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.: FAK113581
Title: A Phase I, Randomized, Single-Blind, Placebo-Controlled Dose-Escalation Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics and Preliminary Food Effect Following Single Oral Doses of the Focal Adhesion Kinase Inhibitor, GSK2256098, in Healthy Subjects
Rationale: This study represents the first administration of GSK2256098 in humans. The primary objectives of this study were to establish the initial safety and pharmacokinetics in healthy subjects before proceeding with studies in patients with cancer. The effect of food on GSK2256098 is unknown; therefore an additional cohort was included to evaluate the effect of administration with a high fat meal on GSK2256098.
Phase: I
Study Period: 27 Oct 2009 to 17 Mar 2010
Study Design: This study was a Phase I randomized, single-blind, placebo-controlled single dose, dose-escalation study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of GSK2256098 in healthy adult subjects. In the last cohort, a pilot assessment of food effect was conducted in 8 subjects. Doses were escalated in a sequential fashion, contingent on the safety and toxicity profile of previous doses. Investigational product (GSK2256098 or placebo) was administered in a fasting state at the clinical research unit, except for the subjects enrolled in the food effect cohort who ate a high fat meal 30 minutes prior to dosing. Subjects remained in the clinic until after the final PK sample on Day 3, and returned for a followup visit 10 to 14 days later.
Centre: Nucleus Network, Melbourne Australia
Indication: Oncology
Treatment: Single oral doses of GSK2256098 or placebo were administered in the research clinic.
Objectives: The primary objectives were to characterize the safety of single doses of GSK2256098 and the single dose pharmacokinetics of GSK2256098 in blood and urine in adult healthy subjects
Statistical Methods: Safety data are presented in tabular and/or graphical format and summarized descriptively. GSK2256098 concentration data were measured from whole blood samples and dried blood spots. Concordance of the concentration results from the 2 matrices was tested by Lin's concordance statistic and Pearson's correlation coefficient. Concentration time data were analyzed by non-compartmental methods with WinNonlin [Version 5.2]. Exploratory assessment of dose proportionality was performed using the power model approach. The effect of food was assessed by a parametric approach to estimate the difference between fed vs. fasted dose-normalized AUC(0-∞) and Cmax along with 90% CI in this pilot assessment. For tmax, the median difference between fed and fasted groups was calculated, along with the associated 90% CI. If the 90% confidence interval for the GLS mean ratio was contained within the interval (0.7, 1.43), the effect of food on the pharmacokinetics of GSK2256098 was considered not to be clinically significant.
Study Population: 38 healthy adult males participated in this study.

Summary of Subject Disposition and Demographic Characteristics:

Number of Subjects	**Placebo (N=10)**	**20 mg (N=4)**	**40 mg (N=4)**	**80 mg (N=4)**	**160 mg (N=4)**	**240 mg (N=4)**	**140 mg +food (N=8)**	**Total (N=38)**
Number of subjects randomized	10	4	4	4	4	4	8	38
Number of subjects included in All subjects (safety) population	10	4	4	4	4	4	8	38
Number of subjects included in PK population	0	4	4	4	4	4	8	28
Number of subjects completed as planned	10	4	4	4	4	4	8	38
Demographics:								
Age in Years, Mean (SD)	29.8 (7.51)	29.3 (10.72)	34.8 (5.62)	28.3 (6.60)	24.5 (4.80)	21.3 (1.26)	22.9 (3.98)	27.2 (7.40)
Sex								
Male:	10	4	4	4	4	4	8	38
Race, n (%)								
Asian – Central/South Asian Heritage	0	1 (25%)	0	1 (25%)	0	1 (25%)	0	3 (8%)
Asian – Japanese/East Asian Heritage/South East Asian Heritage	1 (10%)	0	0	0	1 (25%)	0	3 (38%)	5 (13%)
White – Arabic/North African Heritage	9 (90%)	3 (75%)	3 (75%)	3 (75%)	3 (75%)	3 (75%)	5 (63%)	29 (76%)
Mixed race	0	0	1 (25%)	0	0	0	0	1 (3%)

Safety Results: Adverse event (AE) and serious adverse event (SAE) data were collected starting on Day 1 and continuing through the follow-up contact. No premature withdrawals due to adverse events were reported in this study. Clinically significant changes in clinical laboratory values, vital signs, and ECGs were not observed, with the exception of a single postdose, reversible increase in proteinuria.

