NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis

Generic Drug Name

Dabrafenib/Trametinib

Trial Indication(s)

Subjects with BRAF Mutant Metastatic Melanoma.

Protocol Number

113220

Protocol Title

An Open-Label, Dose-Escalation, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the BRAF Inhibitor GSK2118436 in Combination with the MEK Inhibitor GSK1120212 in Subjects with BRAF Mutant Metastatic Melanoma

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: March 2010 (Actual)
Primary Completion Date: May 2012 (Actual)
Study Completion Date: February 2018 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

Parts A, B, and D comprised the phase Ib part of the study. Part C was the randomized, open-label, multi-center phase II part investigating the efficacy and safety of different doses of dabrafenib and trametinib in combination in subjects with BRAF-mutant metastatic melanoma. The Part C treatment groups were:

- Dabrafenib 150 mg BID (referred to as the monotherapy group)
- Dabrafenib 150 mg BID and trametinib 1 mg daily (referred to as the 150/1 group)
- Dabrafenib 150 mg BID and trametinib 2 mg daily (referred to as the 150/2 group)

Subjects whose disease progressed while receiving dabrafenib monotherapy were permitted to cross over to combination therapy with the approval of the medical monitor.

Centers

16 centers in 2 countries: United States(14), Australia(2)

Objectives:

Primary objectives:

Part A: To determine the PK of single dose dabrafenib (and its metabolite(s), including hydroxydabrafenib), alone and with repeat dose trametinib dosed orally

Part B: To determine the safety, tolerability and range of tolerated doses of dabrafenib and trametinib dosed orally in combination in subjects with BRAF V600 mutation positive metastatic melanoma

Part C:

- To determine the clinical activity of dabrafenib and trametinib in subjects with BRAF V600 mutant metastatic melanoma.

- To determine the safety, tolerability and range of tolerated doses of dabrafenib and trametinib dosed orally in combination in subjects with BRAF V600 mutant metastatic melanoma

Part D:

- To determine single dose and steady-state PK of dabrafenib hydroxypropyl-methylcellulose (HPMC) capsules alone and in combination with trametinib dosed orally
- To determine the safety and tolerability of dabrafenib and trametinib dosed orally in combination in subjects with BRAF V600 mutation positive metastatic melanoma

Secondary objectives:

Part A: To confirm steady-state exposure of trametinib

Part B:

- To characterize the steady-state PK of dabrafenib (and its metabolite(s) including hydroxydabrafenib), and trametinib
- To evaluate the clinical activity of dabrafenib and trametinib in subjects with BRAF mutant metastatic melanoma
- To evaluate the pharmacodynamic response in BRAF mutant colorectal cancer pharmacodynamic cohort after treatment with dabrafenib and trametinib
- To explore relationships between dabrafenib, trametinib PK, MAPK signalling inhibition and clinical endpoint

Part C:

- To characterize the population PK parameters of dabrafenib and trametinib when administered daily in subjects with BRAF mutant metastatic melanoma
- To characterize the durability of response in subjects achieving clinical benefit

Part D:

- To determine the single dose and steady state PK of dabrafenib metabolites using HPMC capsules
- To determine single dose and steady-state PK of trametinib
- To evaluate clinical activity of the dabrafenib and trametinib combination in subjects with BRAF V600 mutation positive metastatic melanoma

Part A was previously reported in full. Primary and secondary objectives for Parts B, C, and D were previously reported while some subjects were ongoing. The study has been completed. This final report includes the final summaries of safety for Parts B, C, and D and limited efficacy data for Part C.

Test Product (s), Dose(s), and Mode(s) of Administration

Dabrafenib and trametinib were taken orally. No reference therapy was administered.

Statistical Methods

The Kaplan-Meier estimates at 60 months post-randomization were presented by treatment group for the full ITT population as well as for 3 subgroups: subjects with normal baseline lactate dehydrogenase (LDH), subjects with elevated baseline LDH, subjects with normal baseline LDH and fewer than 3 disease sites.

The safety criteria noted (AEs, SAEs, deaths, laboratory evaluations, ECG, and LVEF) were summarized.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:
- Capable of given written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
- Male or female age 18 years or greater; able to swallow and retain oral medication.
- BRAF mutation positive melanoma or colorectal cancer; other BRAF mutation positive tumor types may be considered.
- Measurable disease according to RECIST version 1.1.
- Eastern Cooperative Oncology Group Performance Status of 0 or 1 for Parts A and B. Subjects with Eastern Cooperative Oncology Group Performance Status of 2 or less may be entered into Part C with approval of medical monitor.
- Agree to contraception requirements.
- Calcium phosphorus product less than 4.0mmol2/L2.
- Adequate organ system function.

Key Exclusion Criteria:
- Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy, or biologic therapy).
- Part A and Part B: Prior exposure to BRAF or MEK inhibitors unless approved by the GSK Medical Monitor.

- Part C: Prior exposure to BRAF or MEK inhibitors. Prior anti-cancer therapy in the metastatic setting, with the exception of up to one regimen of chemotherapy and/or interleukin-2 (IL-2).
- Part D: Prior exposure to BRAF inhibitors. A washout period of 6 weeks is required for ipilimumab.
- Received an investigational anti-cancer drug within 4 weeks or 5 half-lives (whichever is shorter) of study drug administration--- at least 14 days must have passed between the last dose of prior investigational anti-cancer drug and the first dose of study drug.
- Current use of a prohibited medication or requires any of these medications during treatment with study drug.
- Current use of therapeutic warfarin.
- Any major surgery, radiotherapy, or immunotherapy within the last 4 weeks. Limited radiotherapy within the last 2 weeks.
- Chemotherapy regimens with delayed toxicity within the last 4 weeks. Chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity within the last 2 weeks.
- Unresolved toxicity greater than National Cancer Institute-Common Terminology Criteria for Adverse Events version 4 Grade 1 from previous anti-cancer therapy except alopecia.
- History of retinal vein occlusion, central serous retinopathy or glaucoma.
- Predisposing factors to retinal vein occlusion including uncontrolled hypertension, uncontrolled diabetes, uncontrolled hyperlipidemia, and coagulopathy.
- Visible retinal pathology as assessed by ophthalmologic exam that is considered a risk factor for retinal vein occlusion or central serous retinopathy.
- Intraocular pressure greater than 21mm Hg as measured by tonography.
- Glaucoma diagnosed within one month prior to study Day 1.
- Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism or excretion of drugs.
- Known human immunodeficiency virus, Hepatitis B or Hepatitis C infection.
- Primary malignancy of the central nervous system.
- Untreated or symptomatic brain metastasis, leptomeningeal disease or spinal cord compression. Subjects who are on a stable dose of corticosteroids for more than 1 month or off corticosteroids for 2 weeks can be enrolled with approval of medical monitor. Subjects are not permitted to receive enzyme-inducing anti-epileptic drugs.
- Subjects with brain metastases are excluded, unless
a. All known lesions must be previously treated with surgery or stereotactic radiosurgery, and- b. Brain lesion(s), if still present, must be confirmed stable (i.e. no increase in lesion size) for ≥90 days prior to first dose on study (must be documented with two consecutive MRI or CT scans using contrast), and
c. Asymptomatic with no corticosteroids requirement for ≥ 30 days prior to first dose on study, and
d. No enzyme-inducing anticonvulsants for ≥ 30 days prior to first dose on

study.
- History of alcohol or drug abuse within 6 months prior to screening.
- Psychological, familial, sociological or geographical conditions that do not permit compliance with the protocol.
- QTc interval greater than or equal to 480msecs.
- History of acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting within the past 24 weeks.
- Class II, III, or IV heart failure as defined by the New York Heart Association functional classification system.
- Abnormal cardiac valve morphology (subjects with minimal abnormalities can be entered on study with approval from the medical monitor.
- Treatment refractory hypertension defined as a blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy
- Patients with intra-cardiac defibrillators or permanent pacemakers.
- Cardiac metastases
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study drugs or excipients.
- Pregnant or lactating female.
- Unwillingness or inability to follow the procedures required in the protocol.
- Uncontrolled diabetes, hypertension or other medical conditions that may interfere with assessment of toxicity.
- Subjects with known glucose 6 phosphate dehydrogenase deficiency.

