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.

GSK Medicine: Dabrafenib
Study Number: BRF113771
Title: A Four-Part, Open-Label Study to Evaluate the Effects of Repeat Dose GSK2118436 on the Single Dose Pharmacokinetics of Warfarin, the Effects of Repeat Dose Oral Ketoconazole and Oral Gemfibrozil on the Repeat Dose Pharmacokinetics of GSK2118436, and the Repeat Dose Pharmacokinetics of GSK2118436 in Subjects with BRAF Mutant Solid Tumors
Rationale: The purpose of the study was to determine the repeat dose pharmacokinetics (PK) of dabrafenib prepared in hydroxypropylmethylcellulose (HPMC) capsules, and to investigate the drug-drug interaction potential of dabrafenib. **Part A** of the study was to investigate the effect of repeat doses of dabrafenib (150 mg BID) on the PK of warfarin, a probe substrate for cytochrome P450 (CYP)2C9. The purposes of **Part B** and **Part C** were 1) to evaluate the effect of a potent CYP3A4 inhibitor (ketoconazole) and the effect of a potent CYP2C8 inhibitor (gemfibrozil) on the PK of repeated doses of 75 mg of dabrafenib and 2) to evaluate single and repeat dose PK following administration of 75 mg of dabrafenib as HPMC capsules. **Part D** was to evaluate the single- and repeat-dose PK following administration of 150 mg of dabrafenib prepared in HPMC capsules.
Phase: I
Study Period: 27Jul2011 to 15Nov2012
Study Design: This was a 4-part, multi-center, open-label, fixed sequence study in subjects with BRAF mutant solid tumors. Eligible subjects participated in only one part of the study. In **Part A**, subjects received warfarin 15mg on Day 1 and Day 22 and dabrafenib 150mg twice daily (BID) from Day 8 to Day 29. In **Part B** and **Part C**, subjects received dabrafenib 75mg BID from Day 1 to Day 22, with concomitant ketoconazole 400 mg once daily (Part B) or gemfibrozil 600mg BID (Part C) from Day 19 to Day 22. In **Part D**, subjects received dabrafenib (HPMC capsules) 150mg BID for 18 days. After completion of the study, all subjects had the option to enter Protocol BRF114144, an open-label roll-over study of dabrafenib.
Centres: Eight sites in the United States, 2 sites in United Kingdom, and 1 site in Australia. No subjects were enrolled at the Australian site.
Indication: BRAF V600 mutation-positive tumors
Treatment: Dabrafenib was supplied as 75mg capsules. Warfarin 5mg tablets, ketoconazole 200mg tablets, and gemfibrozil 600mg tablets were sourced locally from commercial stock. All medications were administered with approximately 240 mL (8 fluid ounces) of water.
Objectives: **Part A:** To evaluate the effect of repeat doses of dabrafenib on the single dose pharmacokinetics of S warfarin in subjects with BRAF mutant solid tumors. **Part B and Part C:** To evaluate the effect of repeat oral doses of a CYP enzyme inhibitor, ketoconazole (Part B) or gemfibrozil (Part C) on the repeat dose PK of dabrafenib in subjects with BRAF mutant solid tumors, and to evaluate the single- and repeat-dose PK of dabrafenib and its metabolites (hydroxy-dabrafenib [GSK2285403], desmethyl-dabrafenib [GSK2167542], and carboxy-dabrafenib [GSK2298683]) following administration of dabrafenib 75 mg HPMC capsules **Part D:** To evaluate the single- and repeat dose pharmacokinetics of dabrafenib and its metabolites (hydroxy-dabrafenib, desmethyl-dabrafenib, and carboxy-dabrafenib) following administration of dabrafenib 150 mg BID HPMC capsules. **Part B and Part D**: To evaluate the dose proportionality of dabrafenib and its metabolites (hydroxy-dabrafenib, desmethyl-dabrafenib, and carboxy-dabrafenib) following administration of dabrafenib 75 mg BID (Part B) and 150 mg BID (Part D)
Primary Outcome: The primary outcome of the study was PK. Primary endpoints were: **Part A:** Maximum observed concentration (Cmax), the area under the concentration-time curve (AUC) from time zero to time t [AUC(0-t)]. and the AUC from time zero extrapolated to infinite time [AUC(0-∞)] of S warfarin with and without dabrafenib. **Part B and Part C:** Cmax, and AUC over the 12-h dosing interval [AUC(0-τ)] of dabrafenib with and without inhibitor; Day 1: tmax, Cmax, AUC(0-τ), the AUC from time zero to 24 hours post-dose [AUC(0-24)], AUC(0-∞), t½; Day 18: tmax, Cmax, AUC(0-τ), and steady-state trough plasma concentration (Cτ). **Part D:** Day 1: tmax, Cmax, AUC(0-τ), AUC(0-24), AUC(0-∞), t½; Day 18: tmax, Cmax, AUC(0-τ), Cτ; Time invariance and accumulation ratio.

