Clinical Trials Identifier : NCT00264667
Study No.: ADG103440
Title: A Randomised, Double-blind, Parallel Group, Placebo-Controlled, Multicentre Study to Evaluate the Safety, Tolerability and Efficacy of Oral GW677954 Capsules 2.5 mg, 5 mg, 10 mg and 20 mg a day for 24 Weeks in Overweight Dyslipidaemic Subjects.
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 improve lipid profiles in overweight people with lipid abnormalities.
Phase: II
Study Period: 05 Dec2005 - 23 Nov2006. The study was terminated prior to scheduled completion by the sponsor following safety findings in rodent studies.
Study Design: This was a multi-center, double-blind, randomised, placebo controlled, parallel group dose-ranging study. Throughout the treatment period subjects fasted for 12 hours overnight prior to the clinic visit. Each subject was intended to attend 13 clinic visits over a total duration of 32 weeks maximum. In addition, there was an ophthalmic assessment conducted 6 months (± 1 month) after completing the study or Early Withdrawal in subjects receiving GW677954.
Centres: This study was conducted in 45 centers across 13 countries: Argentina, Australia, Chile, Costa Rica, India, Latvia, Mexico, New Zealand, Pakistan, Romania, Russia, Slovakia, and Spain.
Indication: Dyslipidaemia
Treatment: Eligible subjects were stratified by gender and randomized at Visit 4 in a 1:1:1:1:1 ratio to one of 4 doses of GW677954 or placebo for 24 weeks.
Objectives: The original primary objective of the study was to compare the effect of GW677954 at doses of 2.5 mg, 5 mg, 10 mg and 20 mg with those of placebo on non-HDLc (High density lipoprotein cholesterol) at 24 Weeks in overweight subjects with low HDLc, high TG (Triglyceride) dyslipidaemia.
Primary Outcome/Efficacy Variable: The primary endpoint assessed percentage change from baseline non-HDLc levels from baseline at Week 12 (owing to the early termination of the study and the limited number of subjects who completed week 24, a repeated measures analysis was performed at Week 12, in place of the planned analysis of covariance at week 24 with last observation carried forward (LOCF).
Secondary Outcome/Efficacy Variable(s): Secondary efficacy endpoints were percentage change from baseline in TC (total cholesterol), LDLc (low density lipoprotein cholesterol), HDLc, TGs and change from baseline in weight at Week 12.

Statistical Methods: Due to the early termination of the study and the limited number of subjects who completed week 24 (25 subjects, 9%), a repeated measures analysis was performed at Week 12 (122 subjects, 41%), in place of the planned analysis of covariance at week 24 with last observation carried forward (LOCF).

All efficacy analyses and summaries were based on the Intent-to-Treat (ITT) population which included all randomized subjects who received at least one dose of randomised study medication, had a baseline assessment and had at least one corresponding on-therapy (scheduled or unscheduled) efficacy assessment. The primary endpoint of percentage change from baseline in non-HDLc at Week 12 was analysed using a repeated measures analysis based on log-transformed non-HDLc. The following covariates were included in the model: gender, treatment, log-transformed baseline, time, treatment-by-time and log-transformed baseline-by-time interactions. The same method was used for the analysis of other lipid parameters (HDLc, LDLc, TC and TG). A similar repeated measures analysis was used to assess weight change from baseline at week 12 which included effects for gender, treatment, baseline, time, treatment-by-time and baseline-by-time interactions Of note, the list of secondary efficacy variables to be analysed was reduced to those reported below: lipid parameters and weight. Point estimates and corresponding 95% confidence intervals and p-values at a 2-sided 5% level of significance (comparing GW677954 to placebo) were calculated.

All safety analyses and summaries were based on the safety population which included all subjects who took at least one dose of study medication. AEs and SAEs for the subjects who attended the follow-up examination were listed. Any clinically relevant adverse findings identified at the eye examinations were recorded as adverse events and, were therefore, included in the AE data presentations. The ophthalmic assessment records of the slit lamp full eye examination were retained by the sites.

Study Population: Male and female subjects between ages of 18 and 70 years with low HDLc, high TGs dyslipidaemia who were overweight, as assessed by waist circumference. Another inclusion criterion included LDLc levels that did not require treatment at Visit 1.