Participant Flow Table

Part A (Drug-Drug Interaction)

	Part A: Dabrafenib 75 mg + Trametinib 2 mg	Part B: Dabrafenib 75 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg	Part B: Dabrafenib 150 mg + Trametinib 2 mg	Part C (randomized): Dabrafenib 150 mg	Part C (randomized): Dabrafenib 150 mg + Trametinib 1 mg	Part C (randomized): Dabrafenib 150 mg + Trametinib 2 mg	Part C (crossover): Dabrafenib 150 mg + Trametinib 2 mg	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg	Total
Arm/Group	Participants receive	Melanoma BRAF-positive	Melanoma BRAF-	Melanoma BRAF-	Melanoma BRAF-	Participants received	Participants received	Participants received	Participants who received	Participants receive	Participants receive	Participants receive	Participants receive	

Description	d a single dose of dabrafenib 75 mg gelatin capsules with repeat dose trametinib (Day 15).	participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were	positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalat	positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and	positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily	dabrafenib 150 mg gelatin capsules BID.	dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.	dabrafenib 150 mg capsules BID alone in the Randomized Phase were given the opportunity to receive combination dosing of dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD upon disease progression with approval of the GlaxoSmithKline (GSK) Medical Monitor.	d dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	d dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	d dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	d dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.

		enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	ion decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.									
Started	8	0	0	0	0	0	0	0	0	0	0	0	0	8

Completed	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Not Completed	8	0	0	0	0	0	0	0	0	0	0	0	0	8
Death	1	0	0	0	0	0	0	0	0	0	0	0	0	1
Physician Decision	6	0	0	0	0	0	0	0	0	0	0	0	0	6
Withdrawal by Subject	1	0	0	0	0	0	0	0	0	0	0	0	0	1

Part B (Dose Escalation and Expansion)

	Part A: Dabrafenib 75 mg + Trametinib 2 mg	**Part B: Dabrafenib 75 mg + Trametinib 1 mg**	**Part B: Dabrafenib 150 mg + Trametinib 1 mg**	**Part B: Dabrafenib 150 mg + Trametinib 1.5 mg**	**Part B: Dabrafenib 150 mg + Trametinib 2 mg**	**Part C (randomized): Dabrafenib 150 mg**	**Part C (randomized): Dabrafenib 150 mg + Trametinib 1 mg**	**Part C (randomized): Dabrafenib 150 mg + Trametinib 2 mg**	**Part C (crossover): Dabrafenib 150 mg + Trametinib 2 mg**	**Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg**	**Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg**	**Part D: Dabrafenib 75 mg + Trametinib 2 mg**	**Part D: Dabrafenib 150 mg + Trametinib 2 mg**	**Total**
Arm/Group Description	Participants received a single dose of dabraf	Melanoma BRAF-positive participants who did not receive prior	Melanoma BRAF-positive participants who	Melanoma BRAF-positive participants who	Melanoma BRAF-positive participants who	Participants received dabrafenib 150 mg gelatin	Participants received dabrafenib 150 mg gelatin capsules	Participants received dabrafenib 150 mg gelatin capsules	Participants who received dabrafenib 150 mg capsules BID alone in the	Participants received dabrefinib 75 mg HPMC	Participants received dabrefinib 150 mg HPMC	Participants received dabrefinib 75 mg HPMC	Participants received dabrefinib 150 mg	

enib 75 mg gelatin capsules with repeat dose trametinib (Day 15).	treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting	did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made	did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data	received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did	capsules BID.	BID and trametinib 1 mg tablets QD.	BID and trametinib 2 mg tablets QD.	Randomized Phase were given the opportunity to receive combination dosing of dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD upon disease progression with approval of the GlaxoSmithKline (GSK) Medical Monitor.	capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	capsules BID and trametinib 2 mg tablets QD.	HPMC capsules BID and trametinib 2 mg tablets QD.

		toxicities (DLTs) occurring during the first 3 weeks of treatment.	based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	not proceed beyond these doses of dabrafenib and trametinib.									
Started	0	6	23	27	94	0	0	0	0	0	0	0	0	150
Completed	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Not Completed	0	6	23	27	94	0	0	0	0	0	0	0	0	150

Death	0	4	18	21	68	0	0	0	0	0	0	0	0	111
Physician Decision	0	0	2	0	4	0	0	0	0	0	0	0	0	6
Lost to Follow-up	0	1	0	1	6	0	0	0	0	0	0	0	0	8
Study closed/terminated	0	0	3	2	10	0	0	0	0	0	0	0	0	15
Withdrawal by Subject	0	1	0	3	6	0	0	0	0	0	0	0	0	10

Part C (Phase II: Randomized Phase)

	Part A: Dabrafenib 75 mg + Trametinib 2 mg	Part B: Dabrafenib 75 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg	Part B: Dabrafenib 150 mg + Trametinib 2 mg	Part C (randomized): Dabrafenib 150 mg	Part C (randomized): Dabrafenib 150 mg + Trametinib 1 mg	Part C (randomized): Dabrafenib 150 mg + Trametinib 2 mg	Part C (crossover): Dabrafenib 150 mg + Trametinib 2 mg	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg	Total
Arm/Group Description	Participants received a single dose of dabrafenib 75 mg gelatin	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF	Melanoma BRAF-positive participants who did not receive prior	Melanoma BRAF-positive participants who did not receive prior	Melanoma BRAF-positive participants who received prior	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg	Participants who received dabrafenib 150 mg capsules BID alone in the Randomized Phase were	Participants received dabrefinib 75 mg HPMC capsules BID. These	Participants received dabrefinib 150 mg HPMC capsules BID. These	Participants received dabrefinib 75 mg HPMC capsules BID and	Participants received dabrefinib 150 mg HPMC capsules BID	

capsules with repeat dose trametinib (Day 15).	inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring	treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all availab	treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4	treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed	tablets QD.	tablets QD.	given the opportunity to receive combination dosing of dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD upon disease progression with approval of the GlaxoSmithKline (GSK) Medical Monitor.	participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	trametinib 2 mg tablets QD.	and trametinib 2 mg tablets QD.

		during the first 3 weeks of treatment.	le PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	beyond these doses of dabrafenib and trametinib.									
Started	0	0	0	0	0	54	54	54	0	0	0	0	0	162
Completed	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Not Completed	0	0	0	0	0	54	54	54	0	0	0	0	0	162
Death	0	0	0	0	0	44	34	39	0	0	0	0	0	117

Physician Decision	0	0	0	0	0	1	1	1	0	0	0	0	0	3
Lost to Follow-up	0	0	0	0	0	0	3	3	0	0	0	0	0	6
Study closed/terminated	0	0	0	0	0	6	9	11	0	0	0	0	0	26
Withdrawal by Subject	0	0	0	0	0	3	7	0	0	0	0	0	0	10

Part C (Phase II: Crossover Phase [CP])

	Part A: Dabrafenib 75 mg + Trametinib 2 mg	Part B: Dabrafenib 75 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg	Part B: Dabrafenib 150 mg + Trametinib 2 mg	Part C (randomized): Dabrafenib 150 mg	Part C (randomized): Dabrafenib 150 mg + Trametinib 1 mg	Part C (randomized): Dabrafenib 150 mg + Trametinib 2 mg	Part C (crossover): Dabrafenib 150 mg + Trametinib 2 mg	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg	Total
Arm/Group Description	Participants received a single dose of dabrafenib 75 mg gelatin capsules with repeat	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafeni	Melanoma BRAF-positive participants who did not receive prior treatment with	Melanoma BRAF-positive participants who did not receive prior treatment with	Melanoma BRAF-positive participants who received prior treatment with	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.	Participants who received dabrafenib 150 mg capsules BID alone in the Randomized Phase were given the opportunity to	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2	

dose trametinib (Day 15).	b 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of	BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and	BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable particip	BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these	receive combination dosing of dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD upon disease progression with approval of the GlaxoSmithKline (GSK) Medical Monitor.	completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	tablets QD.	mg tablets QD.

