Synopsis

Identifier: ZM2008/00086/00 **Study Number:** PM1108357

Title: A double-blind, placebo-controlled, parallel study to evaluate the effects of GW856553 on endothelial function/vascular compliance in subjects with dyslipidemia

Investigator(s): [redacted] BSc, MB, FRCP; [redacted] MA, BM, MRCP; [redacted] MRCP, PhD.

Study center(s): Three centers in the United Kingdom.

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

Study Period:

Initiation Date:	09 July 2007
Completion Date:	23 April 2008

Phase of Development: IIa

Objectives:

Primary Objective:

- To determine the effect of GW856553 on endothelial function as compared to placebo in subjects with dyslipidemia.

Secondary Objectives:

- To determine the effect of GW856553 on endothelium-independent vasodilation as compared to placebo in subjects with dyslipidemia.
- To determine the effect of GW856553 on basal nitric oxide (NO) activity in endothelium as compared to placebo.
- To characterize vascular compliance modifications in response to GW856553 administration in subjects with dyslipidemia.
- To assess the pharmacodynamic effect of daily doses over 4 weeks of GW856553 (7.5mg twice daily [BID]) as measured by the level of phosphorylated heat shock protein-27 (pHSP-27) in sorbitol induced whole blood cells of patients with dyslipidemia.
- To examine the safety and tolerability of GW856553.

Exploratory Objectives:

- To evaluate the effect of GW856553, compared to placebo, on messenger ribonucleic acid (mRNA) expression of inflammatory and proatherogenic genes using microarray technology or TaqMan.
- To assess the pharmacodynamic effect of daily doses over four weeks of GW856553 (7.5mg BID) as measured by the blood concentration of inflammatory markers.
- To evaluate *in-vivo* macrophage activity in carotid arteries and aorta following 4 weeks treatment of GW856553 (sub-study only).

Methodology:

This was a randomized, repeat-dose, double-blind, placebo-controlled, parallel-group study to evaluate the effects of GW856553 on endothelial function/vascular compliance in subjects with dyslipidemia. Eligible subjects were randomized to receive either GW856553 7.5mg BID or placebo for 4 weeks. Subjects eligible to participate as part of the control group participated in the baseline visit (Day 1) only.

Number of Subjects:

A sufficient number of subjects with hypercholesterolemia were to be recruited so that at least 50 (25 per arm) completed the study. As an exploratory objective, subjects may have been recruited into an imaging sub-study so that at least 12 subjects underwent 2 fluorodeoxyglucose (FDG)-positron emission tomography (PET) / computed tomography (CT) scans.

In addition, 12 male subjects were to be recruited as a normal lipid control group. These control subjects were to be age-matched (SD ± 10 years to the mean for the first 10 subjects at the site).

Subject Disposition and Demographics:

	Subjects with Dyslipidemia		Normal Subjects
Number of Subjects	GW856553 7.5mg BID	Placebo	
Number of subjects planned, N	25	25	12
Number of subjects randomized/enrolled, N	27	29	12
Number of subjects included in Safety Population, n (%)	27 (100)	29 (100)	12 (100)
Number of subjects completed as planned, n (%)	26 (96)	28 (97)	12 (100)
Number of subjects withdrawn (any reason), n (%)	1 (4)	1 (3)	0
Number of subjects withdrawn for SAE, n (%)	0	0	0
Number of subjects withdrawn for AE, n (%)	0	1 (3)	0
Primary Reason for Subject Withdrawal, n (%)			
Lost to follow-up	0	0	0
Adverse event	0	1 (3)	0
Protocol violation	0	0	0
Other	1 (4)[1]	0	0
Demographics	GW856553 7.5mg BID	Placebo	Normal Subjects
Age in Years, Mean (Min, Max)	54.6 (23, 71)	55.7 (35, 72)	43.0 (33, 64)
Sex, n (%)			
Female	7 (26)	10 (34)	0
Male	20 (74)	19 (66)	12 (100)
BMI in kg/m^2, Mean (Min, Max)	26.5 (20.5, 31.9)	26.6 (22.0, 35.2)	25.9 (20.9, 30.2)
Height in cm, Mean (Min, Max)	173.1 (157, 185)	172.3 (153, 182)	176.8 (163, 184)
Weight in kg, Mean (Min, Max)	79.3 (59.3, 93.2)	79.1 (58.5, 100.2)	81.0 (61.0, 102.3)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	27 (100)	29 (100)	12 (100)
Race, n (%)			
African American/African Heritage	1 (4)	2 (7)	1 (8)
White – White/Caucasian/European Heritage	26 (96)	27 (93)	11 (92)

