of baseline FPG among some of the groups and a difference of >0.5% in mean baseline HbA_{1c} among the groups. This difference in baseline glycemic measure was considered clinically meaningful; therefore, an analysis of covariance was used in the efficacy analysis with the baseline values as the covariates

The change in FPG at each of the treatment weeks for patients having data at each week is displayed in Fig. 1. The treatment groups of 500 mg q.d., 250 mg b.i.d., and 500 mg b.i.d. had statistically significant ($P < 0.05$) decreases in FPG compared with the placebo group at weeks 1, 2, 3, and 4 of the double-masked treatment period. Observed mean reductions at week 4 were −3.1 ± 0.7 mmol/l, −2.3 ± 0.6 mmol/l, and −1.2 ± 0.7 mmol/l for the 250 mg b.i.d., 500 mg b.i.d., and 500 mg q.d. treatment groups, respectively compared with placebo (0.7 ± 0.6 mmol/l). An analysis performed on data carried forward for patients who discontinued before week 4 showed similar results with additional statistically significant decreases in FPG compared with placebo seen for the 50 mg b.i.d. at weeks 3 and 4. The changes from baseline in FPG are listed for each week by treatment group in Table 3.

The changes from baseline by treatment group for the other efficacy variables are listed in Table 4. FRUC rather than HbA_{1c} was used as one of the primary efficacy variables, because the treatment period was only 4 weeks in duration. FRUC measures glycated proteins for evaluation of glycemic control (11). Because of the shorter half-life of glycated proteins compared to glycated hemoglobin, glucose status over a 1- to 3-week period rather than a 2- to 3-month period can be assessed. There was a statistically significant ($P < 0.05$) decrease in FRUC for the 500 mg q.d. (−13 ± 9 μmol/l), 250 mg b.i.d. (−55 ± 10 μmol/l), and 500 mg b.i.d. (−40 ± 12 μmol/l) groups compared with placebo (15 ± 11 μmol/l). This paralleled the changes seen for FPG.

Although the treatment period was only 4 weeks in duration, there were statistically significant changes seen for HbA_{1c} for the 250 mg b.i.d. (0.0 ± 0.5%) and the 500 mg b.i.d. (−0.2 ± 0.4%) treatment

Table 2—*Baseline efficacy variables*

	Placebo	BTS 67 582				
		100 mg q.d.	500 mg q.d.	50 mg b.i.d.	250 mg b.i.d.	500 mg b.i.d.
n	14	17	16	18	18	15
FPG (mmol/l)	12.8 ± 0.8	14.0 ± 0.7	13.3 ± 0.7	14.5 ± 0.4	14.8 ± 0.6	13.5 ± 0.9
FRUC (μmol/l)	350 ± 12	379 ± 15	364 ± 20	400 ± 16	399 ± 16	382 ± 29
HbA_{1c} (%)	8.3 ± 1.2	9.0 ± 1.1	8.6 ± 1.6	9.3 ± 0.9	9.3 ± 1.3	9.3 ± 1.7
FSI (μU/ml)	20 ± 2	11 ± 1	19 ± 2	16 ± 2	14 ± 2	21 ± 4
Fasting serum C-peptide (nmol/l)	1.1 ± 0.1	0.8 ± 0.1	1.0 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	1.2 ± 0.2
Plasma glucose AUC_i (mmol · l^{-1} · h^{-1})	9.8 ± 0.8	9.6 ± 1.2	7.7 ± 0.3	9.1 ± 0.9	9.0 ± 0.8	10.0 ± 1.4
Serum insulin AUC_i (μU · ml^{-1} · h^{-1})	80.6 ± 19.3	46.2 ± 7.9	79.2 ± 10.8	56.0 ± 8.2	65.5 ± 10.8	78.4 ± 17.6

Data are means ± SE, except for HbA_{1c}, which are means ± SD.