Part B and Part D: Dose proportionality on Day 1 PK parameters (Cmax, AUC(0-24), AUC(0-∞)) and Day 18 PK parameters [Cmax, Cτ, and AUC(0-τ)]

Secondary Outcomes:

Part A: Cmax, AUC(0-t) and AUC(0-∞) of R warfarin with and without dabrafenib; time of occurrence of Cmax (tmax), the terminal phase half-life (t½) for R- and S-warfarin; Cτ, and Cmax of dabrafenib; adverse events (AEs); electrocardiogram (ECG); changes in laboratory values and vital signs; international normalized ratio (INR).

Part B and Part C:Day 22: tmax, and Cτ for dabrafenib; AUC(0-τ), Cmax, tmax, Cτ of hydroxy-dabrafenib, desmethyl-dabrafenib, and carboxy-dabrafenib, and AUC(0-τ) ratio of metabolite to parent (dabrafenib); safety and tolerability data including vital signs, ECG data, clinical laboratory tests, and AEs; ketoconazole and gemfibrozil concentrations on Day 22.

Part D: AEs; ECGs; changes in laboratory values and vital signs.

Statistical Methods: The 'All Treated Subjects Population' included subjects who received at least 1 dose of study medication. The 'PK Population' included subjects for whom at least one PK sample was obtained and analyzed. Study population data were listed by cohort and subject, and summarized by cohort. Safety data (including AEs/SAEs) were listed by subject, treatment, and study period and summarized by treatment and study period. Summaries of laboratory data were provided at each planned assessment time and by maximum toxicity grade. Summaries of vital signs and changes from baseline in heart rate, temperature, systolic blood pressure and diastolic blood pressure were also provided. ECG findings and interval values were listed and summarized descriptively.

Part A PK: The primary statistical analysis for Part A was to evaluate the effect of repeat doses of dabrafenib on the single dose pharmacokinetics of S-warfarin. For continuous PK parameters [AUC(0-∞), AUC(0-t) and Cmax], an estimation approach was used. Following loge-transformation, AUC(0-∞), AUC(0-t) and Cmax of S-warfarin were separately analyzed by a mixed effects model, fitting a fixed effect term for treatment (warfarin alone and warfarin combined with dabrafenib) and a random effect for subject. The mixed model was fit using SAS Proc Mixed. For each primary pharmacokinetic endpoint on the $\log_e$ scale, PEs and corresponding 90% CIs were constructed for the difference between the mean of S-warfarin with dabrafenib (test) to the mean of S-warfarin alone (reference), μ(test)-μ(reference). The PEs and associated 90% CIs were then back-transformed to provide point estimates and 90% CIs for the geometric mean ratio Test: Reference.

Part B and Part C PK: PK parameters for dabrafenib and metabolites were derived from the plasma concentration-time data from Day 1 (single dose dabrafenib), Day 18 (repeat dose dabrafenib), and Day 22 (dabrafenib + ketoconazole or dabrafenib + gemfibrozil). The single- and repeat- dose PK of dabrafenib and its metabolites hydroxy-carboxy-, and desmethyl-dabrafenib were assessed following administration of dabrafenib 75 mg BID on Day 1 and Day 18 and with ketoconazole or gemfibrozil on Day 22. PK parameters were evaluated and summarized on Day 1, Day 18, and Day 22. To evaluate the single- and repeat-dose PK of dabrafenib and its metabolites following administration of dabrafenib 75 mg HPMC capsules, AUC(0-∞), AUC(0-τ) and Cmax were separately analyzed following $\log_e$-transformation using a mixed effects model, fitting day as a fixed effect and subject as a random effect. PEs and associated 90% CIs for the difference (Day 18-Day 1) were constructed using the residual variance. The PEs and associated 90% CIs were then exponentially back-transformed to provide PEs and 90% CIs for the ratios Day 18: Day 1 (e.g. Ro, Rt and Rcmax). To evaluate the effect of repeat oral doses of an inhibitor, ketoconazole (Part B) or gemfibrozil (Part C) on the repeat dose PK of dabrafenib, following $\log_e$-transformation, AUC (0-τ) and Cmax of dabrafenib were separately analyzed using a mixed effects model with treatment as a fixed effect and subject as a random effect. PEs and corresponding 90% CIs were constructed for the difference, Test (dabrafenib + ketoconazole/gemfibrozil) – Reference (dabrafenib alone). The PEs and associated 90% CIs were then back-transformed to provide PEs and 90% CIs for the geometric mean ratio Test: Reference. In addition, for each metabolite, the metabolite to parent ratio for AUC(0-t) and AUC(0-τ) was calculated after adjusting for differences in molecular weight when data were sufficient.

Part D PK: The primary objective was to evaluate the single- and repeat-dose PK of dabrafenib and its metabolites following administration of dabrafenib 150mg BID as HPMC capsules. Following $\log_e$-transformation, AUC(0-∞), AUC(0-τ) and Cmax were separately analyzed using a mixed effects model, fitting day as a fixed effect and subject as a random effect. PEs and associated 90% CI for the difference (Day 18-Day 1) were constructed using the residual variance. The PEs and associated 90% CI were then exponentially back-transformed to provide PEs and 90% CI for the ratios Day 18: Day 1.