1. Subject could not commit to availability for Day 28 assessment.

Diagnosis and Main Criteria for Inclusion:

Subjects with Hypercholesterolemia: Healthy adult male and female subjects aged between 18 and 75 years inclusive, with body weight >50kg and body mass index (BMI) between 19 and 32kg/m^2, fasting low density lipoprotein cholesterol (LDLc) level >4.1 mmol/L (160 mg/dL) and fasting triglyceride (TG) level <4.5 mmol/L (400 mg/dL). Female subjects had to have a negative pregnancy test and be of non-childbearing potential or of childbearing potential and agree to commit to one of the protocol-approved methods of contraception.

Subjects with Hypercholesterolemia for FDG-PET/CT Sub-Study: Healthy adult male and female subjects aged between 50 and 75 years inclusive were eligible for the sub-study. Female subjects had to have a negative pregnancy test and be of non-childbearing potential. Subjects who had previously participated in a research and/or a medical protocol involving nuclear medicine, PET or radiological investigations with significant radiation burden, or any subjects who had been exposed to ionizing radiation above background levels were excluded. Subjects were also excluded if they were diabetic subjects, had a contraindication to magnetic resonance imaging (MRI) scanning, or were unable to lie comfortably on a bed inside a PET camera with their head in the field of view for at least 60 minutes as assessed by physical examination and medical history.

Healthy Control Subjects: Healthy adult male subjects aged between 18 and 75 years inclusive, with body weight >50kg and BMI between 19 and 32kg/m^2, blood pressure ≤140 mmHg systolic and/or ≤90mmHg diastolic, LDLc < 2.6 mmol/L (100 mg/dL), fasting TG level <1.7 mmol/L (150 mg/dL), and high density lipoprotein cholesterol (HDLc) >1.0 mmol/L (40mg/dL). Subjects had to be non-smokers.

Treatment Administration:

Treatment	Drug	Dose / Form / Route	Frequency/ Duration	Batch Number
GW856553	GW856553	1 x 2.5mg tablet and 1 x 5mg tablet / oral	BID (every morning and evening) for 28 days	2.5mg tablet: DP133855 AK, PP142379 5mg tablet: DP129779 AE, PP142382
Placebo	Placebo to match GW856553	2 x placebo tablets / oral	BID (every morning and evening) for 28 days	PB101874 1EZ, PP142383

Criteria for Evaluation:

Primary Endpoint:

- Forearm blood flow (FBF) ratio, as measured by venous occlusion plethysmography, in response to maximum dose of intra-arterial acetylcholine (ACh) infusion. The comparison of FBF ratio in the GW856553 group compared with the placebo group on Day 28 was designated as the primary comparison of interest.

Secondary Endpoints:

- FBF ratio, as measured by venous occlusion plethysmography, in response to maximum dose of intra-arterial sodium nitroprusside (SNP) infusion. The comparison of FBF ratio in the GW856553 group compared with the placebo group on Day 28 was designated as the primary comparison of interest.
- FBF ratio, as measured by venous occlusion plethysmography, in response to maximum dose of intra-arterial L-N-monomethyl arginine (L-NMMA) infusion. The comparison of FBF ratio in the GW856553 group compared with the placebo group on Day 28 was designated as the primary comparison of interest.
- Augmentation Index (an indicator of arterial stiffness) as estimated by radial arterial pulse contours.
- Pulse wave velocity measured between carotid and femoral artery.
- Measurement of total and phosphorylated heat shock protein-27 (pHSP-27) levels in sorbitol induced whole blood cells of patients with dyslipidemia.
- Safety and tolerability parameters, including physical examination, blood pressure, heart rate, 12-lead electrocardiograms (ECGs), clinical laboratory tests, and adverse event (AE) reporting.