		treatment.	other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	ants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	doses of dabrafenib and trametinib.									
Started	0	0	0	0	0	0	0	0	45	0	0	0	0	45
Completed	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Not Completed	0	0	0	0	0	0	0	0	45	0	0	0	0	45
Death	0	0	0	0	0	0	0	0	37	0	0	0	0	37
Physician Decision	0	0	0	0	0	0	0	0	1	0	0	0	0	1
Study closed/terminated	0	0	0	0	0	0	0	0	4	0	0	0	0	4

Withdrawal by Subject	0	0	0	0	0	0	0	0	3	0	0	0	0	3

Part D (HPMC Capsules)

	Part A: Dabrafenib 75 mg + Trametinib 2 mg	Part B: Dabrafenib 75 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg	Part B: Dabrafenib 150 mg + Trametinib 2 mg	Part C (randomized): Dabrafenib 150 mg	Part C (randomized): Dabrafenib 150 mg + Trametinib 1 mg	Part C (randomized): Dabrafenib 150 mg + Trametinib 2 mg	Part C (crossover): Dabrafenib 150 mg + Trametinib 2 mg	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg	Total
Arm/Group Description	Participants received a single dose of dabrafenib 75 mg gelatin capsules with repeat dose trametinib (Day 15).	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuou	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.	Participants who received dabrafenib 150 mg capsules BID alone in the Randomized Phase were given the opportunity to receive combination dosing of dabrafenib 150 mg gelatin capsules BID and	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.	

s daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants	gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled	cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.
trametinib 2 mg tablets QD upon disease progression with approval of the GlaxoSmithKline (GSK) Medical Monitor.	period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	

			and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	based on DLTs occurring during the first 3 weeks of treatment.										
Started	0	0	0	0	0	0	0	0	0	12	16	43	39	110
Completed	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Not Completed	0	0	0	0	0	0	0	0	0	12	16	43	39	110
Death	0	0	0	0	0	0	0	0	0	10	12	28	26	76
Physician Decision	0	0	0	0	0	0	0	0	0	0	1	1	1	3
Lost to Follow-up	0	0	0	0	0	0	0	0	0	0	1	1	3	5
Study closed/terminated	0	0	0	0	0	0	0	0	0	2	1	10	9	22
Withdrawal by Subject	0	0	0	0	0	0	0	0	0	0	1	3	0	4

Baseline Characteristics

	Part A: Dabrafenib 75 mg + Trametinib 2 mg	Part B: Dabrafenib 75 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg	Part B: Dabrafenib 150 mg + Trametinib 2 mg	Part C: Dabrafenib 150 mg	Part C: Dabrafenib 150 mg + Trametinib 1 mg	Part C: Dabrafenib 150 mg + Trametinib 2 mg	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg	Total
Arm/Group Description	Participants received a single dose of dabrafenib 75 mg gelatin capsules with repeat dose trametinib (Day 15).	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuo	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafe	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.	

all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	us daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.	nib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.

Number of Participants [units: participants]	8	6	23	27	94	54	54	54	12	16	43	39	430
Age Continuous (units: Years) Mean ± Standard Deviation													
	52.8±16.04	48.2±7.28	54.2±13.24	52.2±12.09	52.4±12.99	51.8±15.19	49.9±14.70	55.9±11.85	51.8±12.39	53.1±17.04	52.8±14.57	56.7±14.08	52.8±13.74
Sex: Female, Male (units:) Count of Participants (Not Applicable)													
Female	2	2	10	12	56	25	24	20	6	8	18	14	197
Male	6	4	13	15	38	29	30	34	6	8	25	25	233
Race/Ethnicity, Customized (units: Participants)													
White	7	6	22	26	92	52	54	53	12	16	43	39	407
Asian	1	0	0	0	2	0	0	1	0	0	0	0	1
African American	0	0	0	1	0	0	0	0	0	0	0	0	1
Missing	0	0	1	0	0	2	0	0	0	0	0	0	3

Summary of Efficacy

Primary Outcome Result(s)

Part A: Maximum plasma concentration (Cmax) of a single dose of dabrafenib administered alone and in combination with trametnib

(Time Frame: Day 15)

	Part A: Dabrafenib 75 mg	Part A: Dabrafenib 75 mg + Trametinib 2 mg
Arm/Group Description	Participants received a single dose of dabrafenib 75 mg gelatin capsules alone on Day 1.	Participants received a single dose of dabrafenib 75 mg gelatin capsules with repeat dose trametinib (Day 15).
Number of Participants Analyzed [units: participants]	8	8
Part A: Maximum plasma concentration (Cmax) of a single dose of dabrafenib administered alone and in combination with trametnib (units: Nanograms per milliliter (ng/mL)) Geometric Mean (95% Confidence Interval)		
GSK2118436	509 (379 to 685)	524 (390 to 705)
GSK2285403	259 (190 to 352)	255 (196 to 331)
GSK2298683	724 (595 to 879)	747 (587 to 951)
GSK2167542	8.37 (4.82 to 14.5)	8.16 (5.68 to 11.7)

Statistical Analysis

Groups	Part A: Dabrafenib 75 mg, Part A: Dabrafenib 75 mg + Trametinib 2 mg	
Non-Inferiority/Equivalence Test	Yes	Cmax of dabrafenib was log e transformed and analyzed by a linear mixed effect model with fixed effect for treatment (dabrafenib alone and combined with trametinib) and participant as a random effect. Geometric mean ratio (Day 15/Day 1) and 90% confidence interval were provided.
Other Geometric Mean Ratio	1.03	Geometric mean ratio (Day 15 Cmax/Day 1 Cmax) and 90% confidence interval for dabrafenib were calculated.
90 % Confidence Interval TWO_SIDED	0.79 to 1.34	

Statistical Analysis

Groups	Part A: Dabrafenib 75 mg, Part A: Dabrafenib 75 mg + Trametinib 2 mg	
Non-Inferiority/Equivalence Test	Yes	Cmax of GSK2285403 was log e transformed and analyzed by a linear mixed effect model with fixed effect for treatment (dabrafenib alone and combined with trametinib) and participant as a random effect. Geometric mean ratio (Day 15/Day 1)

		and 90% confidence interval were provided.
Other Geometric Mean Ratio	.99	Geometric mean ratio (Day 15 Cmax/Day 1 Cmax) and 90% confidence interval for GSK2285403 were calculated.
90 % Confidence Interval TWO_SIDED	0.78 to 1.25	

Statistical Analysis

Groups	Part A: Dabrafenib 75 mg, Part A: Dabrafenib 75 mg + Trametinib 2 mg	
Non-Inferiority/Equivalence Test	Yes	Cmax of GSK2298683 was log e transformed and analyzed by a linear mixed effect model with fixed effect for treatment (dabrafenib alone and combined with trametinib) and participant as a random effect. Geometric mean ratio (Day 15/Day 1) and 90% confidence interval were provided.
Other Geometric Mean Ratio	1.03	Geometric mean ratio (Day 15 Cmax/Day 1 Cmax) and 90% confidence interval for GSK2298683 were calculated.
90 % Confidence Interval TWO_SIDED	0.84 to 1.27	

Statistical Analysis

Groups	Part A: Dabrafenib 75 mg, Part A: Dabrafenib 75 mg + Trametinib 2 mg	
Non-Inferiority/Equivalence Test	Yes	Cmax of GSK2167542 was log e transformed and analyzed by a linear mixed effect model with fixed effect for treatment (dabrafenib alone and combined with trametinib) and participant as a random effect. Geometric mean ratio (Day 15/Day 1) and 90% confidence interval were provided.
Other Geometric Mean Ratio	.98	Geometric mean ratio (Day 15 Cmax/Day 1 Cmax) and 90% confidence interval for GSK2167542 were calculated.
90 % Confidence Interval TWO_SIDED	0.66 to 1.45	

Part A: AUC (0-t) and AUC (0-inf) of dabrafenib and its metabolites

(Time Frame: Day 15)