Number of Subjects	Placebo	2.5 mg	5 mg	10 mg	20 mg
Planned, N	58	58	58	58	58
Randomised,	56	56	54	55	56
Safety Population	56	56	55	56	55
Intent to Treat Population (ITT) n	50	53	53	53	54
Completed, n (%)	6 (11)	4 (7)	4 (7)	6 (11)	5 (9)
Total Number Subjects Withdrawn, n (%)	50 (89)	52 (93)	51 (93)	50 (89)	50 (91)
Withdrawn due to Adverse Events, n (%)	4 (7)	4 (7)	1 (2)	2 (4)	4 (7)
Withdrawn due to Lack of Efficacy, n (%)	0	0	0	0	0
Withdrawn due to sponsor study, termination, n (%)	37 (66)	42 (75)	45 (82)	39 (70)	43 (78)
Withdrawn for other reasons n (%)	9 (17)	10 (19)	5 (10)	9 (17)	3 (6)
Demographics					
N (Safety population) [1]	56	56	55	56	55
Females: Males	57/43	59/41	60/40	59/41	62/38

Age (years), Mean (SD)	41 (11)	44 (12)	43 (11)	41 (11)	44 (12)
Range	18-64	18-68	23-68	19-64	19-66
White, n (%)	55	63	62	66	64
Primary Efficacy Results: **Non-HDLc mmol/L (Change from baseline to Week 12 ; ITT without LOCF population)**					
N	49	53	53	52	53
Baseline: Geometric Mean (CV %)	3.89(25.0)	4.04(23.1)	4.22 (18.3)	4.23 (25.7)	4.17 (26.4)
Week 12: Geometric Mean (CV %)	3.94 (19.4)	3.75 (17.4)	3.82 (22.3)	3.51 (21.5)	3.77 (28.4)
Model Adj.% Difference from Baseline; Geometric mean	1.3	-5.9	-5.7	-13.7	-9.7
Relative Difference in % change from placebo (95% CI)	-	-7.1 (-13.5,-0.2)	-7 (-13.3, -0.1)	-14.8 (-20.7,-8.5)	-10.9 (-17.1,-4.3)
p-value for relative difference		0.043	0.046	<0.001	0.002
Secondary Outcome Variable(s)					
TG mmol/L (Change from baseline to Week 12; ITT without LOCF population)					
N	49	53	53	52	53
Baseline: Geometric Mean (CV %)	2.33 (49.2)	2.36 (47.3)	2.50 (47.6)	2.55 (48.7)	2.66 (60.1)
Week 12: Geometric Mean (CV %)	2.39 (54.0)	1.89 (38.2)	2.02 (57.2)	1.64 (33.9)	1.83 (43.0)
Model Adj.% Difference from Baseline; Geometric mean	-1.2	- 19.6	-18.2	-36.0	-31.9
Relative Difference in % change from placebo (95% CI)	-	-18.6 (-31.0, -2.8)	-17.2 (-30.5 ,-1.2)	-35.2 (-45.8,-22.6)	-31 .0 (-42.3,-17.6)
HDLc mmol/L (Change from baseline to Week 12; ITT without LOCF population)					
N	49	53	53	52	53
Baseline: Geometric Mean (CV %)	0.95 (21.5)	1.01 (18.7)	0.96 (25.0)	1.02 (23.9)	0.98 (19.8)
Week 12: Geometric Mean (CV %)	0.97(22.)	1.09 (19.8)	1.09 (24.3)	1.17 (25.7)	1.10 (29.9)
Model Adj.% Difference from Baseline; Geometric mean	0.9	7.0	11.8	18.3	13.9
Relative Difference in % change from placebo (95% CI)	-	6.1 (-1.9,14.6)	10.8 (2.6, 19.6)	17.2 (8.4, 26.7)	12.8 (4.4, 21.9)
LDLc mmol/L (Change from baseline to Week 12 ; ITT without LOCF Population)					
N	49	53	53	52	53
Baseline: Geometric Mean (CV %)	2.82 (31.8)	3.11 (30.8)	3.23 (21.0)	3.15(31.6)	3.18 (27.08)
Week 12: Geometric Mean (CV %)	2.92 (37.9)	3.12 (22.8)	3.29 (21.0)	3.13 (23.3)	3.30 (29.1)