Exploratory Endpoints:

- FBF ratio, as measured by venous occlusion plethysmography in response to intra-arterial acetylcholine, sodium nitroprusside and L-NMMA infusion, for dyslipidemic subjects compared with healthy control subjects on Day 1.
- Baseline corrected blood concentration of protein biomarkers including the following markers (including but not limited to PLA2G7 [Lp-PLA2] [phospholipase A2, group VII platelet-activating factor acetylhydrolase, plasma], secreted phosphoprotein 1 [OPN], interleukin [IL]-6, IL-1β, tumor necrosis factor [TNF]-α, high sensitivity C reactive protein [hsCRP], serpin peptidase inhibitor [PAI-1], active fibrinogen, soluble intercellular adhesion molecule 1 [sICAM1], sP-selectin, matrix metallopeptidase 2 [MMP2], CD40L and nitrosylation assay.
- Baseline corrected mRNA expression levels of biomarkers in circulating peripheral blood mononuclear cells [PBMCs], measured by TaqMan, including the following: IL-1β, prostaglandin-endoperoxide synthase 2 (PTGS2), arachidonate 5-lipoxygenase (ALOX5), arachidonate 5-lipoxygenase-activating protein (FLAP), PAI-1 fibrinogen, IL-6, TNFα, toll-like receptor 2 (TLR2]) chemokine (C-C motif) receptor 2 (CCR2), heme oxygenase (decycling) 1 (HO-1), myeloperoxidase (MPO), Fas ligand (TNF superfamily, member 6) (FASL), MMP9, and MMP2 and control house keeper genes βactin, cyclophilin, ribosomal protein L32 (RPL32), and ribosomal protein L27 (RPL27).
- Endothelial progenitor cell (EPC) cell count.

- Changes in mean standard uptake values (tissue to background ratio [TBR] and /or standard uptake value [SUV]) of fluorodeoxyglucose (FDG) uptake in aortic and carotid arteries as assessed by FDG-positron emission tomography (PET) / computed tomography (CT) (sub-study only).
- Relationship between GW856553 trough plasma concentrations and pharmacodynamic (PD) endpoints.

Statistical Methods:

Sample Size:

The target sample size was 50 subjects. Based on a standard deviation of 0.234 on the loge-scale of change from baseline FBF ratio, a sample size of 25 subjects per treatment arm provided 90% power to detect a 20% difference in change from baseline FBF ratio at the alpha=5% level of significance. (The 20% difference is symmetric on the $\log_e$-scale and corresponds to either a 20% reduction or 25% increase on the original scale).

Venous Occlusion Plethysmography:

Primary Endpoint: Response Following Acetylcholine Infusion

Primary Analysis

The comparison of the FBF ratio (FBF in infused arm divided by FBF in the control arm) for the GW856553 group versus the placebo group on Day 28, following the maximum dose of acetylcholine infusion, was designated as the primary endpoint.

Following $\log_e$-transformation, acetylcholine-induced FBF ratio was analyzed using analysis of covariance (ANCOVA), including terms for regimen (GW856553 or placebo), infusion dose, the interaction of regimen and infusion dose, gender, and adjusting for Day 1 FBF ratio (in $\log_e$ scale) and infusion agent baseline as covariates (infusion agent baseline=$\log_e$-FBF ratio of saline preceding each drug infusion), with subject fitted as a random effect. Point estimates and corresponding 95% confidence intervals (CIs) for comparison of GW856553 vs Placebo were obtained for each infusion dose level.

Exploratory Analysis

Within each treatment group (GW856553 or Placebo), a comparison of the change in FBF ratio (FBF in infused arm divided by FBF in the control arm) from Day 1 to Day 28 was also performed.