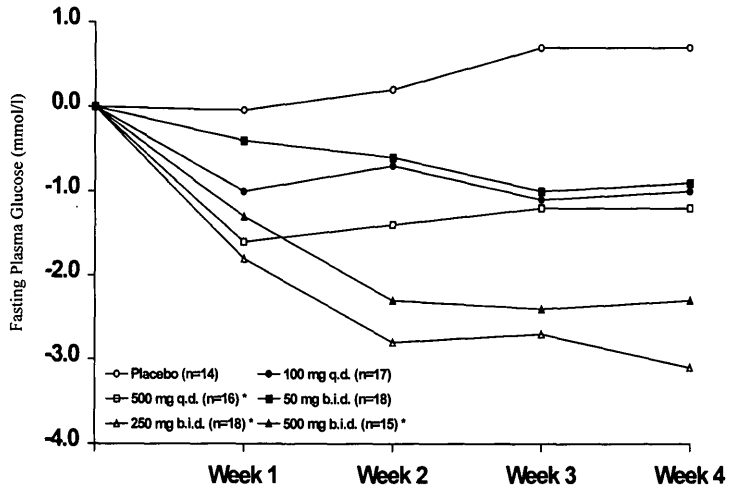

Figure 1—*Mean change from baseline in FPG. ○, placebo; ●, 100 mg q.d.; □, 500 mg q.d.; ■, 50 mg b.i.d.; △, 250 mg b.i.d.; ▲, 500 mg b.i.d. BTS 67 582. * P < 0.05 vs. placebo using two-way ranked analysis of covariance followed by Dunnett's multiple comparison procedure.*

groups compared with placebo (0.6 ± 0.8%). There were no significant changes among the treatment groups in FSI or C-peptide levels.

The mean challenge meal plasma glucose and serum insulin levels for each treatment group taken with the last dose of treatment medication at week 4 are illustrated in Fig. 2. The incremental AUCs (AUC_i) were calculated, and the changes from baseline by treatment group are displayed in Table 4. The AUC_i data were not analyzed statistically; however, there are marked decreases in the glucose AUC_i for the 500 mg q.d. and the 250 mg b.i.d. groups at the last visit. The 500 mg b.i.d. group also showed a decrease in AUC_i with the first dose of study medication (-2.53 ± 1.05 mmol · l^{-1} · h^{-1}); however, this was not evident at the week 4 visit. The change in serum insulin AUC_i showed a dose-related increase compared with placebo (Table 4).

Safety

All patients receiving at least one dose of study medication were included in the safety analyses. These were composed of 17 patients on placebo, 18 patients in the 100-mg q.d. group, 20 patients in the 500-mg q.d. group, 21 patients in the 50-mg b.i.d. group, 19 patients in the 250-mg b.i.d. group, and 18 patients in the 500-mg b.i.d group. There were eight placebo patients (47%), 11 (61%) patients in the 100-mg q.d. group, 13 (65%) patients in the 500-mg q.d. group, nine (43%) patients in the 50-mg b.i.d. group, eight (42%) patients in the 250-mg b.i.d. group, and 14 (78%) patients in the 500-mg b.i.d. group who reported at least one adverse event (including intercurrent illnesses) during the double-masked treatment period. Overall, the most frequently reported adverse events were asthenia (7.3% drug-treated vs. 0% placebo patients), headache (10.4% drug-treated vs. 12% placebo patients), infection (8.3% drug-treated vs. 6% placebo patients), and thirst (7.3% drug-treated vs. 6% placebo patients). There were no treatment-related changes in urinalysis, hematology, serum chemistry, and lactic acid laboratory analyses, vital signs, electrocardiogram results, and physical examination findings.

There were two patients who reported symptoms indicative of hypoglycemia; however, these were not confirmed by an instantaneous blood glucose reading. One patient receiving the 500-mg b.i.d. treatment reported two episodes (10 and 15 days after starting double-masked treatment) and the other patient had one episode (midafternoon of day 12). In both cases, symptoms were relieved with a snack.

CONCLUSIONS — There is now no question that the microvascular complications of diabetes are related in a cause-and-effect manner to the level of glycemia in diabetic individuals. The results of the Diabetes Control and Complications Trial (12) and Stockholm Diabetes Intervention Study (13) showed that in IDDM patients, the incidence and progression of microvascular complications were associated with the level of overall glycemia. This had been previously reported for the microvascular complication of retinopathy in NIDDM patients by the Wisconsin Epidemiologic Study of Diabetic Retinopathy (14). Better glycemic control in both types of diabetic patient populations would have a beneficial effect in reducing the risk for development and progression of microvascular complications.

The 6-year results of the U.K. Prospective Diabetes Study showed that NIDDM patients treated with pharmacological agents had better glycemic control than those treated with diet therapy alone (15). In addition, the oral agents used in that study (metformin, glyburide, glipizide, and chlorpropamide) had comparable efficacy as single-use agents over the 6-year period. To achieve better glycemic control in NIDDM patients over time, combination therapy with oral agents or the addition or substitution of insulin is usually required. With the recent approval in the U.S. of oral agents with different mechanisms of action, such as metformin and acarbose, combination therapy with oral agents can be explored before the need to initiate insulin therapy.

