MAY 2000 VOLUME 49 SUPPLEMENT 1

diabetes

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION®
www.diabetes.org/diabetes

60th Scientific Sessions
San Antonio
Henry B. Gonzalez Convention Center · San Antonio, Texas
June 9-13, 2000

ABSTRACT BOOK

60th Scientific Sessions

Friday, June 9–Tuesday, June 13, 2000

Henry B. Gonzalez Convention Center
Marriott Riverwalk and Marriott Rivercenter
San Antonio, Texas

decreases of ≥ -0.7% for the 5mg or 10mg doses. The overall tolerability profile of GI262570 was similar to that observed with other PPARγ agonists, with dose-related weight gain, hemoglobin decreases, and peripheral edema. These data suggest that GI262570 will have clinical utility in the treatment of T2DM.

Parameter	P	1mg	2mg	5mg	10mg
Number of subjects (Intent-to-Treat)	67	59	61	58	67
Baseline (B) FSG (mg/dL)	201	205	208	204	206
FSG Δ from B at 4 weeks	+21	-10^{+}	-20^{+}	-34^{+}	-54^{+}
FSG Δ from B at 12 weeks	+22	-8^{+}	-28^{+}	-48^{+}	-66^{+}
% of subjects with ≥ -30 mg/dL FSG Δ from B	11%	33%*	48%$^{+}$	74%$^{+}$	85%$^{+}$
Baseline HbA1c (%)	8.1	7.8	8.0	8.1	8.1
HbA1c Δ vs. P at 12 weeks	—	-0.4$^{\Psi}$	-0.8^{+}	-1.4^{+}	-1.9^{+}
HbA1c Δ from B at 12 weeks	+1.1	+0.7	+0.3	-0.3	-0.7
% of subjects with ≥ -0.7% HbA1c Δ from B	3%	9%	19%*	41%$^{+}$	54%$^{+}$

Significance levels vs. P: $^{\Psi}$ = < 0.05 * = < 0.005 $^{+}$ = < 0.001

158-OR

Monotherapy with GI262570, a Tyrosine-Based Non-Thiazolidinedione PPARγAgonist, Significantly Reduces Triglyceride and Increases HDL-C Concentrations in Patients with Type 2 Diabetes Mellitus

GREG G. WILSON,[1,2] MARTHA ABOU-DONIA,[1,2] LUCY FRITH,[1,2] JAI PATEL,[1,2] FRED T. FIEDOREK,[1,2] STUDY GROUP- PPA20005,[1] *Research Triangle Park, NC; Greenford, Middlesex, United Kingdom*

GI262570 is a novel, non-thiazolidinedione, L-tyrosine-based peroxisome proliferator-activated receptor gamma (PPARγ) agonist that is ~1000-fold more selective for human PPARγ compared to the human PPARα isoform. A total of 376 Type 2 diabetes mellitus (T2DM) patients were randomized to receive either placebo (P) or one of 5 daily doses of GI262570 (0.25, 1, 2, 5, or 10mg) in a 12-week double-blind placebo-controlled study. Mean baseline fasting triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) concentrations are listed in the table. Approximately 60% of T2DM patients had mild fasting hypertriglyceridemia (HT) defined as TG > 150 mg/dL. Twelve weeks of treatment with GI262570 resulted in significant metabolic improvement in fasting TG and HDL-C (see table) along with changes in glycemic parameters that are described in a separate abstract. The maximum reduction in TG was achieved within 4 weeks and the effect was maintained over 12 weeks. While metabolic improvement in TG and HDL-C levels was observed across the range of T2DM patients regardless of baseline TG status, the greatest reductions were observed in subjects with mild/moderate HT. Apolipoprotein B levels fell by 8-14% for the 5mg and 10mg doses and there was also a non-significant decrease in LDL-C at these two GI262570 doses. These findings suggest that GI262570 will enhance overall metabolic control for T2DM patients by improving the high TG/low HDL-C dyslipidemia associated with T2DM as well as by improving hyperglycemia.

PARAMETER	P	1mg	2mg	5mg	10mg
Number of subjects (Intent-to-Treat)	67	59	61	58	67
Baseline (B) TG (mg/dL)	170	200	185	199	179
% TG Δ from B at 12 weeks	+3%	-6%	-13%$^{\Psi}$	-30%$^{+}$	-43%$^{+}$
Baseline TG (mg/dL) HT group	269	302	261	322	268
% TG Δ from B at 12 wks HT group	-7%	-18%	-19%	-44%	-53%
Baseline HDL-C (mg/dL)	42	42	42	40	42
% HDL-C Δ from B at 12 weeks	0%	+4%	+13%*	+12%*	+15%$^{+}$

Significance levels vs. P: $^{\Psi}$ = p < 0.05 * = p < 0.005 $^{+}$ = p < 0.001

159-OR

Rosiglitazone Liver Safety Update

HAROLD E. LEBOVITZ,[1,2] ALAN SALZMAN,[1,2] *Brooklyn, NY; Collegeville, PA*

Rosiglitazone is a potent thiazolidinedione for the treatment of type 2 diabetes. The thiazolidinedione troglitazone has been associated with hepatotoxicity, including liver failure and hepatic-related deaths. To date, no signal of hepatotoxicity has been seen with rosiglitazone, which has been extensively evaluated.

