Synopsis

Identifier: RM2006/00133/00 **Study Number:** PAD20001

Title: A multicenter, two-staged with interim analysis, parallel, randomized, double blind, placebo-controlled, dose-ranging study of the safety, tolerability, and effects on plasma high-density lipoprotein cholesterol (HDLc) of 12 weeks treatment with 2.5mg, 5mg and 10mg daily doses of GW501516 in subjects with low HDLc

Investigator(s): Multicenter

Study center(s): The study was conducted at 51 centers in 12 countries in Europe (Belgium, Denmark, Estonia, Finland, France, Germany, Lithuania, Netherlands, Norway, Poland, Portugal, and Sweden).

Publication(s): None at the time of this report

Study Period: 26 August, 2004 – 17 June 2005 (Stage 1)
20 November, 2005 – 20 June 2006 (Stage 2)

Phase of Development: II

Objectives: The primary objectives were to assess the safety and tolerability of once daily dosing of 2.5mg, 5mg, and 10mg GW501516 for 12 weeks in subjects with low HDLc, and to compare the effect of three doses of GW501516 on plasma concentrations of HDLc with respect to change from baseline relative to placebo.

Secondary objectives were: to determine the effect of the three doses of GW501516 on plasma concentrations of total cholesterol, triglycerides (TG), LDLc, very low density lipoprotein cholesterol (VLDLc), Apolipoprotein (Apo) A1, ApoA2, ApoB, free fatty acid (FFA), insulin, fibrinogen, and high sensitivity C-reactive protein (hsCRP) concentrations with respect to change from baseline relative to placebo; to determine the optimal doses of GW501516 to take forward into subsequent clinical trials based on safety and efficacy results; to characterize the population pharmacokinetics (PK) of GW501516 in subjects with low HDLc; to explore the relationship between GW501516 exposure and lipid parameters; and to explore the effect of GW501516 on apolipoproteins and other metabolic and inflammatory markers.

Methodology: This was a multicenter, two-staged with interim analysis, randomized, parallel, double-blind, placebo-controlled, dose-ranging study of 12-weeks treatment with three different daily doses of GW501516 (2.5mg, 5mg, and 10mg) in subjects with low plasma concentrations of HDLc. The continuation of the study after Stage 1 (which evaluated daily doses of 2.5 and 5.0mg GW501516 and placebo), and the doses carried forward in Stage 2 (which evaluated daily doses of 5 and 10mg GW501516 and placebo) were determined base on the results of an interim analysis and the recommendation of the IDMC (Independent Data Monitoring Committee). Each stage of the study consisted of a 2-week placebo run-in period, a 12-week double-blind treatment period, and a 2-week (Stage 1) or 4-week (Stage 2) follow-up period.

Number of subjects:

		GW501516			
	Placebo	2.5mg	5mg	10mg	Total
Randomized, N	84	50	86	63	283
ITT Population	84	50	86	63	283
Safety Population[1]	86	50	88	66	290
Completed, n (%)	78 (91)	46 (92)	80 (91)	58 (88)	262 (90)
Total number of Subjects Withdrawn	8 (9)	4 (8)	8 (9)	8 (12)	28 (10)
Withdrawn due to Adverse Events	0	1 (2)	1 (1)	1 (2)	3 (1)
Withdrawn for other reasons	8 (9)	3 (6)	7 (8)	7 (11)	25 (9)

1. Includes 7 additional subjects who erroneously received double-blind medication during the placebo run-in period (2 in the placebo group, 2 in the GW501516 5mg group, and 3 in the 10mg group).

Diagnosis and main criteria for inclusion: Male or female subjects 18 to 75 years of age with fasting plasma HDLc concentration ≤45mg/dL (≤1.16mmol/L), plasma LDLc levels that did not require treatment according to the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) guidelines, and fasting plasma TG concentration ≤500mg/dL (≤5.65mmol/L) were eligible for the study.

Treatment administration: Following completion of the 2-week placebo run-in period, subjects were randomized in Stage 1 in a 1:1:1 ratio to placebo, 2.5mg or 5.0mg GW501516 for 12 weeks of treatment. After the interim analysis, a second cohort of subjects was randomized in Stage 2 in a 1:1:2 ratio to placebo, 5mg or 10mg GW501516 for 12 weeks of treatment. Subjects were dispensed two bottles (Labeled Bottle 1 and Bottle 2) of blinded study medication and instructed to take by mouth 1 tablet in the morning from each bottle. This corresponded to the following treatments: Placebo (Stage 1 and 2), 2.5mg GW501516 once daily (Stage 1 only), 5.mg GW501516 once daily (Stage 1 and 2), and 10mg GW501516 once daily (Stage 2 only).

