diabetes

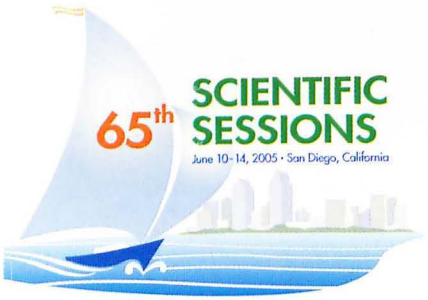
JOURNAL OF THE
MERICAN DIABETES
SSOCIATION ®
vw.diabetes.org/diabetes

ABSTRACT BOOK

65th Scientific Sessions

Friday, June 10–Tuesday, June 14, 2005

The San Diego Convention Center
San Diego, California



MULTIPLE AGENT THERAPY FOR TYPE 2 DIABETES

9-OR

Comparison of Exenatide and Insulin Glargine in MET and SU-Treated Patients with Type 2 Diabetes: Exenatide Achieved Equivalent Glycemic Control, with Weight Reduction and Less Nocturnal Hypoglycemia

ROBERT J. HEINE, LUC F. VAN GAAL, DON JOHNS, MICHAEL J. MIHM, MARIO H. WIDEL, ROBERT G. BRODOWS. *Amsterdam, Netherlands; Antwerp, Belgium; Indianapolis, IN*

Clinical studies have shown that exenatide improves glycemic control with a low incidence of hypoglycemia and the absence of weight gain in patients with type 2 diabetes inadequately controlled by MET and/or SU. The addition of basal insulin is common practice when orals fail, but is complicated by increased hypoglycemia and weight gain. This 26-week, multi-center, phase 3 trial was designed to determine if exenatide can be used safely and effectively as an alternative to basal insulin glargine. Patients were randomized to exenatide (5µg BID for first 4 wks, 10µg BID for remainder of study, n=283) or glargine QD (n=268), adjunctive to pre-existing MET+SU. Baseline A1C were 8.2±1.0% and 8.3±1.0%, respectively. At endpoint, exenatide and glargine achieved similar A1C reductions (-1.0±0.1% vs -1.1±0.1%, respectively; 95% CI for exenatide–glargine difference was -0.1 to 0.2%) and percent of patients to A1C≤7% (48% vs 46%). Weight change was -2.3±0.2kg for exenatide, +1.8±0.2kg for glargine (p<0.001). As measured by 7-point glucose monitoring, exenatide reduced postprandial excursions following breakfast and dinner, while glargine predominantly reduced fasting glucose (-1.2±0.2 vs -2.9±0.2mmol/L, p<0.001). Exenatide reduced glucose excursions following a test meal, but glargine did not reduce post-meal excursions (incremental glucose $AUC_{0\text{-}4hrs}$ = -0.3±1.0mmol-hr/L, n=41 vs 7.0±1.2mmol-hr/L, n=37, p<0.001). The most common adverse event for exenatide was nausea (57%), which was generally mild-to-moderate (6% discontinuation due to nausea) with decreasing incidence during the study. Rates of symptomatic hypoglycemia were similar between treatments, but nocturnal hypoglycemia was lower for exenatide (0.9±0.4 vs 2.4±0.4 mean events/patient year, p<0.001). Exenatide has potential as an alternative to insulin glargine in the management of type 2 diabetes sub-optimally controlled on MET+SU.

10-OR

Effects of DAC-GLP:1 (CJC-1131) on Glycemic Control and Weight over 12 Weeks in Metformin-Treated Patients with Type 2 Diabetes

ROBERT E. RATNER, POL-HENRI GUIVARC'H, JEAN-FRANÇOIS DREYFUS, JEAN-PAUL CASTAIGNE, DANIEL J. DRUCKER, JEAN-PIERRE HALLÉ, STUART A. ROSS, MARK S. KIPNES. *Bethesda, MD; Montreal, QC, Canada; Toronto, ON, Canada; San Antonio, TX; Calgary, AL, Canada*

CJC-1131 is a GLP-1 analogue binding covalently to albumin in vivo, with a 10-day half-life in man. This study assessed the effects of CJC-1131 on glycemic control in patients (PT) with type 2 diabetes inadequately controlled with their current dose (1.5-2.25 g) of metformin (MET) alone or with sulfonylurea (SFU). The 12-wk investigation was a randomized, double-blind, placebo (PBO)-controlled multicenter study.

After a 4-wk baseline period and washout for those on SFU, 81 PT, 51M/30F, age 56±8.8 yr (mean±SD), BW 92.5±18.05 kg, BMI 32.0±4.49 kg/m^2, HbA1c 7.9±0.83 %, FPG 9.5±2.61 mmol/L, were randomized to CJC-1131 low (LD) or high (HD) dose or matching PBO. PT on SFU (n=40) were washed out and equally allocated to each arm. All subjects continued MET with unchanged doses. Weekly visits during the 1st month allowed CJC-1131 dose adjustment. The average daily dose was 2.1±1.06 µg/kg (LD) & 2.6±0.97 µg/kg (HD).