To estimate these day differences, a separate ANCOVA model was applied to both Day 1 and Day 28 data, in which $\log_e$ transformed FBF ratio was fitted with a mixed effects model with a term for regimen (GW856553 or Placebo, visit (Day 1 or Day 28), infusion dose, interaction of regimen*visit, regimen*infusion dose and visit*infusion dose, and gender, with subject as a random effect, and $\log_e$ transformed saline FBF ratio as a covariate. The point estimate and corresponding 95% CI for Day 28 vs Day1 was obtained by regimen and infusion dose level.

Additional Exploratory Analysis

The following additional exploratory analyses were performed to evaluate the FBF response following acetylcholine infusion:

- FBF in the control arm, using repeated measures analysis.
- FBF in the infused arm, using repeated measures analysis.

  These additional exploratory analyses of FBF in the control arm and infused arm for the GW856553 group versus the placebo group on Day 28 were performed, so that the vasoregulatory response of GW856553 could be properly assessed without diluting the signal by including data from the non-responsive control arm.
- FBF ratio, using repeated measures analysis.

  The FBF ratio for the GW856553 group versus the placebo group on Day 28 was reanalyzed using a repeated measures mixed effects model, in which saline FBF ratio was treated as infusion dose 0 in contrast to the primary analysis, in which saline FBF ratio was treated as a covariate.

For each of these additional exploratory analyses, $\log_e$-transformed data were analyzed using a repeated measures mixed effects model, fitting fixed terms for regimen, day, infusion dose within day, gender and the interaction of regimen and dose within day, and subject as a random effect. Saline was treated as infusion dose 0 in the analyses. The point estimate and corresponding 95% CI for Day 28 vs Day 1 were obtained by regimen and infusion dose level. The point estimate and corresponding 95% CI for GW856553 vs placebo were obtained by study day and infusion dose level.

Secondary Endpoints: Responses Following Sodium Nitroprusside Infusion and L-NMMA Infusion

Primary Analysis

Comparisons of the FBF ratio (FBF in infused arm divided by FBF in the control arm) for the GW856553 group versus the placebo group on Day 28, following the maximum dose of sodium nitroprusside infusion, and following the maximum dose of L-NMMA infusion, were designated as secondary endpoints.

These endpoints were analysed using an ANCOVA model, as described previously for the acetylcholine-induced FBF ratio (primary analysis of the primary endpoint).

Exploratory Analysis

Within each treatment group (GW856553 or Placebo), comparisons of the change in FBF ratio (FBF in infused arm divided by FBF in the control arm) from Day 1 to Day 28 were also performed for sodium nitroprusside infusion and L-NMMA infusion.

To estimate these day differences, a separate ANCOVA model was applied, as described for the acetylcholine-induced FBF ratio (exploratory analysis of the primary endpoint).

Additional Exploratory Analysis

The following additional exploratory analyses were performed to evaluate the FBF response following sodium nitroprusside infusion and following L-NMMA infusion:

- FBF in the control arm, using repeated measures analysis.
- FBF in the infused arm, using repeated measures analysis.
- FBF ratio, using repeated measures analysis.

These repeated measures analyses were performed as described for the acetylcholine-induced response (additional exploratory analysis of the primary endpoint).

Exploratory Analysis: FBF Ratio for Dyslipidemic Subjects vs Healthy Subjects

FBF ratio for dyslipidemic subjects (GW856553 and placebo groups combined) vs normal control subjects on Day1 was analyzed using a repeated measures ANOVA model, including a repeated factor for dose level (with saline set as 0 dose), group (dyslipidemic, normal control), and with compound symmetry within subject covariance structure.

Pulse Wave Analysis and Pulse Wave Velocity:

Following $\log_e$-transformation, augmentation index data were analyzed using a mixed effects model including fixed effect terms for regimen, day, interaction of day and regimen, and subject as a random effect. Similar analyses were performed for heart rate during pulse wave analysis (HRp), mean arterial pressure (MAP), augmentation pressure (AP) and aortic pulse wave velocity.

Heat Shock Protein:

Following $\log_e$-transformation, phosphorylated HSP-27 ratio data (phosphorylated HSP-27 in sorbitol-stimulated whole blood / phosphorylated HSP-27 in whole blood in RPMI medium control) were analyzed using repeated measures analysis of variance (ANOVA) including a term for regimen, day, hours within day, two-way and three-way interaction of regimen, day and hours, and subject as a random effect. Total HSP-27 ratio data (total HSP-27 stimulated / total HSP-27 RPMI control) were analyzed separately using a similar model.