The incidence in rosiglitazone-treated patients of ALT elevations greater than 3x the upper limit of normal (ULN) was low and similar to placebo/comparators at the time of FDA filing in November 1998, at which time total exposure to rosiglitazone was 3600 patient years. Subsequently, exposure to rosiglitazone in clinical trials has substantially increased and as of November 1999 comprised over 5000 patient years including more than 1000 patients treated for ≥ 2 years. For all rosiglitazone-treated patients (including monotherapy and combination with SU or metformin), the rate of ALT levels > 3x the ULN is 0.30 cases per 100 patient years (see Table below). This compares to 0.59 cases per 100 patient years for placebo-treated patients and 0.73 cases per 100 patient years for SU- or metformin-treated patients. These are similar to the rates seen 1 year prior.

Rates of ALT Levels > 3x ULN in the Rosiglitazone Trial Program
(expressed as cases per 100 patient years)

	Rosiglitazone*	Placebo	SU or Metformin
November 1998	0.35	0.59	0.78
November 1999	0.30	0.59	0.73

*Includes monotherapy and combination with SU or metformin

In addition, rosiglitazone has been prescribed to over 250,000 patients, and thus far the clinical trial experience has been predictive of the rosiglitazone safety experience in the marketplace.

In conclusion, the current clinical trial and postmarketing experience with rosiglitazone indicate no evidence of troglitazone-like hepatotoxicity.

160-OR

Treatment with a DPP-IV Inhibitor, NVP-DPP728, Increases Prandial Intact GLP-1 Levels and Reduces Glucose Exposure in Humans

PAUL ROTHENBERG,[1,2] JYOTI KALBAG, HAROLD SMITH, RONALD GINGERICH, JERRY NEDELMAN, EDWIN VILLHAUER, JAMES MCLEOD, THOMAS HUGHES, *East Hanover, NJ; St. Charles, MO*

NVP-DPP728 is a highly selective, orally active inhibitor of dipeptidyl peptidase-IV (DPP-IV) designed to augment the glucose-lowering activity of endogenously secreted GLP-1. Recent studies have demonstrated that NVP-DPP728 prevents N-terminal degradative inactivation of GLP-1 and improves glucose tolerance in insulin-resistant rats. The present crossover trial evaluated the single dose pharmacodynamics of NVP-DPP728 administered to 12 healthy normoglycemic volunteers. After an overnight fast, subjects were administered 100 mg NVP-DPP728 or placebo, followed 30 minutes later by a 1000 kcal solid meal (23g protein, 42g fat, 36g carbohydrate, standard FDA breakfast). Blood samples were obtained predose and for up to 24 hours after each dose for analysis of plasma glucose and insulin levels and also for active, undegraded GLP-1 levels by direct ELISA (Linco Research). NVP-DPP728 increased peak plasma levels of active GLP-1 (15±2 vs. 9±2 pmol/l, p = 0.018) and also increased active GLP-1 prandial exposures, $AUC_{GLP\text{-}1(0\text{-}4h)}$ (28±4 vs. 14±4 $pmol.l^{-1}.h^{-1}$, p < 0.0001). Prandial glucose excursions above baseline were reduced by NVP-DPP728 relative to placebo (12±3 vs. 20±4 $mg.dl^{-1}.h^{-1}$, respectively, p = 0.04), while glucose excursions below baseline were unchanged (-22±4 vs. -16±4, p=0.3). Insulin excursions were not affected. No clinically significant adverse events were observed. In addition, administration of NVP-DPP728 to fasting individuals was unaccompanied by clinically significant changes in plasma glucose levels.

Thus NVP-DPP728 increased prandial active GLP-1 levels with concomitant reduction in prandial glucose exposure in normal subjects without causing hypoglycemia. These results provide the first direct clinical demonstration that DPP-IV inhibition is a viable new pharmacological approach for potentiating endogenous GLP-1 activity, and support the investigation of the glucose-lowering potential of NVP-DPP728 for the treatment of type 2 diabetics.

A numeral beside an author's name indicates a duality of interest. See page 93.