Part B, C, and D Dose Proportionality: Day 1 and Day 18 PK parameter data from Parts B, C, and D were pooled for an assessment of dose-proportionality of dabrafenib (administered as HPMC capsules) and its metabolites. Dose proportionality was assessed using analysis of variance (ANOVA) with the following PK parameters:

- Day 1: Cmax, AUC(0-24), and AUC(0-∞)
- Day 18: Cmax, Cτ, and AUC(0-τ)

The PE and associated 90% CI for the ratio 150 mg:75 mg were provided.

Study Population: Major inclusion criteria for subjects in all parts included BRAF V600 mutation-positive tumor as confirmed in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory or equivalent (the local BRAF testing was subject to subsequent verification by centralized testing); Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1, and adequate organ function. Major exclusion criteria for subjects in all parts included receiving cancer therapy within the last 3 weeks preceding the first administration of study medication or chemotherapy regimens without delayed toxicity within the last 2 weeks preceding the first administration of study medication; history of sensitivity to heparin or heparin-induced thrombocytopenia; unresolved toxicity greater than National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (Grade 2 from previous anti-cancer therapy except alopecia); and presence of active gastrointestinal (GI) disease or other condition (e.g., small bowel or large bowel resection) that would have interfered significantly with the absorption of drugs**.**

	A	**B**	**C**	**D**
Number of subjects planned, N:	12	12	12	10 to 12
Number of subjects enrolled, N:	14	16	17	13
Number of enrolled subjects that completed as planned, n (%):	13 (93)	14 (88)	15 (88)	11 (85)
Number of subjects withdrawn (any reason), n (%):	1 (7)	2 (13)	2 (12)	2 (15)
SAE, n (%):	0	1 (6)	0	1 (8)
Protocol deviation, n (%):	1 (7)	1 (6)	1 (6)	1 (8)
Investigator discretion	0	0	1 (6)	0
Demographics	**A**	**B**	**C**	**D**
Gender, n (%):				
Female:	7 (50)	6 (38)	6 (35)	7 (54)
Male:	7 (50)	10 (63)	11 (65)	6 (46)
Age in Years				
Mean (SD):	58.8 (13.95)	58.6 (11.53)	54.4 (16.94)	52.0 (13.40)
Race, n (%)				
White – White/Caucasian/European Heritage:	14 (100)	16 (100)	17 (100)	13 (100)

Primary and Secondary PK Results:

Part A: Plasma S-Warfarin Pharmacokinetic Parameters After Single Dose Warfarin 15 mg Alone (Day 1) and After Repeated Doses of Dabrafenib 150 mg Twice Daily (Day 22)

		Geometric mean (95% CI) and (CVb%)	
Parameter	**n**	**Day 1**	**Day 22**
Cmax (ng/mL)	14	807 (655, 995) (37.4)	957 (817, 1122) (26.7) [b]
Tmax[a] (hr)	14	1.0 (1.0 – 24.2)	1.0 (1.0 – 2.0) [b]
AUC(0-τ) (hr·ng/mL)	14	28246 (23359, 34155) (33.8)	17355 (14273, 21103) (33.2)
AUC(0-∞) (hr·ng/mL)	13	28201 (23781, 33442) (28.8)	17815 (14592, 21750) (34.0)
t1/2 (hr)	14	40.6 (34.2, 48.2) (30.3)	31.7 (28.3, 35.6) (19.1) [b]
CL/F (mL/hr)	13	532 (449, 631) (28.8)	842 (690, 1028) (34.0)

a. Median (range): b. N=13

Part A: Comparison of Plasma S-Warfarin Pharmacokinetic Parameters After Single Dose Administration of Warfarin 15 mg Alone and After Repeated Doses of Dabrafenib 150 mg Twice Daily

		Geometric Least Squares Mean			**90% CI [a]**	
Parameter	**n**	**Warfarin 15 mg plus Dabrafenib 150 mg Twice Daily (Day 22, Test)**	**Warfarin 15 mg (Day 1, Reference)**	**Ratio [a]**	**Lower**	**Upper**
AUC(0-∞) (ng*h/mL)	13	17815	28201	0.63	0.59	0.68
AUC(0-t)	14	18195	28246	0.64	0.60	0.69
Cmax	14	956	808	1.18	1.02	1.37

a. Warfarin plus Dabrafenib :Warfarin alone ratio

Part A: Plasma R-Warfarin Pharmacokinetic Parameters After Single Dose Warfarin 15 mg Alone (Day 1) and After Repeated Doses of Dabrafenib 150 mg Twice Daily (Day 22)

		Geometric mean (95% CI) and (CVb%)	
Parameter	**n**	**Day 1**	**Day 22**
Cmax (ng/mL)	14	828 (702, 976) (29.2)	991 (859, 1144) (24.0) [b]
Tmax [a] (h)	14	1.0 (1.0 – 24.2)	1.0 (1.0 – 2.0) [b]
AUC(0-t) (ng*h/mL)	14	50712 (44713, 57516) (22.1)	35603 (31399, 40370) (21.0) [b]
AUC(0-∞) (ng*h/mL)	12	57335 (49717, 66120) (22.7)	38660 (33748, 44287) (22.8) [b]
t1/2 (h)	14	63.1 (54.1, 73.6) (27.0)	44.9 (40.4, 49.9) (17.6) [b]
CL/F (mL/h)	12	262 (227, 302) (22.7)	388 (339, 444) (22.8) [b]

a. Median (range); b. n=13

Part A: Comparison of Plasma R-Warfarin Pharmacokinetic Parameters After Single Dose Administration of Warfarin 15 mg Alone and After Repeated Doses of Dabrafenib 150 mg Twice Daily