Protein Biomarkers:

Following log_e-transformation, concentrations of inflammatory biomarkers in blood were analyzed using ANCOVA, fitting terms for regimen, day, interaction of day and regimen, subject as a random effect, and baseline biomarker at Day 1 as a covariate. A similar analysis model was applied for normalized mRNA inflammatory biomarker expression data from Taqman.

Endothelial Progenitor Cells:

Following log_e-transformation, the ratio of EPC counts were analyzed using an ANCOVA model, including a term for regimen and log_e-transformed ratio of total leukocytes (Day28/Day1) as the covariate.

Summary:

Pharmacodynamics:

Venous Occlusion Plethysmography:

Primary Endpoint: Response Following Acetylcholine Infusion

Primary Analysis

For the primary endpoint of FBF ratio following intra-arterial acetylcholine (15μg) infusion (endothelium-dependent response), there was a 20% increase (95% CI: -6%, +53%; p=0.15) in the GW856553 group compared with the placebo group on Day 28.

Exploratory Analysis

For the GW856553 group there was a trend for an increase in the acetylcholine response on Day 28 compared with Day 1 (14% increase for 15μg dose of acetylcholine); no such trends were evident in the placebo group when Day 28 was compared with Day 1.

Additional Exploratory Analysis

When data for the infused arm separately were considered, there was an improvement of FBF for GW856553 compared with placebo following acetylcholine infusion (24% increase [95% CI: -1%, 55%] for both doses combined).

Additional exploratory analyses of FBF ratio using a repeated measures mixed effect model also suggested an improvement of FBF ratio for GW856553 compared with placebo following acetylcholine infusion (25% increase [95% CI: +5%, +48%] for both doses combined).

Secondary Endpoint: Response Following Sodium Nitroprusside Infusion

Primary Analysis

For the secondary endpoint of FBF ratio following intra-arterial sodium nitroprusside (10nmol) infusion (endothelium-independent response), there was a 33% increase (95% CI: +7%, +65%; p=0.01) in the GW856553 group compared with the placebo group on Day 28.

Exploratory Analysis

For the GW856553 group there was a trend for an increase in the sodium nitroprusside response on Day 28 compared with Day 1 (13% increase for 10nmol dose of sodium nitroprusside); no such trends were evident in the placebo group when Day 28 was compared with Day 1.

Additional Exploratory Analysis

When data for the infused arm separately were considered, there was an improvement of FBF for GW856553 compared with placebo following sodium nitroprusside infusion (36% increase [95% CI: +15%, +62%] for both doses combined).

Additional exploratory analyses of FBF ratio using a repeated measures mixed effect model also suggested an improvement of FBF ratio for GW856553 compared with placebo following sodium nitroprusside infusion (20% increase [95% CI: +3%, +40%] for both doses combined).

Secondary Endpoint: Response Following L-NMMA Infusion

Primary Analysis

For the secondary endpoint of FBF ratio following intra-arterial L-NMMA (4μmol) infusion, the response was similar in the GW856553 and placebo groups on Day 28 (2% increase; 95% CI: -9%, +15%).

Exploratory Analysis

There was no difference in the L-NMMA response on Day 28 compared with Day 1 in the GW856553 group or the placebo group.

Additional Exploratory Analysis

FBF was observed to be higher for GW856553 compared with placebo in both the control arm (13% increase [95% CI: -2%, +30%]) and the infused arm (24% increase [95% CI: +7%, +44%]) following infusion of the vasoconstrictor L-NMMA for both doses combined (i.e., the magnitude of the vasoconstrictor response was smaller for GW856553 than placebo). However, the absolute magnitude of the response following L-NMMA infusion was small. Furthermore, when corrected to the non-infused arm, as indicated by the FBF ratio in a repeated measures analysis, the difference was not significant.

