Clinical Trials Identifier : NCT00196989
Study No.: ADG20001
Title: A Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Placebo-Controlled, Study to Evaluate Efficacy, Safety and Tolerability of Oral GW677954 Capsules (2.5, 5, 10, 15 And 20 mg Once A Day) as a Monotherapy (Diet and/or exercise treated) or as an Add-On to Metformin for 16 Weeks Duration in Subjects with Type 2 Diabetes Mellitus
Rationale: In pre-clinical models GW677954 acts as an agonist at all 3 of the Peroxisomal Proliferator Activator Receptor (PPAR) subtypes (α, γ, and δ) Simultaneous agonism of PPAR subtypes α, γ, and δ may provide both glucose-lowering and lipid improvements in patients with type 2 diabetes mellitus.
Phase: II
Study Period: 23Sep2005 to 03Nov2006. Before recruitment to the study was complete, safety findings in rodent studies with GW677954 became available which led to the sponsor's decision to terminate ADG20001 before study completion.
Study Design: A multicenter, randomized, double-blind, double-dummy, dose-ranging, parallel group, placebo and active controlled study.
Centres: A total of 87 centers in the United States (38), Canada (17), Mexico (6), Australia (5), Argentina (5), Peru (4), New Zealand (4), Costa Rica (2), Russia (2), Czech Republic (2), Ecuador (1), Colombia (1).
Indication: Type 2 diabetes mellitus (T2DM)
Treatment: Eligible subjects were stratified by gender and background therapy (diet and exercise; metformin) and randomly assigned (1:1:1:1:1:1:1 ratio) to one of 5 doses of GW677954 or placebo qd for 16 weeks, or to pioglitazone (30 mg for 4 weeks followed by up-titration to 45 mg for a further 12 weeks).
Objectives: The primary objective of this study was to evaluate the dose response and efficacy of 5 doses (2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg qd) of GW677954 ($\pm$ metformin) versus placebo ($\pm$ metformin) on the reduction of hyperglycemia (assessed by glycated hemoglobin [HbA1c]) after 16 weeks of dosing in subjects with T2DM.
Primary Outcome/Efficacy Variable: The primary efficacy variable was change from baseline in fasting HbA1c levels at Week 16.
Secondary Outcome/Efficacy Variable(s): Secondary efficacy variables/outcomes included change from baseline in a number of metabolic parameters (fasting HBA1c, fasting FPG, fasting fructosamine), proportion of subjects achieving the protocol defined target HbA1c and FPG levels, proportion of subjects achieving the protocol defined target decrease in HbA1c and FPG levels, percent change from baseline and absolute change from baseline in a variety of lipid parameters, change from baseline in fasting insulin, C-peptide, HOMA-S and QUICKI, and change from baseline in the pioglitazone arm in markers of glycemia, lipids, tolerability and safety. As a result of the early termination of the study (and the consequent limited number of subjects who had completed the study) the list of secondary efficacy variables to be analysed was reduced to those reported below: Tg, HDLc and LDLc.

Statistical Methods: The Intent-to-treat (ITT) Population was used to assess efficacy and consisted of all randomised subjects who received at least one dose of study medication, had a baseline assessment and had at least one corresponding on-therapy efficacy assessment. The Safety Population was used to assess the safety data and consisted of all subjects who received at least one dose of study medication. Change from baseline in HbA1c at Week 16 was assessed using a Repeated Measures analysis model. Due to the early termination of the study and the limited number of subjects who completed week 16, a repeated measures analysis was performed, in place of the standard analysis of covariance at week 16 with last observation carried forward. A multivariate linear model analysis incorporating on therapy values at all time points was employed. The effects in the model were gender, background therapy (diet and exercise treated; metformin), treatment, baseline measurement, time, and treatment-by-time and baseline-by-time interaction. Point estimates and corresponding 95% confidence intervals and p-values at a 2-sided 5% level of significance (for GW677954 treatment groups only)) were calculated. The repeated analysis model as described for the primary endpoint was also employed for the secondary efficacy endpoints.