In the 57 PT evaluated for efficacy, the mean difference from PBO (mean ± SEM) for HbA1c changes from baseline was -1.1±0.23 % (p<0.0001) (HD) & -0.6 ±0.25 % (p<0.03) (LD); 58 % of HD patients with baseline HbA1c>7.0 % achieved HbA1c≤7.0 %; FPG was significantly reduced in the HD & LD arms compared to PBO (p<0.02 & p<0.04 respectively). Body weight was reduced in the 3 arms, more with CJC-1131: -2.5±2.18 kg (mean±SD) than PBO: -1.6±1.59 kg (p<0.05). The most frequent AEs were GI intolerance mostly during the first 4 wk: moderate nausea was reported at least once by 13 PT and severe nausea once by 1 PT (overall incidence 25%); 6 PT reported moderate nausea during the next 4 wk and 1 during the last 4 wk of treatment. There were no signs of local intolerance or immunogenicity. In conclusion, CJC-1131 in combination with MET significantly reduced HbA1c without increasing the risk of hypoglycemia, in PT previously inadequately treated with MET or MET+SFU.

11-OR

Effect of Adding MK-0431 to On-Going Metformin Therapy in Type 2 Diabetic Patients Who Have Inadequate Glycemic Control on Metformin

RONALD BRAZG, KAREN THOMAS, PENG ZHAO, LEI XU, XUN CHEN, PETER STEIN. *Renton, WA; Rahway, NJ*

MK-0431, an oral, potent, and selective DPP-IV inhibitor is currently in development for treatment of type 2 diabetes (T2D). Metformin is a commonly used first-line antihyperglycemic agent. Combination treatment with MK-0431 and metformin may be useful since these agents target different pathophysiolic processes leading to hyperglycemia in T2D. Patients (pts) with T2D and inadequate glycemic control on metformin monotherapy (on a stable dose of ≥1500 mg/d for ≥6 wks) were recruited for a double-blind, randomized, placebo (Pbo)-controlled, 2-period crossover study. After a 5-wk screening/diet run-in period, 28 pts (baseline A1C range: 6.5-9.6%) receiving metformin were randomized into of 1 of 2 treatment sequences: adding Pbo for 4 wks followed by adding MK-0431 50 mg b.i.d. for 4 wks, or vice versa. At the end of each period, pts were domiciled for 24 hrs at the investigational site for frequent blood sampling. Results from Period 2 showed that pts who had received MK-0431 in Period 1 did not return to their pre-treatment baseline level at the end of the 4-wk Pbo treatment in Period 2, suggesting a substantial carryover effect. Because of the carryover effect, Period 1 results may provide a better estimate of treatment effect, and hence are the focus of this report (Table). No weight gain, increases in GI adverse events or hypoglycemia events were observed. In this study, the combination of MK-0431 and metformin was efficacious and generally well-tolerated as a treatment regimen for pts with T2D.

Parameter	Metformin + Placebo	Metformin + MK-0431 50 mg b.i.d.	Difference in LS means	P value
24-hr WMG (mg/dl)	157.9	125.0	-32.9	< 0.001
Change in FPG (mg/dl)	-3.4	-23.8	-20.3	< 0.001
Change in fructosamine (mmol/l)	5.0	-28.7	-33.7	0.003
Change in MDG (mg/dl)	4.9	-23.1	-28.0	0.046

Group data are LS means or mean change from baseline; WMG = weighted mean glucose; MDG = mean daily glucose calculated as the mean of 7-point fingerstick glucose determinations

12-OR

Low Dose Rosiglitazone Significantly Improves Glycemic Control without Increasing Adverse Events in Patients with T2DM Not Well Controlled on Insulin

PRISCILLA HOLLANDER, WAYDE M. WESTON, CHUN HUANG, HUBERT CHOU, LISA E. PORTER. *Houston, TX; King of Prussia, PA; San Diego, CA*

Insulin-using T2DM patients generally exhibit substantial insulin resistance. The addition of insulin sensitizers may complement exogenous insulin to optimize glycemic control. In this 24-wk trial, subjects with inadequate glycemic control on INS alone were randomized to double-blind treatment with the addition of RSG 2mg od (n=209), RSG 2mg bd (n=209) or placebo (n=212).

HbA_{1c} (mean±SD) (ITT subjects)	INS+PBO N=186	INS+RSG 2mg od N=193	INS+RSG 2mg bd N=189
Baseline	9.1±1.3	8.9±1.1	9.0±1.2
Wk 24	8.7±1.4	8.3±1.3	8.2±1.3
Change from Baseline	-0.44±1.2[1]	-0.64±1.1[1]	-0.78±1.1[1]
Comparison to INS+PBO	-0.26[1]	-0.38[1]	
Subjects with reduction from baseline ≥0.7% (n[%])	73 (39.5)	80 (41.5)	103 (54.8)
Comparison to INS+PBO (95%CI)	1.99 (-8.00, 11.98)	15.33 (5.27, 25.38)	

	INS+PBO N=212	INS+RSG 2mg od N=209	INS+RSG 2mg bd N=209
Subjects reporting hypoglycemia (n[%])	87 (41.0)	95 (45.5)	94 (45.0)
Confirmed (BG<50mg/dL)	47 (22.2)	63 (30.1)	57 (27.3)
Withdrawals	1 (0.5)	2 (1.0)	0
Total edema and edema-related AEs	23 (10.9)	12 (5.7)	23 (11.0)
Withdrawals	3 (1.4)	4 (1.4)	2 (1.0)

[1]p<0.05

INS+RSG treatment significantly reduced HbA_{1c} relative to baseline and to INS alone. C-reactive protein levels showed statistically significant, dose-ordered reductions from baseline in INS+RSG-treated subjects (-22.0% and -34.2%, p<0.05), and a small, nonsignificant increase in INS+PBO-treated subjects (+2.4%). Reports of hypoglycemia (total and confirmed by blood glucose measurement) were similar between subjects receiving INS alone