Exploratory Endpoint: FBF Ratio for Dyslipidemic Subjects vs Healthy Subjects

Compared to the age-matched healthy controls, the dyslipidemic subjects had impaired vasoregulatory response in terms of endothelium-dependent acetylcholine response (24% lower [95% CI: -40%, -5%]), endothelium-independent sodium nitroprusside response (20% lower [95% CI: -37%, +1%]), and basal NO synthesis as evidenced by L-NMMA response (16% lower [95% CI: -29%, -1%]).

Pulse Wave Analysis and Pulse Wave Velocity:

No treatment effect was observed for the augmentation index, determined from pulse wave analysis in the sitting or supine position. Similarly, no treatment effect was observed for heart rate during pulse wave analysis, mean arterial pressure, augmentation pressure, or aortic pulse wave velocity.

Heat Shock Protein Phosphorylation:

A sustained inhibition of HSP-27 phosphorylation was observed at 3 and 6 hours after dosing on both Day 1 (decrease of 36% [95% CI: -53%, -13%] and 33% [95% CI: -47%, -16%], respectively) and Day 28 (decrease of 45% [95% CI: -61%, -23%] and 35% [95% CI: -49%, -15%] respectively) in the GW856553 group, compared with pre-dose values. No changes in the levels of HSP-27 phosphorylation from pre-dose to post-dose were evident in the placebo group.

Protein Biomarker Concentration in Blood:

There was a reduction in the concentration of hsCRP (decrease of 57% [95% CI: -81%, -6%]) after 28 days treatment in the GW856553 group compared with the placebo group. There was no difference in the concentrations of other protein biomarkers tested (CD40L, IL-1β, IL-6, $LpPLA_2$, MMP2, OPN, sP-selectin, PAI-1-active, TNF-α, and sICAM-1) in the GW856553 group compared with the placebo group.

mRNA Expression of Protein Biomarkers:

TaqMan analyses suggested a reduction of MPO (decrease of 19% [95% CI: -35%, 0%]) and PAI-1 (decrease of 23% [95% CI: -39%, -4%]) mRNA expression in PBMC after 28 days treatment in the GW856553 group compared with the placebo group. There was no difference in the mRNA expression of other protein biomarkers tested (HO-1, IL-6, IL-1β, TNF-α, PTGS2, ALOX5, FLAP, TLR2, CCR2, FASL, MMP2, MMP9, STK39) in the GW856553 group compared with the placebo group.

Endothelial Progenitor Cells:

A small increase in circulating CD45+/CD34+/CD133+ EPCs (increase of 18% [95% CI: -9%, +54%]) and CD45+/CD34+ hematopoietic stem cells (increase of 20% [95% CI: -5%, +51%]) was observed for the Day 28/Day 1 ratio for the GW856553 group compared with the placebo group.

Imaging Sub-Study:

There were insufficient numbers of subjects participating in the imaging sub-study to draw any conclusions with regard to the degree of metabolic activity measured using 18-fluorodeoxyglucose FDG-PET/CT.

Safety:

	Number (%) of Subjects with AE		
	GW856553 7.5mg BID	Placebo	Total
Preferred Term	N=27	N=29	N=56
Subjects with Any AE	22 (81)	18 (62)	40 (71)
Subjects with Any Drug-Related AE	15 (56)	12 (41)	27 (48)
Most Common AEs (Occurring in ≥2 Subjects in Any Treatment Group)			
Headache	9 (33)	10 (34)	19 (34)
Gamma-glutamyltransferase increased	2 (7)	2 (7)	4 (7)
Cough	2 (7)	2 (7)	4 (7)
Dizziness	2 (7)	1 (3)	3 (5)
Bacteria urine identified	2 (7)	1 (3)	3 (5)
Protein urine present	2 (7)	1 (3)	3 (5)
White blood cells urine	2 (7)	1 (3)	3 (5)
Influenza like illness	3 (11)	0	3 (5)
Dyspepsia	2 (7)	1 (3)	3 (5)
Pharyngolaryngeal pain	1 (4)	2 (7)	3 (5)
Nasopharyngitis	2 (7)	1 (3)	3 (5)
Alanine aminotransferase increased	0	2 (7)	2 (4)
Fatigue	2 (7)	0	2 (4)
Muscle spasms	2 (7)	0	2 (4)

There were no deaths, non-fatal serious adverse events (SAEs), or pregnancies. One subject (3%) in the placebo group was withdrawn from the study due to an AE of lung neoplasm which started pre-treatment; this AE was not considered to be related to study drug.