		Geometric Least Squares Mean			90% CI[a]	
Parameter	**n**	**Warfarin 15 mg plus Dabrafenib 150 mg Twice Daily (Day 22, Test)**	**Warfarin 15 mg (Day 1, Reference)**	**Ratio [a]**	**Lower**	**Upper**
AUC(0-∞)	13	38660	58109	0.67	0.62	0.71
AUC(0-t)	14	36102	50712	0.71	0.67	0.75
Cmax	14	985	828	1.19	1.08	1.31

a. Warfarin plus Dabrafenib : Warfarin alone ratio

Part B: Plasma Dabrafenib Pharmacokinetic Parameters After Single Dose (Day 1) and Repeat Dose (Day 18) Administration of Dabrafenib 75 mg BID Alone and with CYP3A4 Inhibitor Ketoconazole (Day 22)

		Geometric mean (95% CI) and (CVb%)		
Parameter	**n**	**Day 1 Single Dose**	**Day 18 Repeat Dose without Ketoconazole**	**Day 22 Repeat Dose with Ketoconazole**
Cmax (ng/mL)	16	952 (699, 1297) (63.1)	966 (783, 1192) (39.4)	1252 (1083, 1447) (25.5)
Tmax [a] (h)	16	1.8 (0.5 – 10.1)	1.1 (1.0, 3.0) [b]	2.0 (0.5 – 4.0) [c]
AUC(0-τ) (ng*h/mL)	16	3651 (2823, 4722) (51.2) [b]	2966 (2484, 3542) (32.9)	4867 (4140, 5722) (28.6) [c]
AUC(0-24) (ng*h/mL)	15	3906 (2971, 5134) (52.6)	NA	NA
AUC(0-∞) (ng*h/mL)	15	3941 (3003, 5172) (52.2)	NA	NA
t1/2 (h)	15	3.6 (3.0, 4.3) (34.0)	NA	NA
Cτ	15	NA	17.5 (11.5, 26.6) (88.4)	47.7 (33.8, 67.4) (65.5) [c]
CL/F	15	19.0 (14.5, 25.0) (52.2)	25.3 (21.2, 30.2) (32.9)	15.4 (13.1, 18.1) (28.6) [c]
Ro [d]	16	NA	0.82 (0.68, 0.99)	NC
Rt [d]	16	NA	0.75 (0.63, 0.90)	NC
Rcmax [d]	16	NA	1.03 (0.81, 1.31)	NC

NA = not applicable; NC = not calculated
Ro – observed AUC(0-τ) accumulation ratio
Rt – time invariance ratio [AUC(0-τ) Day 18/AUC(0-∞) single dose]
Rcmax – observed Cmax accumulation ratio
a. Median (range); b. n=15; c. n=14; d. Reported as Day 18:Day 1 geometric least squares mean ratio (90% confidence interval)

Part C: Plasma Dabrafenib Pharmacokinetic Parameters After Single Dose (Day 1) and Repeat Dose (Day 18) Administration of Dabrafenib 75 mg BID Alone and with CYP2C8 Inhibitor Gemfibrozil (Day 22)

		Geometric mean (95% CI) and (CVb%)		
Parameter	**n**	**Day 1 Single Dose**	**Day 18 Repeat Dose without Gemfibrozil**	**Day 22 Repeat Dose with Gemfibrozil**
Cmax (ng/mL)	17	1203 (994, 1457) (38.5)	1137 (923, 1399) (40.6) [b]	1117 (848, 1472) (53.1) [c]
Tmax [a] (h)	17	2.0 (1.0 – 10.0)	1.7 (1.0 – 4.0) [b]	2.0 (0 – 4.1) [c]
AUC(0-τ) (ng*h/mL)	17	4633 (3840, 5589) (37.8)	3288 (2610, 4141) (45.4) [b]	4904 (4009, 5999) (37.6) [c]

AUC(0-24) (ng*h/mL)	17	5169 (4186, 6382) (42.8)	NA	NA
AUC(0-∞) (ng*h/mL)	16	5087 (4118, 6284) (41.3)	NA	NA
t1/2 (h)	16	4.2 (3.6, 5.0) (32.0)	NA	NA
Cτ (ng/mL)	16	NA	24.6 (17.3, 35.2) (74.9)	93.3 (67.1, 130) (65.3) [c]
CL/F (L/h)	16	14.7 (11.9, 18.2) (41.3)	22.8 (18.1, 28.7) (45.4)	15.3 (12.5, 18.7) (37.6) [c]
Ro [d]	17	NA	0.70 (0.59, 0.83)	NC
Rt [d]	17	NA	0.63 (0.53, 0.73)	NC
Rcmax [d]	17	NA	0.94 (0.77, 1.14)	NC