Study Population: Male and female subjects between the ages of 18 to 70 years with Type 2 Diabetes Mellitus (HbA1c≥8.0% but ≤10.0% at the pre-screening visit) currently treated with diet and/or exercise (must not have taken antidiabetic medications for at least two months prior to the pre-screening visit) or metformin monotherapy (subjects needed to have been on the same dose, formulation and regimen of metformin for at least two months prior to the pre-screening visit). Other inclusion criteria included a body mass index of 25-40 kg/m^2 and a FPG<270 mg/dL at the pre-screening visit.

	Placebo	2.5 mg	5 mg	10 mg	15 mg	20 mg	Pioglitazone
Number of Subjects:							
Planned, N	64	64	64	64	64	64	64
Randomised,	49	51	51	49	51	52	50
Safety Population	47	51	51	49	51	52	50
Intent to Treat (ITT) Population, n	46	48	46	48	49	51	47
Completed, n (%)	25 (53%)	25 (49%)	19 (37%)	29 (59%)	26 (51%)	23 (44%)	27 (54%)
Total Number Subjects Withdrawn, n (%)	22 (47%)	26 (51%)	32 (63%)	20 (41%)	25 (49%)	29 (56%)	23 (46%)
Withdrawn due to Adverse Events, n (%)	1 (2%)	2 (4%)	3 (6%)	0	4 (8%)	4 (8%)	2(4%)
Withdrawn due to Lack of Efficacy, n (%)	3 (6%)	3 (6%)	4 (8%)	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Withdrawn due to sponsor study, termination, n (%)	13 (28%)	15 (29%)	14 (27%)	11 (22%)	12 (24%)	16 (31%)	12 (24%)
Withdrawn for other reasons n (%)	5 (11%)	6 (12%)	11 (22%)	8 (16%)	6 (12%)	7 (13%)	8 (16%)
Demographics							

N (Safety Population)[1]	47	51	51	49	51	52	50
Females: Males	22:25	26:25	24:27	23:26	26:25	26:26	24:26
	Placebo	2.5 mg	5 mg	10 mg	15 mg	20 mg	Pioglitazone
Age (years), Mean (SD)	50.5 (12.14)	49.4 (9.46)	52.2 (9.39)	55.0 (7.74)	50.8 (8.78)	51.5 (9.10)	52.4 (10.40)
White, n (%)	26 (55%)	23 (45%)	28 (55%)	24 (49%)	26(51%)	25 (48%)	34 (68%)
Time since first diagnosis with diabetes (years)							
Mean (SD)	5.1 (4.2)	5.5 (5.3)	6.3 (5.0)	5.3 (4.5)	5.1 (4.1)	5.8 (4.6)	6.6 (6.3)
Median	4.1	4.1	4.9	4.7	3.7	4.6	4.8
Range	0.3-19.3	0.2-22.3	0.3-28.3	0.3-17.5	0.3-16.0	0.3-17.0	0.3-30.7
Background therapy							
Diet and Exercise, n (%)	17 (36)	17 (33)	17 (33)	15 (31)	17 (33)	20 (38)	18 (36)
Metformin, n (%)	30 (64)	34 (67)	34 (67)	34 (69)	34 (67)	32 (62)	32 (64)
Primary Efficacy Results:							
HbA1c, % [Repeated measures analysis of change (ITT population)]							
N	40	44	43	44	40	42	43
Baseline: Mean (SD)	8.66 (0.82)	8.64 (0.80)	8.68 (0.82)	8.68 (0.83)	8.65 (0.67)	8.62 (0.88)	8.80 (0.73)
Week 16: Mean (SD)	7.93 (1.09)	7.93 (1.23)	8.45 (0.90)	8.22 (1.19)	8.25 (1.11)	8.42 (1.86)	7.68 (1.13)
Model adjusted change from baseline to week 16: Mean (SE)	-0.40 (0.21)	-0.35 (0.20)	0.0 (0.21)	-0.32 (0.20)	-0.22 (0.21)	-0.19 (0.21)	-1.08 (0.20)
Difference from placebo							
Mean		0.06	0.40	0.08	0.18	0.21	-0.68
95% CI		-0.51; 0.63	-0.19; 0.99	-0.49; 0.65	-0.40; 0.76	-0.37; 0.80	-1.25; -0.10
p-value		0.84	0.18	0.78	0.54	0.48	
Secondary Outcome Variable(s):							
Triglycerides, mmol/L [Repeated measures analysis of change (ITT population)]							
N	43	47	45	48	45	45	45
Baseline: Geometric Mean (CV %)	2.1 (43)	2.1 (40)	1.9 (54)	2.3 (57)	2.0 (51)	2.1 (49)	2.2 (66)