There were no clinically relevant differences between the GW856553 and placebo groups with regard to clinical chemistry values (including liver function tests), hematology values, vital signs, or ECGs over time. No subject had a liver function test that met pre-defined criteria for potential clinical importance.

Pharmacokinetics:

The mean trough GW856553 plasma concentration was slightly higher than the mean concentration previously observed in healthy volunteers. The relationship between trough concentration and the percent change in HSP-27 phosphorylation and hsCRP showed evidence of an effect of GW856553 on these PD endpoints; however, the data are insufficient for developing a PK/PD relationship.

Conclusions:

GW856553 7.5mg BID for 28 days had a positive effect on vascular function in dyslipidemic subjects and was generally well-tolerated:

- For the primary endpoint of FBF ratio following intra-arterial acetylcholine (15μg) infusion, there was a 20% increase (95% CI: -6%, +53%; p=0.15) in the GW856553 group compared with the placebo group on Day 28.
- For the secondary endpoint of FBF ratio following intra-arterial sodium nitroprusside (10nmol) infusion, there was a 33% increase (95% CI: +7%, +65%; p=0.01) in the GW856553 group compared with the placebo group on Day 28.
- For the secondary endpoint of FBF ratio following intra-arterial L-NMMA (4μmol) infusion, the response was similar in the GW856553 and placebo groups on Day 28.
- Exploratory analyses for blood flow on the infused arm suggested improvements of FBF for both doses combined for GW856553 vs placebo based on acetylcholine infusion (24% increase [95% CI: -1%, 55%]) and sodium nitroprusside infusion (36% increase [95% CI: 15%, 62%]).
- Compared to the age-matched healthy controls, dyslipidemic subjects had impaired endothelium-dependent acetylcholine response (24% lower [95% CI: -40%, -5%]), endothelium-independent sodium nitroprusside response (20% lower [95% CI: -37%, +1%]), and basal NO synthesis as evidenced by the L-NMMA response (16% lower [95% CI: -29%, -1%]).
- No treatment effect was observed for the augmentation index determined from pulse wave analysis, or aortic pulse wave velocity.
- A sustained inhibition of HSP-27 phosphorylation was observed at 3 and 6 hours after dosing on Day 1 (decreases of 36% and 33%, respectively) and Day 28 (decreases of 45% and 35%, respectively) in the GW856553 group, compared with pre-dose values.
- There was a reduction in the concentration of hsCRP (decrease of 57%) after 28 days treatment in the GW856553 group compared with the placebo group. There was no difference in the concentrations of other protein biomarkers tested.
- TaqMan analyses suggested a reduction of MPO (decrease of 19%) and PAI-1 (decrease of 23%) mRNA expression after 28 days treatment in the GW856553 group compared with the placebo group. There was no difference in the mRNA expression of other protein biomarkers tested.
- An increase in circulating CD45+/CD34+/CD133+ endothelial progenitor cells (increase of 18%) and CD45+/CD34+ hematopoietic stem cells (increase of 20%) was observed for the Day 28/Day 1 ratio for the GW856553 group compared with the placebo group.
- The AE profile was similar across treatment groups, with the exception that influenza like illness was reported by more subjects in the GW856553 group (3 subjects, 11%) than the placebo group (zero subjects, 0%). No AEs were of significant clinical concern.

- There were no deaths, non-fatal SAEs, or pregnancies in this study. One subject in the placebo group was withdrawn from the study due to an AE; this AE was not considered to be related to study drug.
- There were no clinically relevant differences between the GW856553 and placebo groups with regard to clinical chemistry values (including liver function tests), hematology values, vital signs, or ECGs over time. No subject had a liver function test that met pre-defined criteria for potential clinical importance.

Date of Report: February 2009