	Part A: Dabrafenib 75 mg	Part A: Dabrafenib 75 mg + Trametinib 2 mg
Arm/Group Description	Participants received a single dose of dabrafenib 75 mg gelatin capsules alone on Day 1.	Participants received a single dose of dabrafenib 75 mg gelatin capsules with repeat dose

		trametinib (Day 15).
Number of Participants Analyzed [units: participants]	8	8
Part A: AUC (0-t) and AUC (0-inf) of dabrafenib and its metabolites (units: ng*hour/mL (ng*hr/mL)) Geometric Mean (95% Confidence Interval)		
GSK2118436 AUC (0-t)	2734 (2205 to 3390)	2751 (2219 to 3411)
GSK2118436 AUC (0-inf)	3128 (2578 to 3797)	2949 (2445 to 3556)
GSK2285403 AUC (0-t)	2232 (1684 to 2959)	2287 (1899 to 2753)
GSK2285403 AUC (0-inf)	2819 (2231 to 3562)	2497 (2097 to 2974)
GSK2298683 AUC (0-t)	12761 (10347 to 15738)	13053 (10475 to 16266)
GSK2298683 AUC (0-inf)		
GSK2167542 AUC (0-t)	270 (188 to 390)	276 (230 to 332)
GSK2167542 AUC (0-inf)		

Statistical Analysis

Groups	Part A: Dabrafenib 75 mg, Part A: Dabrafenib 75 mg + Trametinib 2 mg

Non-Inferiority/Equivalence Test	Yes	AUC(0-t) of dabrafenib was log e transformed and analyzed by a linear mixed effect model with fixed effect for treatment (dabrafenib alone and combined with trametinib) and participant as a random effect. Geometric mean ratio (Day 15/Day 1) and 90% confidence interval were provided.
Other Geometric Mean Ratio	1.01	Geometric mean ratio (Day 15 AUC(0-inf)/ Day 1 AUC(0-inf)) and 90% confidence interval for dabrafenib were calculated.
90 % Confidence Interval TWO_SIDED	0.85 to 1.19	

Statistical Analysis

Groups	Part A: Dabrafenib 75 mg, Part A: Dabrafenib 75 mg + Trametinib 2 mg	
Non-Inferiority/Equivalence Test	Yes	AUC(0-inf) of dabrafenib was log e transformed and analyzed by a linear mixed effect model with fixed effect for treatment (dabrafenib alone and combined with trametinib) and participant as a random effect. Geometric mean ratio (Day 15/Day 1) and 90% confidence interval were provided.

Other Geometric Mean Ratio	0.94	Geometric mean ratio (Day 15 AUC(0-inf)/ Day 1 AUC(0-inf)) and 90% confidence interval for dabrafenib were calculated.
90 % Confidence Interval TWO_SIDED	0.82 to 1.08	

Statistical Analysis

Groups	Part A: Dabrafenib 75 mg, Part A: Dabrafenib 75 mg + Trametinib 2 mg	
Non-Inferiority/Equivalence Test	Yes	AUC(0-t) of GSK2285403 was log e transformed and analyzed by a linear mixed effect model with fixed effect for treatment (dabrafenib alone and combined with trametinib) and participant as a random effect. Geometric mean ratio (Day 15/Day 1) and 90% confidence interval were provided.
Other Geometric Mean Ratio	1.02	Geometric mean ratio (Day 15 AUC(0-t)/ Day 1 AUC(0-t)) and 90% confidence interval for GSK2285403 were calculated.
90 % Confidence Interval TWO_SIDED	0.84 to 1.25	

Statistical Analysis

Groups	Part A: Dabrafenib 75 mg, Part A: Dabrafenib 75 mg + Trametinib 2 mg	
Non-Inferiority/Equivalence Test	Yes	AUC(0-inf) of GSK2285403 was log e transformed and analyzed by a linear mixed effect model with fixed effect for treatment (dabrafenib alone and combined with trametinib) and participant as a random effect. Geometric mean ratio (Day 15/Day 1) and 90% confidence interval were provided.
Other Geometric Mean Ratio	0.92	Geometric mean ratio (Day 15 AUC(0-inf)/ Day 1 AUC(0-inf)) and 90% confidence interval for GSK2285403 were calculated.
90 % Confidence Interval TWO_SIDED	0.81 to 1.03	

Statistical Analysis

Groups	Part A: Dabrafenib 75 mg, Part A: Dabrafenib 75 mg + Trametinib 2 mg	
Non-Inferiority/Equivalence Test	Yes	AUC(0-t) of GSK2298683 was log e transformed and analyzed by a linear mixed effect model with fixed effect for treatment (dabrafenib alone and combined with trametinib) and participant as a random effect. Geometric

		mean ratio (Day 15/Day 1) and 90% confidence interval were provided.
Other Geometric Mean Ratio	1.02	Geometric mean ratio (Day 15 AUC(0-t)/ Day 1 AUC(0-t)) and 90% confidence interval for GSK2298683 were calculated.
90 % Confidence Interval TWO_SIDED	0.81 to 1.29	

Statistical Analysis

Groups	Part A: Dabrafenib 75 mg, Part A: Dabrafenib 75 mg + Trametinib 2 mg	
Non-Inferiority/Equivalence Test	Yes	AUC(0-t) of GSK2167542 was log e transformed and analyzed by a linear mixed effect model with fixed effect for treatment (dabrafenib alone and combined with trametinib) and participant as a random effect. Geometric mean ratio (Day 15/Day 1) and 90% confidence interval were provided.
Other Geometric Mean Ratio	1.02	Geometric mean ratio (Day 15 AUC(0-t)/ Day 1 AUC(0-t)) and 90% confidence interval for GSK2167542 were calculated.
90 % Confidence Interval TWO_SIDED	0.76 to 1.37	

Part B: Number of participants with any Adverse Event (AE) or Serious Adverse Event (SAE)

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 8 years))

	Part B: Dabrafenib 75 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg	Part B: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.

		participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	occurring during the first 3 weeks of treatment.	
Number of Participants Analyzed [units: participants]	6	23	27	94
Part B: Number of participants with any Adverse Event (AE) or Serious Adverse Event (SAE) (units: Participants) Count of Participants (Not Applicable)				
Any AE	6	23	27	93
Any SAE	1	15	14	55

Part B: Number of participants with worst-case Chemistry Toxicity Grade Change from Baseline

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 8 years))

	Part B: Dabrafenib 75 mg + Trametinib 1 mg	**Part B: Dabrafenib 150 mg + Trametinib 1 mg**	**Part B: Dabrafenib 150 mg + Trametinib 1.5 mg**	**Part B: Dabrafenib 150 mg + Trametinib 2 mg**
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve

	as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.
Number of Participants Analyzed [units: participants]	6	23	27	94
Part B: Number of participants with worst-case Chemistry Toxicity Grade Change from Baseline (units: Participants) Count of Participants (Not Applicable)				
Albumin : Increase to Grade 3	0	0	1	3
Albumin : Increase to Grade 4	0	0	0	0

Alkaline Phosphatase : Increase to Grade 3	1	2	1	10
Alkaline Phosphatase : Increase to Grade 4	0	0	0	0
Alanine Amino Transferase : Increase to Grade 3	0	0	1	2
Alanine Amino Transferase : Increase to Grade 4	0	0	0	0
Amylase : Increase to Grade 3	0	0	0	0
Amylase : Increase to Grade 4	0	0	0	0
Aspartate Amino Transferase : Increase to Grade 3	0	0	1	5
Aspartate Amino Transferase : Increase to Grade 4	0	0	0	0
Total Bilirubin : Increase to Grade 3	0	0	0	2
Total Bilirubin : Increase to Grade 4	0	0	0	0
Calcium (Hypercalcemia) : Increase to Grade 3	0	0	0	0
Calcium (Hypercalcemia) : Increase to Grade 4	0	0	0	0
Calcium (Hypocalcemia) : Increase to Grade 3	0	0	1	1
Calcium (Hypocalcemia) : Increase to Grade 4	0	0	0	1

Creatine Kinase : Increase to Grade 3	0	0	0	0
Creatine Kinase : Increase to Grade 4	0	0	0	0
Creatinine : Increase to Grade 3	0	0	0	0
Creatinine : Increase to Grade 4	0	0	1	0
Gamma Glutamyl Transferase : Increase to Grade 3	1	0	3	13
Gamma Glutamyl Transferase : Increase to Grade 4	0	0	0	0
Glucose (Hyperglycemia) : Increase to Grade 3	0	2	2	5
Glucose (Hyperglycemia) : Increase to Grade 4	0	0	0	0
Glucose (Hypoglycemia) : Increase to Grade 3	0	0	0	1
Glucose (Hypoglycemia) : Increase to Grade 4	0	0	0	0
Potassium (Hyperkalemia) : Increase to Grade 3	0	0	0	1
Potassium (Hyperkalemia) : Increase to Grade 4	0	0	0	0
Potassium (Hypokalemia) : Increase to Grade 3	0	0	1	4
Potassium (Hypokalemia) : Increase to Grade 4	0	0	0	0
Lipase : Increase to Grade 3	0	0	0	0