Criteria for evaluation: The primary efficacy endpoint was the percentage change from baseline in fasting plasma HDLc concentration between each dose of GW501516 and placebo at the end of 12 weeks of double-blind treatment. Secondary efficacy endpoints included comparisons of change from baseline at Week 12 in total cholesterol, TG, LDLc, VLDLc, Apolipoprotein (Apo) A1, ApoA2, ApoB, FFA, insulin, fibrinogen, and hsCRP concentrations.

Statistical methods: Following the interim analyses, sample size re-estimation was performed as the observed variability for HDLc appeared lower than the estimated variability used in the original calculation. The total number of subjects randomized for the study (an aggregate for Stage 1 and Stage 2) was reduced from approximately 424 to 290. Under the revised assumption, a sample size of n = 15 per group would be sufficient to detect a 20% increase in HDLc at endpoint between any GW501516 treatment group and placebo with at least 90% power at the two-sided $\alpha = 0.05$ level. However, a sample size of 30, 30, and 60 evaluable subjects for placebo, 5mg and 10mg GW501516 treatment groups, respectively, was chosen for Stage 2 to obtain a better understanding of drug safety by having a larger sample size.

Two populations were analyzed: Intent-to-Treat (ITT; comprised all subjects randomized to study medication that had a baseline efficacy evaluation and at least one efficacy evaluation during the double-blind treatment period) and Safety (comprised of subjects who took at least one dose of randomized study medication).

The primary efficacy endpoint was the percentage change from baseline in fasting plasma HDLc concentration at Week 12 using the LOCF approach for missing data. Each GW501516 dose was compared with placebo using a general linear model (ANCOVA). Control of the Type 1 error rate for these multiple comparisons was managed through a pre-specified hierarchical testing sequence, starting with the highest dose where testing did not proceed to the next step unless the previous test was found to be significant. Since this study employed a sequential design, the nominal one-sided p-value for efficacy at the interim analysis was 0.0026 and for the final analysis was 0.0243.

Secondary efficacy endpoints were percentage change from baseline at Week 12 (LOCF principle) in: fasting plasma total cholesterol, TG, LDLc, VLDLc, ApoA1, ApoA2, ApoB, FFA, insulin, fibrinogen, and hsCRP concentrations. Secondary efficacy variables were analyzed using similar methodology as the primary efficacy analysis noted above.

Adverse events were tabulated for each treatment group. Clinical laboratory values, urinalysis parameters, calculated creatinine clearance, vital signs, and ECG data were summarized by treatment group.

Summary:

Efficacy: GW501516 at doses of 2.5mg, 5mg or 10mg produced the following results:

- A statistically significant increase from baseline in HDLc (mmol/L) compared with placebo at each dose level at Week 12. The greatest increase over placebo (13.3%; 95% CI: 7.6, 18.9; $p<0.001$) was seen in the 10mg group, whereas the 2.5mg and 5mg doses produced similar increases (9.3% and 8.1%, respectively).
- A dose-related decrease from baseline in LDLc (mmol/L) that was statistically significant from placebo at Week 12 in the GW501516 5mg (-5.7%; 95% CI: -10.4, -0.9; $p=0.019$) and 10mg (-11.2%; 95% CI: -16.4, -6.0; $p<0.001$) treatment groups.
- A dose-related decrease from baseline in total cholesterol (mmol/L) that was statistically significant from placebo at Week 12 in the 5mg (-6.6%; 95% CI: -10.1, -3.1; $p<0.001$) and 10mg (-10.6%; 95% CI: -14.4, -6.8; $p<0.001$) treatment groups.
- A dose-related decrease from baseline in triglycerides (mmol/L) that was statistically significant from placebo at Week 12 in the 5mg (-17.6%; 95% CI: -27.2, -8.0; $p<0.001$) and 10mg (-29.2%; 95% CI: -39.7, -18.6; $p<0.001$) treatment groups.
- A dose-related decrease from baseline in VLDLc (mmol/L) that was statistically significant from placebo at Week 12 in the 5mg (-14.3%; 95% CI: -23.7, -4.9; $p=0.003$), and 10mg (-29.3%; 95% CI: -39.6, -18.9; $p<0.001$) treatment groups.

