The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: HMA112795

Title : A two part, multicenter Phase IIa, placebo controlled study, to examine the safety, tolerability, and effects of GSK256073 on lipids in subjects with dyslipidemia

Rationale: HMA112795 was designed to be a 2-part study (Part A and Part B) to establish the nature of the PK/PD relationship between exposure and lipid effects.

Phase: II

Study Period: 15 June 2009-16 February 2010

Study Design: This was planned to be a 2-part study (Part A and Part B). The study was terminated after completion of Part A for futility. For the purposes of this summary, details are presented below for Part A only.
Part A was a multi-center, randomized, placebo controlled, single-blind (subjects and investigators were blinded, GSK internal personnel were not blinded), parallel-group study in subjects with dyslipidemia characterized by low HDLc.

Centres: This study was conducted at 11 centers in the United States.

Indication: Dyslipidemia

Treatment: Eligible subjects were randomized to 1 of 4 possible treatment regimens (in a 1:1:1:1 ratio) (with stratification of gender) by means of an interactive voice response system (IVRS). Treatment descriptions are provided below:

Regimen	Treatment Description
A	GSK256073 (5mg) for 60 days
B	GSK256073 (50mg) for 60 days
C	GSK256073 (150mg) for 60 days
D	GSK256073-matched placebo for 60 days

GSK256073 tablets and matching placebo were supplied by GlaxoSmithKline. Regimen A (5 mg GSK256073) was administered as 7.35 mg GSK256073F TRIS salt tablet containing 5 mg of active GSK256073. Regimen B (50 mg GSK256073) was administered as 73.5 mg GSK256073F TRIS salt tablet containing 50 mg of active GSK256073. Regimen C (150 mg GSK256073) was administered as three 73.5 mg GSK256073F TRIS salt tablet, with each tablet containing 50 mg of active GSK256073. Treatment administration details are provided in the table below.

Drug	Dose/Form/Route	Frequency/Duration	Batch Number
GSK256073	5 mg / tablet / oral	Once daily for 60 days	081166805
GSK256073	50 mg / tablet / oral	Once daily for 60 days	081167318
GSK256073	150 mg / tablet / oral	Once daily for 60 days	081167318
Placebo	tablet / oral	Once daily for 60 days	081167058

Objectives: The Part A primary objective was to characterize the exposure-response relationship for the effect of GSK256073 on high density lipoprotein cholesterol (HDLc) levels following approximately 8 weeks of daily dosing.

Statistical Methods: The sample size for Part A was not based on formal sample size calculations.
The PK/PD model that was used for the simulations in the study design was to be refined with the Part A observed AUC exposures and HDLc levels. This refined model allowed for determination of the exposure-response relationship with the administered doses from Part A. The PK/PD modelling was used to decide to continue or not continue this study to Part B and if the study had continued, to choose the appropriate doses in Part B to allow for a statistical comparison of increasing HDLc levels by GSK256073 versus placebo.
Percent changes from baseline in PD/biomarker endpoints were separately analyzed using a mixed effect model (or non-parametric method was used for non-normal distributed endpoints), fitting regimen, visit, and regimen by visit as fixed effects and a random term for subject. Baseline data and gender were included in the model as covariates. Least square mean differences at Week 8 between each dose level of GSK256073 and placebo were explored, and corresponding SDs were derived. The results were evaluated based on mixed effect models for the differences of percent change from baseline PD endpoints between doses of GSK256073 and placebo (i.e., Regimen A – Regimen D, Regimen B – Regimen D and Regimen C - Regimen D) and their corresponding 95% CI. The relationships between percent change from baseline HDLc and ApoA1, HDLc and NEFA were assessed by computing the Pearson correlation coefficient and Spearman correlation coefficient for each treatment group in Part A. The trend over dose and time plot for HDLc and ApoA1 were also evaluated. One variable, Gender, was added to the model as a covariate term for analyses of percent change from baseline in PD/biomarker endpoints.
Values for the maximum observed plasma concentration (Cmax) and the first time to reach Cmax (tmax) were estimated following administration of single and multiple doses of GSK256073. In addition, the area under the plasma concentration-time curve over the dosing interval [AUC(0-t)] was calculated by a combination of linear and logarithmic trapezoidal methods. The linear trapezoidal method was used for all incremental trapezoids arising from increasing concentrations, and the logarithmic trapezoidal method was used for those arising from decreasing concentrations. Plasma GSK256073 PK parameter estimates were listed by subject and treatment. Individual plasma GSK256073 parameter estimates were plotted by treatment on linear scales. Plasma GSK256073 PK parameter values were summarized by treatment.
No formal statistical analyses of the safety data were planned or performed. Safety data were listed and summarized.