BTS 67 582 represents a different class (morpholinoguanidine chemical structure) of insulinotropic agents. In this study, BTS 67 582 once-daily dosing (100 mg and 500 mg) did produce decreases in FPG and FRUC compared with placebo.

Table 3—*Changes from baseline in FPG*

		BTS 67 582				
	Placebo	100 mg q.d.	500 mg q.d.	50 mg b.i.d.	250 mg b.i.d.	500 mg b.i.d.
n	14	17	16	18	18	15
Week 1	−0.04 ± 0.4	−1.0 ± 0.4	−1.6 ± 0.5*	−0.4 ± 0.4	−1.8 ± 0.4*	−1.3 ± 0.6*
Week 2	0.2 ± 0.5	−0.7 ± 0.4	−1.4 ± 0.4*	−0.6 ± 0.3	−2.8 ± 0.7*	−2.3 ± 0.8*
Week 3	0.7 ± 0.5	−1.1 ± 0.5	−1.2 ± 0.6*	−1.0 ± 0.4	−2.7 ± 0.8*	−2.4 ± 0.7*
Week 4	0.7 ± 0.6	−1.0 ± 0.5	−1.2 ± 0.7*	−0.9 ± 0.4	−3.1 ± 0.7*	−2.3 ± 0.6*

Data are mean changes from baseline ± SE. *$P < 0.05$ vs. placebo using ranked two-way analysis of covariance followed by Dunnett's multiple comparison procedure.

Table 4—*Changes from baseline in other efficacy variables*

	Placebo	BTS 67 582 100 mg q.d.	BTS 67 582 500 mg q.d.	BTS 67 582 50 mg b.i.d.	BTS 67 582 250 mg b.i.d.	BTS 67 582 500 mg b.i.d.
n	14	17	16	18	18	15
FRUC (μmol/l)	15 ± 11	−5 ± 9	−13 ± 9*	0 ± 8	−55 ± 10*	−40 ± 12*
HbA_{1c} (%)	0.6 ± 0.8	0.2 ± 0.7	0.1 ± 0.6	0.4 ± 0.5	0.0 ± 0.5*	−0.2 ± 0.4*
FSI (μU/ml)	1.1 ± 1.4	1.0 ± 1.0	1.7 ± 1.6	0.3 ± 1.4	1.9 ± 1.1	−1.2 ± 2.2
Fasting serum C-peptide (nmol/l)	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.0	0.2 ± 0.0	0.0 ± 0.1
Plasma glucose AUC_i (mmol · l^{-1} · h^{-1})	−0.33 ± 0.73	−0.59 ± 0.62	−1.97 ± 0.73	−0.16 ± 0.52	−1.95 ± 0.66	−0.25 ± 0.69
Serum insulin AUC_i (μU · ml^{-1} · h^{-1})	−9.8 ± 8.4	11.9 ± 4.1	47.2 ± 11.5	13.0 ± 5.7	26.0 ± 8.6	67.3 ± 13.2

Data are mean changes from baseline ± SE. *$P < 0.05$ vs. placebo using ranked two-way analysis of covariance followed by Dunnett's multiple comparison procedure.

Although statistically significant for the 500-mg q.d. group, the actual mean changes in FPG and FRUC were not as clinically meaningful as the changes seen with the twice-daily dosing of 250 mg and 500 mg. The change from baseline in FPG relative to the difference from placebo for the 250-mg b.i.d group was −3.7 mmol/l and for the 500-mg b.i.d. group was −2.9 mmol/l over a 4-week period. These changes were comparable with the changes from baseline seen for FRUC, which resulted in a −70 μmol/l difference from placebo for the 250-mg b.i.d. dose-group and a −55 μmol/l difference from placebo for the 500-mg b.i.d. dose group. Although the changes in HbA_{1c} over a 4-week treatment period are not as clinically relevant due to the long half-life of HbA_{1c}, the trend for each treatment group did parallel the changes seen for FPG and FRUC.

All doses of BTS 67 582 showed decreases or no change from baseline in both FPG and FRUC, whereas the placebo group showed an increase in the value of these variables over the 4-week treatment period. The improved glycemic response seen with BTS 67 582 was not associated with weight changes during the study. All groups had a mean weight loss of 0–2 pounds, and there were no differences compared with placebo. Although the b.i.d. treatment groups of 250 mg and 500 mg had the best overall efficacy, the 50-mg b.i.d. dose was the least efficacious (an FPG difference from placebo of −1.5 mmol/l and FRUC of −15 μmol/l). Future studies will need to determine whether twice-daily doses between 50 and 250 mg are efficacious. In addition, the 6-year results of the U.K. Prospective Diabetes Study showed that the overall efficacy of single-use oral agents is comparable, and combination therapy is needed in certain patients to maintain glycemic control. The use of BTS 67 582 with other oral glucose-lowering agents needs to be explored given that its effectiveness is comparable to the other agents.