- A dose-related increase from baseline in ApoA1 (G/L) that was statistically significant from placebo at Week 12 in the 10mg (7.0%; 95% CI: 3.1, 10.9; p<0.001) treatment group.
- A dose-related increase from baseline in ApoA2 (G/L) that was statistically significant from placebo at Week 12 in the 2.5mg (9.2%; 95% CI: 4.2, 14.3; p<0.001), 5mg (15.2%; 95% CI: 10.9, 19.5; p<0.001), and 10mg (20.8%; 95% CI: 16.1, 25.5; p<0.001) treatment groups.
- A dose-related decrease from baseline in ApoB (G/L) that was statistically significant from placebo at Week 12 in the 2.5mg (-5.8%; 95% CI: -10.4, -1.3; p=0.013), 5mg (-9.4%; 95% CI: -13.3, -5.5; p<0.001), and 10mg (-14.2%; 95% CI: -18.5, -9.9; p<0.001) treatment groups.
- A statistically significant decrease from baseline in FFA (mmol/L) compared with placebo at each dose level. The greatest decrease over placebo (-36.4%; 95% CI: -48.6, -24.3; p<0.001) was seen in the 5mg group, whereas the 2.5mg and 10mg doses produced similar decreases (-32.7% and -34.2%, respectively).
- A dose-related decrease from baseline for fibrinogen (G/L) that was statistically significant from placebo in the 5mg (-10.9%; 95% CI: -16.9, -4.8; p<0.001) and 10mg (-17.3%; 95% CI: -23.9, -10.7; p<0.001) treatment groups.
- GW501516 produced an inconsistent response for hsCRP that was not significantly different from placebo in any treatment group at Week 12.
- GW501516 produced a decrease from baseline for insulin. At Week 12, the relative difference in percent change from baseline was statistically significant from placebo in 2.5 mg (-18.2%, 95% CI: -30.2, -4.2 p=0.013) and 5 mg (-14.1%, 95% CI: -25.10, -1.48, p=0.030) treatment groups.
- In general, consistent responses for HDLc, LDLc, and triglycerides were seen across subgroups of country, gender, baseline level, and age. There was some evidence of a greater reduction in LDLc in subjects with lower baseline triglyceride levels and lower baseline weight

Safety: GW50516, at doses of 2.5mg, 5mg, and 10mg was well tolerated during the study.

The incidence and type of adverse events were comparable across groups with the lowest proportion of subjects reporting AEs in the GW501516 10mg group (47%).

		GW501516		
Most frequent Adverse Events – On Therapy	Placebo (N = 86)	2.5mg (N = 50)	5.0mg (N = 88)	10mg (N = 66)
Any Adverse Event, n (%)	49 (57)	32 (64)	53 (60)	31 (47)
Headache	14 (16)	9 (18)	14 (16)	6 (9)
Nasopharyngitis	10 (12)	5 (10)	11 (13)	7 (11)
Fatigue	2 (2)	7 (14)	2 (2)	1 (2)
Back pain	4 (5)	2 (4)	3 (3)	2 (3)
Myalgia	2 (2)	3 (6)	5 (6)	1 (2)

- The most common drug-related AE, reported was headache.

- A total of four subjects reported an SAE during the On-Therapy period: one subject in the placebo group reported pyrexia; one subject in the 2.5mg reported myocardial infarction and another reported appendicitis; and one subject in the 10mg group reported chest pain. Only the SAE of pyrexia was assessed as drug-related by the investigator.

- No deaths occurred during the study.

- A dose-related increase in weight was observed in the GW50156 treatment groups. At Week 12, the difference from placebo was statistically significant for the 10mg group (1.74kg, 95% CI: 0.70, 2.78 p=0.001).

- There was no clinically significant change from baseline in the hematology and clinical chemistry parameters evaluated.

- Apart from weight changes, there were no clinically significant changes from baseline in other vital signs (BP, HR, waist circumference) or ECG measurements evaluated

Conclusions:

To conclude, the study showed statistically significant increases in the plasma HDLc levels in the overall population studied. Exploratory analyses indicated that the magnitude of response may be dependent upon baseline lipid characteristics of the selected population. Other potentially beneficial effects included statistically significant changes in cardiovascular risk factors.

The long term clinical relevance of these findings is currently difficult to ascertain and would need to be further explored in outcome based trials.

Date of Report: January 2008