Lipase : Increase to Grade 4	0	0	0	0
Magnesium (Hypermagnesemia) : Increase to Grade 3	0	0	0	0
Magnesium (Hypermagnesemia) : Increase to Grade 4	0	0	0	0
Magnesium (Hypomagnesemia) : Increase to Grade 3	0	0	0	0
Magnesium (Hypomagnesemia) : Increase to Grade 4	0	0	0	0
Sodium (Hypernatremia) : Increase to Grade 3	0	0	0	0
Sodium (Hypernatremia) : Increase to Grade 4	0	0	0	0
Sodium (Hyponatremia) : Increase to Grade 3	0	2	7	12
Sodium (Hyponatremia) : Increase to Grade 4	0	0	0	0
Blood pH : Increase to Grade 3	0	0	0	0
Blood pH : Increase to Grade 4	0	0	0	0
Phosphorus inorganic : Increase to Grade 3	0	2	6	4
Phosphorus inorganic : Increase to Grade 4	0	0	0	0
Uric acid : Increase to Grade 3	0	0	0	0

Uric acid : Increase to Grade 4	1	0	0	1

Part B: Number of participants with worst-case Chemistry Change from Baseline with respect to Normal Range

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 8 years))

	Part B: Dabrafenib 75 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg	Part B: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib

	(DLTs) occurring during the first 3 weeks of treatment.	from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	and trametinib.
Number of Participants Analyzed [units: participants]	6	23	27	94
Part B: Number of participants with worst-case Chemistry Change from Baseline with respect to Normal Range (units: Participants) Count of Participants (Not Applicable)				
Direct Bilirubin : Decrease to Low	0	0	0	0
Direct Bilirubin : Increase to High	0	0	0	0
Indirect Bilirubin : Decrease to Low	0	0	0	0
Indirect Bilirubin : Increase to High	0	0	0	0
Creatine Kinase MB mass : Decrease to Low	0	0	0	0
Creatine Kinase MB mass : Increase to High	0	0	0	0
Chloride : Decrease to Low	0	4	10	39
Chloride : Increase to High	2	11	8	16

Carbon dioxide content/Bicarbonate : Decrease to Low	1	4	6	16
Carbon dioxide content/Bicarbonate : Increase to High	3	7	11	25
Creatinine clearance : Decrease to Low	2	4	10	19
Creatinine clearance : Increase to High	2	5	5	8
Lactate dehydrogenase : Decrease to Low	1	2	1	4
Lactate dehydrogenase : Increase to High	4	9	11	35
Total protein : Decrease to Low	0	10	10	30
Total protein : Increase to High	3	2	1	7
Troponin I : Decrease to Low	0	0	0	0
Troponin I : Increase to High	0	0	0	0
Trponin T : Decrease to Low	0	0	0	0
Trponin T : Increase to High	0	0	0	0
Urea/BUN : Decrease to Low	2	4	3	17
Urea/BUN : Increase to High	1	10	16	30

Part B: Number of participants with worst-case Hematology Toxicity Grade Change from Baseline

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 8 years))

	Part B: Dabrafenib 75 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg	Part B: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.

		DLTs occurring during the first 3 weeks of treatment.	3 weeks of treatment.	
Number of Participants Analyzed [units: participants]	6	23	27	94
Part B: Number of participants with worst-case Hematology Toxicity Grade Change from Baseline (units: Participants) Count of Participants (Not Applicable)				
Hemoglobin (Increased) : Increase to Grade 3	0	0	0	0
Hemoglobin (Increased) : Increase to Grade 4	0	0	0	0
Hemoglobin (Anemia) : Increase to Grade 3	0	0	3	10
Hemoglobin (Anemia) : Increase to Grade 4	0	0	0	0
Lymphocytes (Increased) : Increase to Grade 3	0	0	0	0
Lymphocytes (Increased) : Increase to Grade 4	0	0	0	0
Lymphocytes (Decreased) : Increase to Grade 3	0	7	4	19
Lymphocytes (Decreased) : Increase to Grade 4	0	1	4	5
Total Neutrophils : Increase to Grade 3	1	3	3	10
Total Neutrophils : Increase to Grade 4	0	0	0	0
Platelet Count : Increase to Grade 3	0	0	2	1

Platelet Count : Increase to Grade 4	0	0	0	1
White Blood Cell Count : Increase to Grade 3	0	2	4	8
White Blood Cell Count : Increase to Grade 4	0	0	0	0

Part B: Number of participants with worst-case Hematology Change from Baseline with respect to Normal Range

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 8 years))

	Part B: Dabrafenib 75 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg	Part B: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants,	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose

	and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	escalation did not proceed beyond these doses of dabrafenib and trametinib.
Number of Participants Analyzed [units: participants]	6	23	27	94
Part B: Number of participants with worst-case Hematology Change from Baseline with respect to Normal Range (units: Participants) Count of Participants (Not Applicable)				
Basophils : Decrease to Low	0	0	0	2
Basophils : Increase to High	0	2	4	7
Eosinophils : Decrease to Low	1	5	6	28
Eosinophils : Increase to High	0	5	7	11
Hematocrit : Decrease to Low	1	5	7	24
Hematocrit : Increase to High	0	0	2	2

Mean Corpuscle Hemoglobin concentration : Decrease to Low	0	6	11	21
Mean Corpuscle Hemoglobin concentration : Increase to High	2	4	5	13
Mean Corpuscle Hemoglobin : Decrease to Low	0	6	8	12
Mean Corpuscle Hemoglobin : Increase to High	0	3	6	11
Mean Corpuscle Volume : Decrease to Low	1	5	6	13
Mean Corpuscle Volume : Increase to High	1	2	4	5
Monocytes : Decrease to Low	2	8	10	21
Monocytes : Increase to High	1	4	9	30
Red Blood Cell count : Decrease to Low	1	9	5	25
Red Blood Cell count : Increase to High	0	0	1	2
Reticulocytes : Decrease to Low	2	1	5	3
Reticulocytes : Increase to High	2	7	6	6

Part B: Number of participants with the indicated worst-case change from Baseline in heart rate and blood pressure

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 8 years))

	Part B: Dabrafenib 75 mg +	Part B: Dabrafenib 150 mg +	Part B: Dabrafenib 150 mg +	Part B: Dabrafenib 150 mg +

	Trametinib 1 mg	Trametinib 1 mg	Trametinib 1.5 mg	Trametinib 2 mg
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.

		3 weeks of treatment.		
Number of Participants Analyzed [units: participants]	6	23	27	78
Part B: Number of participants with the indicated worst-case change from Baseline in heart rate and blood pressure (units: Participants)				
Heart rate, Decrease to <60 bpm	1	2	5	15
Heart rate, Change to normal or no change	3	14	15	37
Heart rate, Increase to >100 bpm	2	7	8	26
SBP, Increase to G3 or G4	0	2	3	8
DBP, Increase to G3 or G4	0	1	3	4

Part C (randomized): Number of participants with BRAF mutant metastatic melanoma with best overall response as assessed by the investigator

(Time Frame: From the first dose of study medication to the first documented evidence of a confirmed complete response or partial response (up to approximately 7 years))

	Part C: Dabrafenib 150 mg	**Part C: Dabrafenib 150 mg + Trametinib 1 mg**	**Part C: Dabrafenib 150 mg + Trametinib 2 mg**
Arm/Group Description	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib

		1 mg tablets QD.	2 mg tablets QD.
Number of Participants Analyzed [units: participants]	54	54	54
Part C (randomized): Number of participants with BRAF mutant metastatic melanoma with best overall response as assessed by the investigator (units: Participants) Count of Participants (Not Applicable)			
CR	2	6	10
PR	27	21	31

Statistical Analysis

Groups	Part C: Dabrafenib 150 mg, Part C: Dabrafenib 150 mg + Trametinib 1 mg	Difference in response rate Arm2 - Arm1
Other Unconditional exact method	-4	
95 % Confidence Interval 2-Sided	-23.1 to 15.9	