Model Adj.% Difference from Baseline; Geometric mean	0.8	0.3	7.3	2.9	4.6
Relative Difference in % change from placebo (95% CI)	-	-0.5 (-9.8, 9.7)	6.4 (-3.4, 17.3)	2.0 (-7.6, 12.6)	3.8 (-6.0, 14.5)
TC mmol/L (Change from baseline to Week 12 ; ITT without LOCF Population)					
N	49	53	53	52	53
Baseline: Geometric Mean (CV %)	4.87(21.)	5.06 (19.4)	5.22 (14.8)	5.31 (20.3)	5.19 (21.7)
Week 12: Geometric Mean (CV %)	4.94 (16. 2)	4.87 (15.1)	4.95 (17.3)	4.74 (17.3)	4.96 (20.0)
Model Adj.% Difference from Baseline; Geometric mean	1.1	-3.7	-2.3	-7.2	-4.7
Relative Difference in % change from placebo (95% CI)	-	-4.8 (-9.8, 0.6)	-3.4 (-8.5, 2.0)	-8.2 (-13.1, -3.0)	-5.7 (-10.8, -0.4)
Weight (Change in weight (Kg) from baseline to Week 12; ITT without LOCF population)					
N	46	46	48	47	46
Baseline (SD)	89.02 (15.9)	96.74 (18.8)	94.89 (18.8)	89.92 (18.7)	90.06 (15.9)
Week 12 Mean (SD)	86.5 (13.1)	99 (21.8)	94.03 (19.5)	90.25 (17.9)	89.97 (15.0)
Model Adj. Difference from baseline (Mean SE)	-0.96 (0.484)	-0.59 (0.450)	-0.77 (0.439)	-0.24 (444)	-1.17 (0.452)
Difference from Placebo (95% CI)	-	0.37 (-0.94 ,1.69)	0.19 (-1.1, 1.48)	0.73 (-0.56;2.02)	-0.2 (-1.51, 1.10)

Safety Results: Safety Results: On therapy AEs and SAEs were defined as those where the onset date was on or after the first dose of double blind study medication and not more than 2 days after the end of study medication. Two days represent at least 5 terminal half-lives of the study medication.					
Most Frequent (greater than or equal to 5 %) Adverse Events – On Therapy (Safety Population)					
Any Event, n (%)	24 (43)	24 (43)	27 (49)	31 (55)	25 (45)
Diarrhoea	2 (4)	4 (7)	3 (5)	3 (5)	3 (5)
Headache	4 (7)	5 (9)	4 (7)	1 (2)	2 (4)
Haematuria	3 (5)	4 (7)	3 (5)	1 (2)	3 (5)
Urinary tract infection	1 (2)	2 (4)	3 (5)	4 (7)	2 (4)
Pharyngitis	1 (2)	0	1 (2)	5 (9)	4 (7)
Back Pain	1 (2)	2 (4)	2 (4)	3 (5)	2 (4)
Influenza	0	1 (2)	2 (4)	3 (5)	3 (5)
Blood CPK (creatinine phosphokinase) increased	1 (2)	2 (4)	0	0	5 (9)
Arthralgia	1 (2)	2 (4)	1 (2)	0	3 (5)
Constipation	1 (2)	1 (2)	0	3 (5)	1 (2)
Dizziness	1 (2)	0	2 (4)	3 (5)	0
Upper respiratory tract infection	3 (5)	1 (2)	0	1 (2)	1 (2)
Pain in extremity	1 (2)	0	0	0	4 (7)
Fatigue	0	0	0	0	3 (5)
Serious Adverse Events occurring on therapy n (%) [n considered by the investigator to be related to study medication					
Subjects with non-fatal SAEs, n(%)	1 (2) [0]	0	1 (2) [0]	1 (2) [0]	1 (2) [0]
Deep Vein Trombosis	1 (2) [0]	0	0	0	0
Urinary Tract Infection	0	0	1 (2) [0]	0	1 (2) [0]
Subjects with fatal SAEs, n (%)	0	0	0	0	0
Serious Adverse Events occurring during 6 month follow up post treatment (post-therapy) n (%) [n considered by the investigator to be related to study medication					
Diverticulitis	0	1 (2) [0]	0	0	0
Cholelithiasis (gallstones)	0	1 (2) [0]	0	0	0
Mania episode	0	0	1 (2) [0]	0	0
Thyroid Cancer	0	0	0	1 (2) [0]	0

Conclusion:

The study showed statistically significant (dose related) improvements versus placebo in non- HDLc (primary endpoint) and other lipid parameters (TC, TGs and HDLc) at Week 12 in all doses studied. No statistically significant change in LDLc levels was observed.

Within the placebo arm, 24 adverse events were reported, the most common of which was headache. Within the 2.5 mg, GW677954 arm, 24 adverse events were reported, the most common of which was headache; within the 5 mg, GW677954 arm, 27 adverse events were reported, the most common of which was headache; within the 10 mg, GW677954 arm, 31 adverse events were reported, the most common of which was pharyngitis; Within the 20 mg, GW677954 arm, 25 adverse events were reported, the most common of which was increased blood CPK. During the study period and the six month follow-up period, two serious adverse events were reported in the placebo and the 2.5 mg, 10 mg, and 20 mg arms, and 3 serious adverse events were reported in the 5 mg arm. No fatalities were reported.

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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