NA = not applicable; NC = not calculated

Ro – observed AUC(0-τ) accumulation ratio

Rt – time invariance ratio [AUC(0-τ) Day 18/AUC(0-∞) single dose]

Rcmax – observed Cmax accumulation ratio

a. Median (range); b. n=16; c. n=15; d. Reported as Day 18:Day 1 geometric least squares mean ratio (90% confidence interval)

Part B and Part C: Comparison of Plasma Dabrafenib AUC(0-τ) and Cmax After Administration of Dabrafenib 75 mg BID Alone (Day 18) and Dabrafenib 75 mg Twice Daily Plus Ketoconazole 400 mg Once Daily or Gemfibrozil 600 mg BID (Day 22)

		Geometric Least Squares Mean			90% CI [a]	
Inhibitor	**N**	**Dabrafenib 75 mg BID plus Inhibitor (Day 22, Test)**	**Dabrafenib 75 mg BID (Day 18, Reference)**	**Ratio[a]**	**Lower**	**Upper**
		Cmax (ng/mL)				
Ketoconazole (CYP3A4)	15	1285	966	1.33	1.14	1.55
Gemfibrozil (CYP2C8)	16	1117	1137	0.98	0.75	1.29
		AUC(0-τ) (ng*h/mL)				
Ketoconazole (CYP3A4)	15	5084	2966	1.71	1.55	1.90
Gemfibrozil (CYP2C8)	16	4835	3288	1.47	1.20	1.80

a. Dabrafenib plus Inhibitor : Dabrafenib alone ratio

Part B: Plasma Dabrafenib Metabolite Pharmacokinetic Parameters After Single Dose (Day 1) and Repeat Dose (Day 18) Administration of Dabrafenib 75 mg BID Alone and with CYP3A4 Inhibitor Ketoconazole (Day 22)

		Geometric mean (95% CI) and (CVb%)								
		Hydroxy-Dabrafenib			Carboxy-Dabrafenib			Desmethyl-Dabrafenib		
Parameter	**n**	**Day 1**	**Day 18**	**Day 22**	**Day 1**	**Day 18**	**Day 22**	**Day 1**	**Day 18**	**Day 22**
Cmax (ng/mL)	16	443 (352, 557) (45.1)	478 (382, 596) (41.8)[b]	600 (519, 694) (25.5)[c]	1628 (1349, 1964) (36.4)	4242 (3118, 5771) (60.2)[b]	3201 (2346, 4368) (58.0)[c]	49.1 (33.9, 71.1) (78.8)	239 (171, 333) (65.9)[b]	398 (275, 577) (71.6)[c]
tmax [a] (hr)	16	3.0 (1.5 – 10.1)	2.0 (0 – 4.0)[b]	4.0 (1.0 – 6.0)[c]	11.8 (8.0 – 23.9)	6.0 (3.0 – 8.0)[b]	8.0 (2.0 – 10.0)[c]	24.0 (12.0 – 24.3)	4.0 (0 – 12.0)[b]	3.0 (0.5 – 12.0)[c]
AUC(0-τ) (ng*h/mL)	16	2580 (2072, 3213) (43.0)	2181 (1737, 2738) (42.9)[b]	3831 (3136, 4680) (35.8)[c]	10283 (8130, 13006) (46.3)	40165 (29271, 55112) (62.1)[b]	32140 (23460, 44031) (58.8)[c]	80.3 (46.3, 139) (138)	1920 (1354, 2724) (70.0)[b]	3130 (2128, 4603) (75.0)[c]
AUC(0-∞) (ng*h/mL)	15	3153 (2482, 4006) (45.3)	NA	NA	NC	NA	NA	NC	NA	NA
AUCm/AUCp	16	0.82 (0.72, 0.94) (25.2)	0.74 (0.62, 0.87) (31.8)[b]	0.79 (0.65, 0.95) (34.1)[c]	6.6 (5.3, 8.2) (42.6)	13.5 (10.2, 17.9) (53.8)[b]	6.6 (4.8, 9.0) (58.4)[c]	0.12 (0.08, 0.19) (95.7)	0.65 (0.45, 0.94) (75.2)[b]	0.64 (0.45, 0.93) (70.0)[c]

t½ (h)	15	4.0 (3.7, 4.4) (14.0)	NC	NC	NC	NC	NC	NC	NC	NC
Cτ (ng/mL)	16	NA	28.6 (19.1, 42.7) (83.0)	112 (81.2, 155) (61.0)[c]	NA	2595 (1845, 3649) (67.9)[b]	2660 (1925, 3674) (60.7)[c]	NA	135 (80.6, 227) (118)[b]	251 (177, 356) (66.5)[c]
Ro [d]	16	NA	0.85 (0.66, 1.08)	NC	NA	3.91 (2.86, 5.33)	NC	NA	24.0 (14.6, 39.4)	NC
Rcmax [d]	16	NA	1.09 (0.90, 1.32)	NC	NA	2.62 (2.19, 3.13)	NC	NA	4.93 (3.36, 6.96)	NC

NA = not applicable; NC = not calculated
AUCm/AUCp calculated as a ratio of AUC(0-t) on Day 1 and AUC(0-τ) on Day 18 and was corrected for small differences in molecular weight. AUC for metabolites were adjusted for differences in molecular weights with a factor of 1.029, 1.058, and 0.973 for hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, respectively
Ro=observed AUC(0-τ) accumulation ratio
Rcmax=observed Cmax accumulation ratio
a. Median (range); b. n=15; c. n=14; d. Reported as Day 18:Day 1 geometric least squares mean ratio (90% confidence interval).