Week 16: Geometric Mean (CV %)	1.9 (49)	1.9 (38)	1.5 (50)	1.4 (43)	1.4 (47)	1.6 (49)	1.9 (62)
Model-adjusted ratio to baseline (% change)							
Geometric mean (-SE, +SE)	-9.0 (-14.4, -3.3)	-12.2 (-17.2, -7.0)	-27.0 (-31.6, -22.1)	-34.0 (-37.6, -30.1)	-32.6 (-36.7. -28.3)	-31.8 (-35.8, -27.4)	-10.2 (-15.5, -4.7)
Ratio to baseline (difference in % change)							
Geometric Mean		-3.5	-19.8	-27.4	-25.9	-25.0	-1.4
95% CI		-18.3, 13.9	-32.8, -4.4	-38.5, -14.4	-37.6, -12.1	-36.8, -11.1	-16.7, 16.8
HDL-C (mmol/L) [Repeated measures analysis of change (ITT population)]							
N	43	47	45	48	45	45	45
	Placebo	2.5 mg	5 mg	10 mg	15 mg	20 mg	Pioglitazone
Baseline: Geometric Mean (CV %)	1.1 (24.1)	1.1 (23.4)	1.2 (27.6)	1.1 (24.7)	1.2 (23.7)	1.1 (20.7)	1.1 (28.6)
Week 16:Geometric Mean (CV%)	1.1 (20.2)	1.2 (22.9)	1.4 (29.0)	1.3 (25)	1.4 (21)	1.2 (22)	1.3 (31)
Model-adjusted ratio to baseline (% change)							
Geometric Mean (-SE, +SE)	-0.5 (-3.0, 2.1)	10.7 (8.0, 13.5)	14.9 (11.8, 18.2)	17.7 (14.8, 20.6)	15.7 (12.7, 18.8)	18.2 (15.2, 21.3)	9.6 (6.3, 11.9)
Ratio to Baseline (difference in % change)							
Geometric Mean		11.2	15.5	18.2	16.3	18.8	9.1
95% CI		3.6, 19.4	7.1, 24.5	10.3, 26.8	8.1, 25.1	10.5, 27.7	2.1, 17.7
LDL-C (mmol/L) [Repeated measures analysis of change (ITT population)]							
N	43	47	45	48	44	45	45
Baseline: Geometric Mean (CV %)	3.27 (22.1)	3.51 (22.7)	3.29 (33.6)	2.93 (35.6)	3.29 (26.5)	3.19 (33.2)	3.08 (35.6)
Week 16:Geometric Mean (CV%)	3.17 (35.8)	3.56 (23.5)	2.88 (32.2)	2.96 (30.9)	2.83 (33.3)	2.90 (26.4)	3.33 (26.3)
Model Adjusted Ratio to Baseline (% change)							
Geometric Mean	-3.2	1.7	-8.2	-2.1	-12.2	-8.5	0.8
-SE, +SE	-6.9, 0.6	-2.0, 5.6	-11.9, -4.4	-5.6, 1.4	-15.6, -8.8	-11.9, -4.9	-2.9, 4.7
Ratio to Baseline (difference in % change)							
Geometric mean		5.1	-5.2	1.1	-9.3	-5.4	4.2