Statistical Analysis

Groups	Part C: Dabrafenib 150 mg, Part C: Dabrafenib 150 mg + Trametinib 2 mg	Difference in response rate Arm3 - Arm1
Other Unconditional exact method	22	

95 % Confidence Interval 2-Sided	2.5 to 40.7

Part C (randomized): Number of participants with BRAF mutant metastatic melanoma with best overall response assessed by Blinded Independent Central Review (BICR)

(Time Frame: From the first dose of study medication to the first documented evidence of a confirmed complete response or partial response (up to approximately 19 months))

	Part C: Dabrafenib 150 mg	Part C: Dabrafenib 150 mg + Trametinib 1 mg	Part C: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	54	54	54
Part C (randomized): Number of participants with BRAF mutant metastatic melanoma with best overall response assessed by Blinded Independent Central Review (BICR) (units: Participants) Count of Participants (Not Applicable)			
CR	4	4	7
PR	21	18	26

Statistical Analysis

Groups	Part C: Dabrafenib 150 mg,	Difference in response rate Arm2- Arm1

	Part C: Dabrafenib 150 mg + Trametinib 1 mg
Other Unconditional exact method	-6
95 % Confidence Interval 2-Sided	-24.9 to 14.1

Statistical Analysis

Groups	Part C: Dabrafenib 150 mg, Part C: Dabrafenib 150 mg + Trametinib 2 mg	Difference in response rate Arm3 - Arm1
Other Unconditional exact method	15	
95 % Confidence Interval 2-Sided	-4.9 to 33.7	

Part C (crossover): Number of participants with BRAF mutant metastatic melanoma with best overall response as assessed by the investigator

(Time Frame: From the first dose of study medication to the first documented evidence of a confirmed complete response or partial response (up to approximately 7 years))

	Part C (crossover): Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants who received dabrafenib 150 mg capsules BID alone in the Randomized Phase were given the

	opportunity to receive combination dosing of dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD upon disease progression with approval of the GlaxoSmithKline (GSK) Medical Monitor.
Number of Participants Analyzed [units: participants]	45
Part C (crossover): Number of participants with BRAF mutant metastatic melanoma with best overall response as assessed by the investigator (units: Participants) Count of Participants (Not Applicable)	
CR	1
PR	5

Statistical Analysis

Groups	Part C (crossover): Dabrafenib 150 mg + Trametinib 2 mg
Other Response rate	6
95 % Confidence Interval 2-Sided	5.1 to 26.8

Part C (randomized): Progression-free Survival (PFS) as assessed by the investigator

(Time Frame: From the date of randomization to the earliest date of disease progression (PD) or death due to any cause (up to approximately 7 years))

	Part C: Dabrafenib 150 mg	Part C: Dabrafenib 150 mg + Trametinib 1 mg	Part C: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	54	54	54
Part C (randomized): Progression-free Survival (PFS) as assessed by the investigator (units: Months) Median (Full Range)			
	5.8 (4.3 to 7.4)	9.2 (5.7 to 11.0)	9.4 (7.6 to 16.6)

Statistical Analysis

Groups	Part C: Dabrafenib 150 mg, Part C: Dabrafenib 150 mg + Trametinib 1 mg
P Value	0.0048

Method	Log Rank	
Hazard Ratio (HR)	0.58	HRs were estimated using the Pike estimator.
95 % Confidence Interval 2-Sided	0.38 to 0.87	

Statistical Analysis

Groups	Part C: Dabrafenib 150 mg, Part C: Dabrafenib 150 mg + Trametinib 2 mg	
P Value	<0.0001	
Method	Log Rank	
Hazard Ratio (HR)	0.44	HRs were estimated using the Pike estimator.
95 % Confidence Interval 2-Sided	0.29 to 0.68	

Part C (crossover): Progression-free Survival (PFS) as assessed by the investigator

(Time Frame: From the first dose of study medication to the earliest date of disease progression (PD) or death due to any cause (up to approximately 7 years))

	Part C (crossover): Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants who received dabrafenib 150 mg capsules BID alone in the Randomized

	Phase were given the opportunity to receive combination dosing of dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD upon disease progression with approval of the GlaxoSmithKline (GSK) Medical Monitor.
Number of Participants Analyzed [units: participants]	45
Part C (crossover): Progression-free Survival (PFS) as assessed by the investigator (units: Months) Median (95% Confidence Interval)	
	3.6 (1.8 to 3.9)

Part C (randomized): Progression-free Survival (PFS) as assessed by the Blinded Independent Central Review (BICR)

(Time Frame: From the date of randomization to the earliest date of disease progression (PD) or death due to any cause (up to approximately 19 months))

Part C: Dabrafenib 150 mg	Part C: Dabrafenib 150 mg + Trametinib 1 mg	Part C: Dabrafenib 150 mg + Trametinib 2 mg

Arm/Group Description	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	54	54	54
Part C (randomized): Progression-free Survival (PFS) as assessed by the Blinded Independent Central Review (BICR) (units: Months) Median (95% Confidence Interval)			
	7.3 (5.5 to 9.4)	8.3 (5.6 to 11.3)	9.2 (7.6 to NA)[1]

[1] NA: Not estimable

Statistical Analysis

Groups	Part C: Dabrafenib 150 mg, Part C: Dabrafenib 150 mg + Trametinib 1 mg	
P Value	0.1667	
Method	Log Rank	
Hazard Ratio (HR)	0.73	HRs were estimated using the Pike estimator.

95 % Confidence Interval 2-Sided	0.45 to 1.18	

Statistical Analysis

Groups	Part C: Dabrafenib 150 mg, Part C: Dabrafenib 150 mg + Trametinib 2 mg	
P Value	0.0119	
Method	Log Rank	
Hazard Ratio (HR)	0.54	HRs were estimated using the Pike estimator.
95 % Confidence Interval 2-Sided	0.32 to 0.90	

Part C (randomized): Duration of response as assessed by the investigator and Blinded Independent Central Review (BICR)

(Time Frame: First documented evidence of PR or CR until the date of the first documented sign of disease progression or the date of death due to any cause (up to approximately 19 months))

	Part C: Dabrafenib 150 mg	Part C: Dabrafenib 150 mg + Trametinib 1 mg	Part C: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.

Number of Participants Analyzed [units: participants]	54	54	54
Part C (randomized): Duration of response as assessed by the investigator and Blinded Independent Central Review (BICR) (units: Months) Median (95% Confidence Interval)			
Investigator assessed	5.6 (3.9 to 7.4)	11.1 (7.4 to 13.2)	10.5 (7.4 to 19.2)
BICR assessed	7.6 (4.7 to NA)[123]	9.5 (5.6 to NA)[123]	NA (6.7 to NA)[123]

[1] NA: Not estimable
[2] NA: Not estimable
[3] NA: Not estimable

Part C (randomized): Number of participants with any Adverse Event (AE) or Serious Adverse Event (SAE)

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 7 years))

	Part C: Dabrafenib 150 mg	**Part C: Dabrafenib 150 mg + Trametinib 1 mg**	**Part C: Dabrafenib 150 mg + Trametinib 2 mg**
Arm/Group Description	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	53	54	55
Part C (randomized): Number of participants with any Adverse Event (AE) or Serious Adverse Event (SAE)			

(units: Participants) Count of Participants (Not Applicable)			
Any AE	53	53	55
Any SAE	15	24	39

Part C (randomized): Number of participants with worst-case Chemistry Toxicity Grade Change from Baseline

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 7 years))

	Part C: Dabrafenib 150 mg	Part C: Dabrafenib 150 mg + Trametinib 1 mg	Part C: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	53	54	55
Part C (randomized): Number of participants with worst-case Chemistry Toxicity Grade Change from Baseline (units: Participants) Count of Participants (Not Applicable)			
Albumin : Increase to Grade 3	0	1	1
Albumin : Increase to Grade 4	0	0	0
Alkaline Phosphatase : Increase to Grade 3	0	3	2