Most Frequent Adverse Events:

System Organ Class Preferred Term	**Placebo (N=10)**	**20 mg (N=4)**	**40 mg (N=4)**	**80 mg (N=4)**	**160 mg (N=4)**	**240 mg (N=4)**	**140 mg +food (N=8)**	**Total (N=38)**
Number of subjects with AEs	4 (40%)	3 (75%)	2 (50%)	4 (100%)	1 (25%)	2 (50%)	6 (75%)	22 (58%)
Number of subjects with Related AEs	3 (30%)	1 (25%)	2 (50%)	4 (100%)	1 (25%)	2 (50%)	3 (38%)	16 (42%)
Most Frequent AEs (≥5% all subjects)								
Headache	2 (20%)	0	1 (25%)	0	0	0	2 (25%)	5 (13%)
Lethargy	0	0	0	3 (75%)	0	0	0	3 (8%)
Dizziness	0	0	1 (25%)	0	0	1 (25%)	0	2 (5%)
Abdominal discomfort	0	1 (25%)	0	0	0	1 (25%)	0	2 (5%)
Catheter site phlebitis	0	0	0	1 (25%)	1 (25%)	0	0	2 (5%)
Epistaxis	0	0	0	1 (25%)	0	0	1 (13%)	2 (5%)

Serious Adverse Events: No SAEs, either fatal or nonfatal, were reported.

Pharmacokinetic Results: GSK2256098 AUC(0-∞) and Cmax were dose proportional over the dose range studied. Concordance (0.9964) was observed between dried blood spot and whole blood concentrations with no apparent systematic biases at high or low concentrations. PK parameters from the Dried Blood Spot assay are summarized below.

PK Parameters	20 mg (N=4)	40 mg (N=4)	80 mg (N=4)	160 mg (N=4)	240 mg (N=4)	140 mg + food (N=8)
Tmax (hr)	1 (0.5-1.25)	1(1.0-1.5)	1 (1.0-1.0)	1(0.5-1.5)	1(1.0-1.0)	3.5(3.0-5.0)
Cmax (ng/mL)	110 (44) (71-168)	208 (51) (133-398)	600(14) (541-728)	1371 (100) (397-2397)	2712 (10) (2508-3161)	499(26) (333-692)
AUC(0-t) (ng*hr/mL)	236 (53) (123-399)	511 (59) (311-1099)	1386(15) (1129-1597)	3874 (54) (2185-7446)	7071 (16) (6345-8923)	2663 (30) (1796-3855)
AUC(0-∞) (ng*hr/mL)	ND	1363[1]	1521 (12)[2] (1327-1655)	4066 (50) (2401-7506)	7220(16) (6411-9104)	2979(30)[3] (1988-4100)
t½ (hr)	ND	6.5[1]	5.1 (38)[2] (4.0-7.8)	6.4 (30) (4.2-8.1)	7.4 (62) (4.1-14.4)	9.2 (32)[3] (6.3-12.3)
fe	0	0	0	0.0036	0.0023	0.0026

Results are presented as geometric mean (CVb%),(range), except for Tmax, which is reported as median (range). fe is reported as median only; ND=no data; fe=fraction excreted unchanged in urine

1. n=1
2. n=3
3. n=6

Following administration of a high-fat meal, maximal concentrations assayed in dried blood spots were delayed 2.5 h (90% CI: 2 to 4 h) to a median tmax of 3.5 h. The ratio and 90% CI for Cmax and AUC(0-∞) values in the fed to the fasted state were 0.45 (0.26, 0.79) and 0.85 (0.55, 1.33), respectively.