Part C: Plasma Dabrafenib Metabolite Pharmacokinetic Parameters After Single Dose (Day 1) and Repeat Dose (Day 18) Administration of Dabrafenib 75 mg BID Alone and with CYP2C8 Inhibitor Gemfibrozil (Day 22)

		Geometric mean (95% CI) and (CVb%)								
		Hydroxy-Dabrafenib			Carboxy-Dabrafenib			Desmethyl-Dabrafenib		
Parameter	**n**	**Day 1**	**Day 18**	**Day 22**	**Day 1**	**Day 18**	**Day 22**	**Day 1**	**Day 18**	**Day 22**
Cmax (ng/mL)	17	479 (420, 548) (26.3)	526 (464, 596) (23.8)[b]	472 (387, 575) (37.0)[c]	1496 (1263, 1771) (33.8)	4291 (3459, 5323) (42.2)[b]	4674 (3664, 5961) (46.1)[c]	49.2 (35.5, 68.2) (70.6)	266 (211, 337) (46.3)[b]	282 (232, 343) (36.4)[c]
Tmax [a] (h)	17	4.0 (2.0 – 10.0)	3.0 (1.5 – 4.0)[b]	2.3 (0 – 4.1)	11.8 (8.0 – 25.1)	6.0 (3.0 – 10.1)[b]	6.1 (0 – 11.8)[c]	24.0 (9.9 – 25.1)	3.0 (0 – 12.0)[b]	2.0 (0 – 11.8)[c]
AUC(0-τ) (ng*h/mL)	17	3041 (2684, 3446) (24.6)	2425 (2014, 2920) (36.0)[b]	2746 (2180, 3458) (43.5)[c]	8442 (6392, 11149) (58.3)	42269 (33900, 52704) (43.2)[b]	47418 (37129, 60557) (46.4)[c]	74.2 (52.2, 105) (76.9)	2203 (1718, 2823) (49.3)[b]	2281 (1853, 2809) (38.9)[c]
AUC(0-∞) (ng*h/mL)	16	4130 (3442, 4955) (35.2)	NA	NA	NC	NA	NA	NC	NA	NA
AUCm/AUCp	17	0.80 (0.66, 0.96) (36.7)	0.74 (0.59, 0.92) (43.8)[b]	0.56 (0.45, 0.69) (40.0)[c]	4.77 (3.56, 6.38) (61.4)	12.9 (9.71, 17.0) (56.6)[b]	9.67 (6.87, 13.6) (68.1)[c]	0.09 (0.07, 0.13) (70.7)	0.67 (0.47, 0.96) (75.4)[b]	0.47 (0.34, 0.64) (61.5)
t½ (h)	16	4.8 (4.2, 5.4) (23.7)	NC	NC	9.5, 12.6 (n=2)	NC	NC	NC	NC	NC
Cτ (ng/mL)	16	NA	39.3 (28.6, 54.0) (65.3)	79.5 (55.6, 114) (71.8)[c]	NA	3059 (2380,	3682 (2774,	NA	161 (117, 221) (65.2)[b]	157 (127, 195) (40.2)[c]

						3932) (49.8)[b]	4889) (54.7)[c]			
Ro [d]	17	NA	0.80 (0.68, 0.93)	NC	NA	5.00 (3.75, 6.68)	NC	NA	29.32 (21.11, 40.73)	NC
Rcmax [d]	17	NA	1.10 (0.95, 1.27)	NC	NA	2.85 (2.45, 3.31)	NC	NA	5.32 (4.05, 7.00)	NC

NA = not applicable; NC = not calculated
AUCm/AUCp calculated as a ratio of AUC(0-t) on Day 1 and AUC(0-τ) on Day 18 and was corrected for small differences in molecular weight. AUC for metabolites were adjusted for differences in molecular weights with a factor of 1.029, 1.058, and 0.973 for hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, respectively
Ro=observed AUC(0-τ) accumulation ratio
Rcmax=observed Cmax accumulation ratio
a. Median (range); b. N=16; c. N=15; d. Reported as Day 18:Day 1 geometric least squares mean ratio (90% confidence interval).