Alkaline Phosphatase : Increase to Grade 4	0	0	0
Alanine Amino Transferase : Increase to Grade 3	0	2	2
Alanine Amino Transferase : Increase to Grade 4	0	0	0
Aspartate Amino Transferase : Increase to Grade 3	0	1	3
Aspartate Amino Transferase : Increase to Grade 4	0	0	0
Total Bilirubin : Increase to Grade 3	0	2	0
Total Bilirubin : Increase to Grade 4	0	0	0
Calcium (Hypercalcemia) : Increase to Grade 3	0	0	0
Calcium (Hypercalcemia) : Increase to Grade 4	0	1	0
Calcium (Hypocalcemia) : Increase to Grade 3	0	0	0
Calcium (Hypocalcemia) : Increase to Grade 4	0	0	0
Cholesterol : Increase to Grade 3	0	0	0
Cholesterol : Increase to Grade 4	0	0	0
Creatine Kinase : Increase to Grade 3	0	0	0

Creatine Kinase : Increase to Grade 4	0	1	0
Creatinine : Increase to Grade 3	0	1	2
Creatinine : Increase to Grade 4	0	0	1
Gamma Glutamyl Transferase : Increase to Grade 3	1	11	7
Gamma Glutamyl Transferase : Increase to Grade 4	0	0	1
Glucose (Hyperglycemia) : Increase to Grade 3	1	4	6
Glucose (Hyperglycemia) : Increase to Grade 4	0	0	0
Glucose (Hypoglycemia) : Increase to Grade 3	0	0	0
Glucose (Hypoglycemia) : Increase to Grade 4	0	0	0
Potassium (Hyperkalemia) : Increase to Grade 3	2	0	1
Potassium (Hyperkalemia) : Increase to Grade 4	0	0	0
Potassium (Hypokalemia) : Increase to Grade 3	3	1	1
Potassium (Hypokalemia) : Increase to Grade 4	0	0	1
Magnesium (Hypermagnesemia) : Increase to Grade 3	0	2	1

Magnesium (Hypermagnesemia) : Increase to Grade 4	0	0	0
Magnesium (Hypomagnesemia) : Increase to Grade 3	0	0	1
Magnesium (Hypomagnesemia) : Increase to Grade 4	0	0	0
Sodium (Hypernatremia) : Increase to Grade 3	0	0	0
Sodium (Hypernatremia) : Increase to Grade 4	0	0	0
Sodium (Hyponatremia) : Increase to Grade 3	0	10	6
Sodium (Hyponatremia) : Increase to Grade 4	0	0	0
Phosphorus inorganic : Increase to Grade 3	0	6	4
Phosphorus inorganic : Increase to Grade 4	0	0	0
Triglycerides : Increase to Grade 3	0	0	0
Triglycerides : Increase to Grade 4	0	0	0

Part C (randomized): Number of participants with worst-case Chemistry Change from Baseline with respect to Normal Range

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 7 years))

Part C: Dabrafenib 150 mg	Part C: Dabrafenib 150 mg + Trametinib 1 mg	Part C: Dabrafenib 150 mg + Trametinib 2 mg

Arm/Group Description	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	53	54	55
Part C (randomized): Number of participants with worst-case Chemistry Change from Baseline with respect to Normal Range (units: Participants) Count of Participants (Not Applicable)			
Direct Bilirubin : Decrease to Low	0	0	0
Direct Bilirubin : Increase to High	0	0	0
Creatine Kinase MB mass : Decrease to Low	0	0	0
Creatine Kinase MB mass : Increase to High	0	1	0
Chloride : Decrease to Low	7	24	24
Chloride : Increase to High	11	14	12
Carbon dioxide content/Bicarbonate : Decrease to Low	5	8	12
Carbon dioxide content/Bicarbonate : Increase to High	8	14	16
C-Reactive protein : Decrease to Low	0	0	0

C-Reactive protein : Increase to High	0	0	3
Creatinine Clearance : Decrease to Low	7	16	10
Creatinine Clearance : Increase to High	7	11	10
High Density Lipids, Cholesterol : Decrease to Low	0	0	0
High Density Lipids, Cholesterol : Increase to High	0	0	0
Lactate Dehydrogenase : Decrease to Low	2	3	2
Lactate Dehydrogenase : Increase to High	3	24	32
Low Density Lipids, Cholesterol : Decrease to Low	0	0	0
Low Density Lipids, Cholesterol : Increase to High	0	0	0
Total Protein : Decrease to Low	4	10	19
Total Protein : Increase to High	1	8	3
Troponin I : Decrease to Low	0	0	0
Troponin I : Increase to High	0	0	0
Urea/BUN : Decrease to Low	5	4	9

Urea/BUN : Increase to High	8	23	20

Part C (randomized): Number of participants with worst-case Hematology Toxicity Grade Change from Baseline

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 7 years))

	Part C: Dabrafenib 150 mg	Part C: Dabrafenib 150 mg + Trametinib 1 mg	Part C: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	53	54	55
Part C (randomized): Number of participants with worst-case Hematology Toxicity Grade Change from Baseline (units: Participants) Count of Participants (Not Applicable)			
Hemoglobin (Increased) : Increase to Grade 3	0	0	0
Hemoglobin (Increased) : Increase to Grade 4	0	0	0
Hemoglobin (Anemia) : Increase to Grade 3	0	4	2
Hemoglobin (Anemia) : Increase to Grade 4	0	0	0

Lymphocytes (Increased) : Increase to Grade 3	0	0	0
Lymphocytes (Increased) : Increase to Grade 4	0	0	0
Lymphocytes (Decreased) : Increase to Grade 3	3	10	12
Lymphocytes (Decreased) : Increase to Grade 4	0	1	3
Total Neutrophils : Increase to Grade 3	1	2	4
Total Neutrophils : Increase to Grade 4	0	0	4
Platelet Count : Increase to Grade 3	0	2	3
Platelet Count : Increase to Grade 4	0	0	1
White Blood Cell count : Increase to Grade 3	0	3	5
White Blood Cell count : Increase to Grade 4	0	0	0

Part C (randomized): Number of participants with worst-case Hematology Change from Baseline with respect to Normal Range

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 7 years))

	Part C: Dabrafenib 150 mg	Part C: Dabrafenib 150 mg + Trametinib 1 mg	Part C: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrafenib 150 mg	Participants received dabrafenib 150 mg gelatin	Participants received dabrafenib 150 mg gelatin

	gelatin capsules BID.	capsules BID and trametinib 1 mg tablets QD.	capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	53	54	55
Part C (randomized): Number of participants with worst-case Hematology Change from Baseline with respect to Normal Range (units: Participants) Count of Participants (Not Applicable)			
Basophils : Decrease to Low	1	1	3
Basophils : Increase to High	3	6	10
Eosinophils : Decrease to Low	3	11	8
Eosinophils : Increase to High	2	11	9
Hematocrit : Decrease to Low	15	23	27
Hematocrit : Increase to High	2	1	2
Mean Corpuscle Hemoglobin concentration : Decrease to Low	11	16	12
Mean Corpuscle Hemoglobin concentration : Increase to High	2	8	9
Mean Corpuscle Hemoglobin : Decrease to Low	6	11	8
Mean Corpuscle Hemoglobin : Increase to High	4	6	8

Mean Corpuscle Volume : Decrease to Low	8	5	7
Mean Corpuscle Volume : Increase to High	1	5	4
Monocytes : Decrease to Low	5	14	12
Monocytes : Increase to High	17	20	14
Red Blood Cell count : Decrease to Low	11	22	25
Red Blood Cell count : Increase to High	1	4	4
Reticulocytes : Decrease to Low	0	1	2
Reticulocytes : Increase to High	0	0	5

Part C (randomized): Number of participants with the indicated worst-case change from Baseline in heart rate and blood pressure

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 7 years))

	Part C: Dabrafenib 150 mg	Part C: Dabrafenib 150 mg + Trametinib 1 mg	Part C: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.