The postprandial response was analyzed using AUC_i. This value determines whether the increase in glucose after a meal is attenuated (16). Since treatment with BTS 67 582 reduced FPG, the total AUC would be expected to decrease as well (16), especially for the 500-mg q.d., 250-mg b.i.d., and 500-mg b.i.d. groups (Fig. 2). This study showed that doses of 500 mg q.d. and 250 mg b.i.d. were able to reduce the glucose AUC_i, and this effect was still present after 4 weeks of dosing. The 500-mg b.i.d. group had a decrease in glucose AUC_i with the initial dose; however, this was not present after 4 weeks of treatment. The AUC_i calculation is based on the increase in area over the baseline (16) and, as seen in Fig. 2, the 500-mg b.i.d. dose group at week 4 did not have a mean glucose response at 180 min that was at or below the 0-min value. This result contributed to the increase in calculated AUC_i relative to the initial dose.

From this 4-week study, the twice-daily dose regimens of 250 mg and 500 mg appeared comparable in efficacy response. There did appear to be more reports of adverse events, however, in the 500-mg b.i.d. group including two episodes of hypoglycemia in one patient. In addition, the decrease in the glucose response after a challenge meal seen with the first dose of the 500-mg b.i.d. dose was not present after 4 weeks of treatment. Although the patient numbers are small and the events are few, it may be that 500-mg b.i.d. does not have as good a benefit/risk ratio as the 250-mg b.i.d. dose.

There were no differences in fasting insulin or C-peptide levels. There was an increase in the insulin response to a chal-

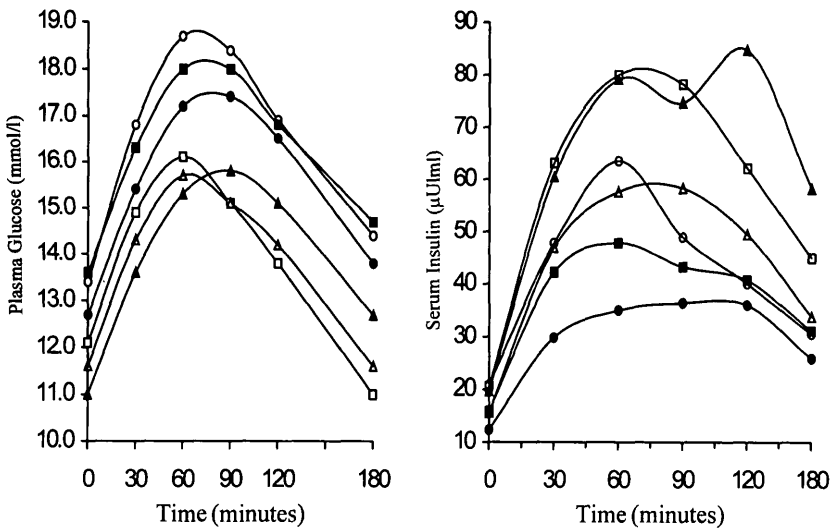

Figure 2—*Mean postprandial (post-Sustacal) plasma glucose and serum insulin responses at week 4. ○, placebo; ●, 100 mg q.d.; □, 500 mg q.d.; ■, 50 mg b.i.d.; △, 250 mg b.i.d.; ▲, 500 mg b.i.d. BTS 67 582.*

lenge meal indicating that BTS 67 582 can reduce the postprandial glycemic rise thus improving overall glycemic burden. Studies to assess the effect of BTS 67 582 on first- and second-phase insulin release and insulin action in NIDDM patients are in progress.

Overall, BTS 67 582 did not produce any treatment-related adverse events or abnormal laboratory or electrocardiogram changes. The drug was well tolerated with the incidence of discontinuations and laboratory and adverse event safety profile comparable to placebo. In addition, the drug is predominately renally excreted and therefore does not have altered pharmacokinetic parameters in subjects with hepatic disease. The elimination of BTS 67 582 correlates with creatinine clearance in subjects with renal impairment. Protein binding is minimal (40%), eliminating drug interactions associated with high protein binding.

BTS 67 582 is a safe and effective oral agent for the treatment of NIDDM patients. It may provide an alternative choice for NIDDM patients in which other agents may be contraindicated or are limited by side effects.

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