Part B and Part C: Mean Plasma Concentrations of CYP3A4 Inhibitor Ketoconazole and CYP2C8 Inhibitor Gemfibrozil

Time (h)	**Ketoconazole (ng/mL)**				**Gemfibrozil (ng/mL)**			
	n	Mean	Min	Max	n	Mean	Min	Max
Predose	13	69.6	0	613.1	15	1877.9	572.0	7677.6
1	14	4172.0	0	7789.8	14	11845.2	783.0	21950.3
2	14	5123.4	156.7	10810.6	15	13019.8	671.4	23709.8
4	14	3026.8	79.6	6529.5	14	6680.2	593.0	11830.6
8	14	372.3	38.1	1642.5	14	1929.0	285.9	5651.0
12	14	85.1	0	535.3	15	896.9	126.9	2566.4

Part D: Plasma Dabrafenib PK parameters After Single Dose (Day 1) and Repeat Dose (Day 18) Administration of Dabrafenib 150 mg BID as the HPMC Capsule

Parameter	**Day 1 (n=13)**	**Day 18 (n=11)**
Cmax[a] (ng/mL)	2521 (1849, 3435) (55)	2458 (1583, 3818) (73)
tmax[b] (h)	2.0 (0.5 – 3.1)	1.5 (1.0 – 2.1)
AUC(0-τ)[a] (ng*hr/mL)	9359 (7115, 12311) (48)	6545 (4383, 9771) (61)[d]
AUC(0-24)[a] (ng*hr /mL)	10274 (7610, 13871) (53)	NA
AUC(0-∞)[a,c] (ng*hr /mL)	9626 (7342, 12622) (45)[c]	NA
t½[a] (h)	4.15 (3.07, 5.61) (53)	2.13 (1.61, 2.81) (43)
Cτ [b](ng/mL)	103.2 (40.2 – 1036.2)	31.1 (12.9 – 120.5)[d]
Ro[e]	NA	0.73 (0.62, 0.86)
Rt[e]	NA	0.68 (0.57, 0.80)
Rcmax[e]	NA	1.00 (0.80, 1.24)

NA – not applicable; Ro – observed AUC(0-τ) accumulation ratio; Rt – time invariance ratio
Rcmax – observed Cmax accumulation ratio
a. Data presented as geometric mean (95% CI) and (CVb %); b. Median (range); c. n = 12; d. n=10; e. Reported as geometric least squares mean ratio (90% CI).

Dose Proportionality: Comparison of Dabrafenib and Metabolites (Hydroxy-Dabrafenib, Carboxy-Dabrafenib, and Desmethyl-Dabrafenib) Pharmacokinetic Parameters Between 150 mg and 75 mg Single Doses on Day 1

			Geometric Least Squares Mean (ng/mL)			**90% CI [a]**	
Parameter	**Analyte**	**N**	**Dabrafenib 150 mg**	**Dabrafenib 75 mg**	**Ratio [a]**	**Lower**	**Upper**
AUC(0-∞) (ng*h/mL)	Dabrafenib	42	9626	4496	1.07	0.83	1.38
	Hydroxy-Dabrafenib	42	6842	3624	0.94	0.76	1.18

	Carboxy-Dabrafenib	NA	NC	NC	NC	NC	NC
	Desmethyl-Dabrafenib	NA	NC	NC	NC	NC	NC
AUC(0-τ) (ng*h/mL)	Dabrafenib	45	9359	4128	1.13	0.89	1.45
	Hydroxy-Dabrafenib	45	5592	2808	1.00	0.83	1.20
	Carboxy-Dabrafenib	45	20210	9289	1.09	0.8	1.47
	Desmethyl-Dabrafenib	45	212	77	1.37	0.84	2.25
AUC(0-24) (ng*h/mL)	Dabrafenib	44	5137	4532	1.13	0.87	1.47
	Hydroxy-Dabrafenib	44	3468	3533	0.98	0.80	1.21
	Carboxy-Dabrafenib	31	22475	23399	0.96	0.75	1.23
	Desmethyl-Dabrafenib	29	684	503	1.36	0.87	2.12
Cmax (ng/mL)	Dabrafenib	45	2521	1074	1.17	0.89	1.54
	Hydroxy-Dabrafenib	45	975	462	1.06	0.85	1.31
	Carboxy-Dabrafenib	45	3150	1558	1.01	0.83	1.24
	Desmethyl-Dabrafenib	45	135	49	1.37	0.95	1.98

NC=not calculated

a. Dose normalized Dabrafenib 150 mg : Dabrafenib 75 mg ratio

Dose Proportionality: Comparison Between Dabrafenib and Metabolites (Hydroxy-Dabrafenib, Carboxy-Dabrafenib, and Desmethyl-Dabrafenib) Pharmacokinetic Parameters Between 150 mg BID and 75 mg BID on Day 18