Study Population: Eligible subjects included males or non-childbearing potential females 18-75 years of age at screening with a body weight > 50 kg (110 pounds) and body mass index (BMI) between 19 and 39 (inclusive). At screening and within 4 weeks of randomization (if screening occurs > 4 weeks prior to randomization), eligible subjects had LDLc concentration ≥100 mg/dL, fasting TG concentration ≤ 300 mg/dL and HDLc ≤ 45 mg/dL for males or ≤ 55 mg/dL for females. Subject receiving lipid-modifying medication(s) agreed to stop medication(s) for at least 6 weeks prior to randomization [after this washout period LDL, TG and HDL values were re-measured and meet the above criteria prior to randomization in the study].As shown in the table below, demographic characteristics were similar across treatment regimens. The overall population was mostly White (93%) with an approximately even split between males (49%) and females (51%).

	Regimen A	**Regimen B**	**Regimen C**	**Regimen D**	**Total**
Number of Subjects Planned:	20	20	20	20	80
Number of Subjects Enrolled:	19	20	20	21	80
Number of Subjects Completed as Planned:	16	15	15	20	66
Number of Subjects Withdrawn (any reason):	3	5	5	1	14
AE[1]	*0*	*1*	*1*	*0*	*2*
Met stopping criteria[2]	*0*	*2*	*0*	*0*	*2*
Lost to follow-up	*2*	*0*	*1*	*1*	*4*
Withdrew Consent	*1*	*2*	*3*	*0*	*6*
Number of Subjects included in safety analysis:	19	20	20	21	80
Number of Subjects included in PD analysis:	19	20	20	21	80
Age, years					
Mean (SD):	58.3 (8.43)	53.8 (9.77)	57.0 (10.75)	57.7 (10.15)	56.7 (9.80)
Median (Min-Max):	58.0 (41-69)	54.0 (37-71)	58.0 (34-71)	59.0 (37-75)	58.0 (34-75)
Gender, n(%)					
Female:	10 (53)	10 (50)	10 (50)	11(52)	41 (51)
Male:	9 (47)	10 (50)	10 (50)	10 (48)	39 (49)

Height, cm					
Mean (SD):	169.7 (10.22)	172.7 (11.77)	170.7 (7.73)	172.5 (10.15)	171.4 (9.96)
Median (Range):	166.0 (148-189)	173.0 (153-196)	171.0 (157-193)	171.0 (157-193)	171.0 (148-196)
Weight, kg					
Mean (SD):	85.4 (16.04)	88.8(16.96)	87.3 (13.28)	89.0 (16.89)	87.7 (15.63)
Median (Range):	81.8 (53-112)	90.8 (60-122)	88.1 (67-112)	87.8 (58-122)	87.5 (53-122)
BMI, kg/m^2					
Mean (SD):	29.5 (3.99)	29.7(4.31)	29.9 (3.40)	29.8 (4.54)	29.7 (4.01)
Median (Range):	29.5 (23-38)	28.7 (22-38)	28.5 (25-39)	30.1 (22-37)	29.0 (22-39)
Ethnicity, n(%)					
Hispanic or Latino:	2 (11)	4 (20)	1 (5)	1 (5)	8 (10)
Not Hispanic or Latino:	17 (89)	16 (80)	19 (95)	20 (95)	72 (90)
Race					
African American/African Heritage:	1 (5)	2 (10)	1 (5)	2 (10)	6 (8)
American Indian or Alaska Native	0	0	0	1 (5)	1 (1)
White – White/Caucasian/European Heritage:	18 (95)	18 (90)	19 (95)	18 (86)	73 (91)