95% CI		-5.3, 16.8	-15.0, 5.9	-8.8, 12.2	-18.6, 1.0	-15.0, 5.2	-6.3, 15.8
Safety Results: On-therapy AEs and SAEs were defined as those reported from the first dose of double blind study medication to on or before the final visit, or at least 5 terminal half-lives of the study medication.							
Adverse event (On therapy) **Most Frequent (≥5%) AEs in Each Treatment Group**	Placebo N=47	2.5 mg N=51	5 mg N=51	10 mg N=49	15 mg N=51	20 mg N=52	Pioglitazone N=50
Any Event, n (%)	24 (51)	28 (55)	33 (65)	31 (63)	29 (57)	28 (54)	30 (60)
Headache	2 (4)	5 (10)	5 (10)	2 (4)	3 (6)	7 (13)	8 (16)
Urinary tract infection	2 (4)	2 (4)	5 (10)	3 (6)	2 (4)	3 (6)	1 (2)
Back pain	0	4 (8)	3 (6)	1 (2)	1 (2)	1 (2)	2 (4)
Dizziness	1 (2)	0	3 (6)	2 (4)	1 (2)	3 (6)	1 (2)
Naso-pharyngitis	3 (6)	2 (4)	1 (2)	1 (2)	2 (4)	1 (2)	4 (8)
Blood creatinine phosphokinase increased	3 (6)	2 (4)	1 (2)	0	1 (2)	4 (8)	2 (4)
Insomnia	0	0	1 (2)	3 (6)	1 (2)	2 (4)	0
Diarrhea	1 (2)	1 (2)	1 (2)	2 (4)	1 (2)	2 (4)	4 (8)
	Placebo	2.5 mg	5 mg	10 mg	15 mg	20 mg	Pioglitazone
Nausea	1 (2)	1 (2)	3 (6)	1 (2)	1 (2)	2 (4)	3 (6)
Abdominal pain upper	0	1 (2)	1 (2)	2 (4)	1 (2)	3 (6)	1 (2)
Fatigue	1 (2)	3 (6)	1 (2)	2 (4)	0	1 (2)	1 (2)
Abdominal pain	1 (2)	0	3 (6)	1 (2)	1 (2)	0	2 (4)
	Placebo	2.5 mg	5 mg	10 mg	15 mg	20 mg	Pioglitazone
Anemia	1 (2)	0	3 (6)	1 (2)	2 (4)	0	1 (2)
Upper respiratory tract infection	1 (2)	1 (2)	0	0	2 (4)	1 (2)	3 (6)
Pro-thrombin time prolonged	0	0	1 (2)	3 (6)	0	0	0
Edema peripheral	0	1 (2)	0	0	1 (2)	1 (2)	4 (8)
Serious adverse event (On therapy), n (%) [considered by the investigator to be related to study medication]							
Subjects with non-fatal SAEs, n (%)	0	0	1 (2%) [1]	0	0	0	1 (2%) [1]
Local swelling	0	0	1 (2%) [1]	0	0	0	0
Subcutaneous emphysema	0	0	1 (2%) [1]	0	0	0	0

Facial swelling	0	0	1 (2%) [1]	0	0	0	0
Congestive cardiac insufficiency	0	0	0	0	0	0	1 (2%) [1]
6 month Post Treatment Follow-up							
Subjects with fatal SAEs, n (%)	0	0	1 (2%) [0]	0	0	0	0
Myocardial Infarction	0	0	1 (2%) [0]	0	0	0	0

Conclusion:
There were no clinically or statistically significant differences in the mean change from baseline to week 16 in HbA1c compared to placebo for any of the GW677954 doses. The number and types of adverse events reported were similar across all study arms. One fatality was reported in the 6 month post treatment follow up period in the 5 mg GW677954 arm.

Publications: No Publications

1: Summary of demographic data was completed on the safety population and is reflective of the population used for efficacy analysis.

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