			Geometric Least Squares Mean (ng/mL)			**90% CI [a]**	
Parameter	**Analyte**	**N**	**Dabrafenib 150 mg BID**	**Dabrafenib 75 mg BID**	**Ratio [a]**	**Lower**	**Upper**
AUC(0-τ) (ng*h/mL)	Dabrafenib	40	6545	3128	1.05	0.80	1.36
	Hydroxy-Dabrafenib	40	3687	2303	0.80	0.64	1.00
	Carboxy-Dabrafenib	40	66251	41238	0.80	0.61	1.07
	Desmethyl-Dabrafenib	40	4834	2061	1.17	0.84	1.64
Cmax (ng/mL)	Dabrafenib	41	2458	1051	1.17	0.89	1.54
	Hydroxy-Dabrafenib	41	1084	502	1.08	0.88	1.33
	Carboxy-Dabrafenib	41	8016	4267	0.94	0.72	1.23
	Desmethyl-Dabrafenib	41	629	253	1.24	0.91	1.70
Cτ (ng/mL)	Dabrafenib	39	17	21	0.83	0.54	1.27
	Hydroxy-Dabrafenib	39	19	34	0.57	0.38	0.85
	Carboxy-Dabrafenib	39	2010	2825	0.71	0.52	0.97
	Desmethyl-Dabrafenib	39	166	148	1.13	0.73	1.75

a. Dabrafenib 150 mg : Dabrafenib 75 mg ratio

Safety Results: Adverse events (AEs) and serious adverse events (SAEs) were collected and recorded on the electronic case report form starting on Day 1 and continuing until the end of the confinement period. In addition, SAEs assessed as related to study participation or related to a GSK concomitant medication were recorded from the time a subject consented to participate in the study.	
	Part A (n=14)
Most Frequent Adverse Events – On-Therapy	**n (%)**
Subjects with any AE(s), n(%)	12 (86)
AEs Reported in More Than One Subject, n (%)	
Rash	7 (50)
Arthralgia	4 (29)
Flushing	3 (21)
Headache	3 (21)
Abdominal pain upper	2 (14)
Back Pain	2 (14)
Chills	2 (14)
Dry mouth	2 (14)
Edema peripheral	2 (14)
Fatigue	2 (14)
Hyperglycemia	2 (14)
Nausea	2 (14)
Pruritus	2 (14)
Pyrexia	2 (14)
Skin papilloma	2 (14)
Vomiting	2 (14)
	Part B (n=16)
Most Frequent Adverse Events – On-Therapy	**n (%)**
Subjects with any AE(s), n(%)	14 (88)
AEs Reported in More Than One Subject, n (%)	
Pyrexia	5 (31)
Skin papilloma	5 (31)
Headache	4 (25)
Diarrhea	4 (25)
Nausea	4 (25)
Rash[1]	4 (25)
Fatigue	3 (19)
Pain in extremity	3 (19)
Cough	2 (13)
Dyspepsia	2 (13)
Hot flush	2 (13)
Hypokalemia	2 (13)
Myalgia	2 (13)
Nasopharyngitis	2 (13)
	Part C (n=17)
Most Frequent Adverse Events – On-Therapy	**n (%)**
Subjects with any AE(s), n(%)	15 (88)
AEs Reported in More Than One Subject, n (%)	

Skin papilloma	4 (24)
Fatigue	3 (18)
Abdominal pain	2 (12)
Acrochordon	2 (12)
Arthralgia	2 (12)
Edema peripheral	2 (12)
Insomnia	2 (12)
Myalgia	2 (12)
Nausea	2 (12)
Rash[a]	2 (12)
Seborrhoeic keratosis	2 (12)
Vomiting	2 (12)
a. Preferred term of rash includes terms of rash maculo-papular and rash papular, each reported by a different subject.	
	Part D (n=13)
Most Frequent Adverse Events – On-Therapy	**n (%)**
Subjects with any AE(s), n(%)	13 (100)
AEs Reported in More Than One Subject, n (%)	
Skin papilloma	7 (54)
Arthralgia	4 (31)
Palmar-plantar erythrodysesthesia syndrome	4 (31)
Rash [a]	4 (31)
Myalgia	3 (23)
Nausea	3 (23)
Pruritus	3 (23)
Vomiting	3 (23)
Back pain	2 (15)
Chills	2 (15)
Diarrhea	2 (15)
Fatigue	2 (15)
Headache	2 (15)
Musculoskeletal pain	2 (15)
Pain of skin	2 (15)
Pyrexia	2 (15)
a. Preferred term of rash includes terms of rash maculo-papular and rash papular, each reported by a different subject.	

Serious Adverse Events - On-Therapy: No fatal SAEs were reported. One death, due to disease progression, was reported in Part C. Seven subjects reported SAEs; these were pneumonia, lower GI hemorrhage, sepsis, pericardial effusion, dyspnea, pyrexia, small intestinal obstruction, and atrial flutter. Sepsis, pyrexia, and atrial flutter were considered by the investigator to be related to study treatment.

Conclusion:

Concomitant administration of dabrafenib 150 mg twice daily decreased the single dose AUC of S- and R-warfarin and resulted in a small increase in Cmax. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole with dabrafenib at steady-state resulted in an increase in systemic exposure to dabrafenib. Concomitant administration of the strong CYP2C8 inhibitor gemfibrozil with dabrafenib resulted in an increase in systemic exposure to dabrafenib. After single-dose (150 mg) administration of dabrafenib HPMC capsules, plasma concentrations of dabrafenib peaked at approximately 2 hours post-dose and decreased thereafter following a bi-exponential decline. The mean dabrafenib half-life was approximately 4 hours. Across the 4 parts of the study, 86% to 100% of subjects reported non-serious adverse events, with the most common being skin papilloma and rash. Seven subjects reported serious adverse events; none of which were fatal.