1. Subject 2003 (Regimen B) was withdrawn due to an AE of increased blood creatine phosphokinas, and Subject 026 (Regimen C) was withdrawn due to AEs of dermatitis and pruritis.
2. Subjects 1011 and 1045 were determined to have significant medical history at the time of randomization. The subjects are listed as withdrawn due to "Met Stopping Criteria", but the significant medical history at randomization is more accurately identified as a Protocol Deviation (deviation from inclusion criteria). Both subjects are also listed as having protocol deviations

Regimen A – 5 mg of GSK256073 once daily for 60 days
Regimen B – 50 mg of GSK256073 once daily for 60 days
Regimen C – 150 mg of GSK256073 once daily for 60 days
Regimen D – Placebo once daily for 60 days

Pharmacodynamics (PD) and Pharmacokinetic (PK)/PD Endpoints:

For percent change from baseline in NEFA, nuclear magnetic resonance (NMR) of medium particle sized HDLc and hemaglobin A1c at Week 8, the 95% CIs for comparison between 5 mg of GSK256073 and placebo and between 50 mg of GSK256073 and placebo were statistically significant. None of the other comparisons were statistically significant.

Since mixed model assumption (normal distribustion) appeared grossly violated for ApoAII, glucose, insulin and TG in terms of percent change from baseline, a non-parametric method (Mann-Whitney test) was used to analyze these endpoints. Only the difference in TG level between 150 mg of GSK256073 and placebo was statistically significant.

The results of Bayesian predictive probability for comparison between GSK256073 and placebo for HDLc at Week 8 indicated nearly no chance of attaining clinical significant HDLc elevation compared to placebo at the end of Part B (if Part B was progressed) upon administration of the 2 higher doses of GSK256073 (50 mg and 150 mg), and only a 22% chance of attaining clinical significant HDLc elevation at the end of Part B upon administration of the lower dose (5 mg) of GSK256073. That is, the model suggested an overall inverse relationship of effect on HDLc and dose of GSK256073.

Results from the subjects in Part A revealed that a positive PK/PD relationship did not exist between AUCs and HDLc levels. However, a possible trend for a decrease in HDLc levels was noted at the higher dose (150 mg of GSK256073 for 60 days). When plotted, the PK/PD relationship was similar to the placebo or "no effect" simulations performed *a priori*.

Pharmacokinetics (PK) Endpoints:
Selected PK parameters are summarized in the table below.

Regimen	N	AUCss(0-t) (ng·hr/mL)[1]	Cmax (ng/mL)[1]	tmax (hr)[2]
A	15	8352 (100)	924 (128)	2.42 (0.50 – 7.73)
B	15	75588 (71.9)	7224 (35.1)	1.35 (0.63 – 9.00)
C	16	340551 (60.7)	22962 (62.4)	2.50 (0.50 – 26.0)

1. Geometric mean (CVb%)
2. Median (range)

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Safety results:
AE and serious adverse event (SAE) data were collected and recorded on the CRF starting on Day 1 and continuing until the end of the confinement period.
The table below summarizes AEs occurring in more than one subject.

	Number of Subjects (%)			
	Regimen A (N=19)	**Regimen B (N=20)**	**Regimen C (N=20)**	**Regimen D (N=21)**
Number of Subjects (%) with any AE	**8 (42)**	**12 (60)**	**17 (85)**	**14 (67)**
Adverse Events				
Flushing	4 (21)	5 (25)	12 (60)	5 (24)
Nasopharyngitis	2 (11)	2 (10)	0	1 (5)
Headache	1 (5)	0	2 (10)	1 (5)
Nausea	0	0	3 (15)	1 (5)
Pruritis	1 (5)	2 (10)	1 (5)	0
Back pain	1 (5)	0	1 (5)	1 (5)
Blood creatine phosphokinase increased	0	2 (10)	0	1 (5)
Insomnia	0	1 (5)	2 (10)	0
Oropharyngeal pain	0	2 (10)	1 (5)	0
Upper respiratory tract infection	0	0	2 (10)	1 (5)
Constipation	0	1 (5)	0	1 (5)
Dermatitis	0	0	2 (10)	0
Hot flush	0	1 (5)	1 (5)	0
Influenza	1 (5)	0	1 (5)	0
Paraesthesia	0	1 (5)	1 (5)	0
Upper respiratory tract congestion	0	0	1 (5)	1 (5)
Weight increased	0	1 (5)	0	1 (5)

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Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]: None