Number of Participants Analyzed [units: participants]	53	54	55
Part C (randomized): Number of participants with the indicated worst-case change from Baseline in heart rate and blood pressure (units: Participants)			
Systolic BP (mmHg) , G3 or G4	5	4	12
Diastolic BP (mmHg), G3 or G4	4	4	4
Heart rate, Decrease to <60 bpm	9	8	11
Heart rate, Change to normal or no change	34	30	28
Heart rate, Increase to >100 bpm	10	16	18

Part D (Analyte=GSK2118436): Maximum plasma concentration (Cmax) of a single and repeat dose of dabrafenib alone and in combination with trametinib

(Time Frame: Day 1 and Day 21)

	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib

	completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	2 mg tablets QD.	2 mg tablets QD.
Number of Participants Analyzed [units: participants]	15	14	15	15
Part D (Analyte=GSK2118436): Maximum plasma concentration (Cmax) of a single and repeat dose of dabrafenib alone and in combination with trametinib (units: ng/mL) Geometric Mean (95% Confidence Interval)				
Day 1	1117 (914 to 1365)	1669 (1059 to 2631)	1227 (924 to 1764)	2289 (1622 to 3231)
Day 21	1050 (811 to 1358)	1746 (1344 to 2269)	1217 (895 to 1654)	2052 (1472 to 2860)

Statistical Analysis

Groups	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg, Part D: Dabrafenib 150 mg + Trametinib 2 mg

Non-Inferiority/Equivalence Test	Yes	Following loge tranformation, Cmax of dabrafenib after repeat doses from the pooled data in Part B and D were analyzed by a linear model with the following fixed effects as categorical variables: Capsule type (Gelatin or HPMC), BRAF dose (75 or 150 mg BID), Capsule type by BRAF dose interaction, Day (Day 15 or 21), MEK dose (0, 1, 1.5 or 2 mg QD). Geometric mean ratio (HPMC/Gelatin) and the corresponding 90% CI were provided for BRAF dose level 150 mg BID.
Other Geometric Mean Ratio	1.51	Geometric mean ratio (HPMC/Gelatin) and the corresponding 90% CI were provided for BRAF dose level 150 mg BID.
90 % Confidence Interval TWO_SIDED	1.10 to 2.08	

Part D (Analyte=GSK2118436): tmax of a single and repeat dose of dabrafenib alone and in combination with trametinib

(Time Frame: Day 1 and Day 21)

	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received	Participants received	Participants received	Participants received

	dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	15	14	15	15
Part D (Analyte=GSK2118436): tmax of a single and repeat dose of dabrafenib alone and in combination with trametinib (units: Hours) Median (Full Range)				
Day 1	2.00 (1.00 to 3.00)	2.00 (1.00 to 6.00)	2.00 (1.00 to 3.00)	1.50 (1.00 to 10.00)
Day 21	1.50 (1.00 to 2.00)	1.55 (0.98 to 3.00)	1.75 (1.00 to 3.00)	1.50 (1.00 to 3.00)

Part D (Analyte=GSK2118436): AUC (0-tau) and AUC (0-inf) of single and repeat doses of dabrafenib alone and in combination with trametinib

(Time Frame: Day 1 and Day 21)

	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	15	14	15	15

Part D (Analyte=GSK2118436): AUC (0-tau) and AUC (0-inf) of single and repeat doses of dabrafenib alone and in combination with trametinib
(units: ng*hr/mL)
Geometric Mean (95% Confidence Interval)

AUC (0-tau), Day 1	3593 (3008 to 4293)	6507 (4288 to 9872)	4618 (3525 to 6051)	7331 (5355 to 10037)
AUC (0-tau), Day 21	3020 (2390 to 3816)	4663 (3511 to 6194)	3434 (2679 to 4403)	5886 (4608 to 7517)
AUC (0-inf), Day 1	3982 (3325 to 4770)	7291 (4830 to 11005)	5321 (4192 to 6755)	8152 (5860 to 11341)
AUC (0-inf), Day 21				

Statistical Analysis

Groups	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg, Part D: Dabrafenib 150 mg + Trametinib 2 mg	
Non-Inferiority/Equivalence Test	Yes	Following loge transformation, AUC(0-tau) of dabrafenib was analyzed by a linear mixed effect model with dosing chort and day as fixed effects and subject as random effect. Based on the model, geometric mean ratio (Day 21 Dabrafenib 150 mg BID+Trametinib 2 mg QD/Day 21 Dabrafenib 150 mg BID alone) and the corresponding 90% confidence interval were provided.
Other Geometric Mean Ratio	1.23	Geometric mean ratio (Day 21 Dabrafenib 150 mg BID+Trametinib 2 mg

		QD/Day 21 Dabrafenib 150 mg BID alone) and the corresponding 90% confidence interval were provided.
90 % Confidence Interval TWO_SIDED	0.89 to 1.69	

Statistical Analysis

Groups	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg, Part D: Dabrafenib 150 mg + Trametinib 2 mg	
Non-Inferiority/Equivalence Test	Yes	Following loge tranformation, AUC(0-tau) of dabrafenib after repeat doses from the pooled data in Part B and D were analyzed by a linear model with the following fixed effects as categorical variables: Capsule type (Gelatin or HPMC), BRAF dose (75 or 150 mg BID), Capsule type by BRAF dose interaction, Day (Day 15 or 21), MEK dose (0, 1, 1.5, 2 or 2 mg QD). Geometric mean ratio (HPMC/Gelatin) and the corresponding 90% CI were then provided for BRAF dose level 150 mg BID.
Other Geometric Mean Ratio	1.10	Geometric mean ratio (HPMC/Gelatin) and the corresponding 90% CI

	were provided for BRAF dose level 150 mg BID.
90 % Confidence Interval TWO_SIDED	0.84 to 1.44

Part D: Number of participants with any adverse event (AE) or serious adverse event (SAE)

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 7 years))

	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.

Number of Participants Analyzed [units: participants]	15	15	41	39
Part D: Number of participants with any adverse event (AE) or serious adverse event (SAE) (units: Participants) Count of Participants (Not Applicable)				
Any AE	15	15	41	38
Any SAE	8	11	29	30

Part D: Number of participants with worst-case Chemistry Toxicity Grade Change from Baseline

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 7 years))

	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	**Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg**	**Part D: Dabrafenib 75 mg + Trametinib 2 mg**	**Part D: Dabrafenib 150 mg + Trametinib 2 mg**
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.

	mg tablets QD as combination dosing starting on Day 29.	2 mg tablets QD as combination dosing starting on Day 29.		
Number of Participants Analyzed [units: participants]	15	15	41	39
Part D: Number of participants with worst-case Chemistry Toxicity Grade Change from Baseline (units: Participants) Count of Participants (Not Applicable)				
Albumin : Increase to Grade 3	0	2	1	0
Albumin : Increase to Grade 4	0	0	0	0
Alkaline Phosphatase : Increase to Grade 3	1	2	0	3
Alkaline Phosphatase : Increase to Grade 4	0	0	0	0
Alanine Amino Transferase : Increase to Grade 3	2	0	2	1
Alanine Amino Transferase : Increase to Grade 4	0	0	0	0
Amylase : Increase to Grade 3	0	0	0	0
Amylase : Increase to Grade 4	0	0	0	0
Aspartate Amino Transferase : Increase to Grade 3	2	0	3	3

Aspartate Amino Transferase : Increase to Grade 4	0	0	0	0
Total Bilirubin : Increase to Grade 3	1	0	0	1
Total Bilirubin : Increase to Grade 4	0	0	0	0
Calcium (Hypercalcemia) : Increase to Grade 3	0	0	0	1
Calcium (Hypercalcemia) : Increase to Grade 4	0	0	0	0
Calcium (Hypocalcemia) : Increase to Grade 3	0	1	0	1
Calcium (Hypocalcemia) : Increase to Grade 4	0	0	1	0
Cholesterol : Increase to Grade 3	0	0	0	0
Cholesterol : Increase to Grade 4	0	0	0	0
Creatine Kinase : Increase to Grade 3	0	1	2	0
Creatine Kinase : Increase to Grade 4	0	0	0	0
Creatinine : Increase to Grade 3	0	0	1	0
Creatinine : Increase to Grade 4	0	0	0	0
Gamma Glutamyl Transferase : Increase to Grade 3	3	1	6	5
Gamma Glutamyl Transferase : Increase to Grade 4	1	2	0	0

Glucose (Hyperglycemia) : Increase to Grade 3	1	2	4	1
Glucose (Hyperglycemia) : Increase to Grade 4	0	0	0	0
Glucose (Hypoglycemia) : Increase to Grade 3	0	0	0	0
Glucose (Hypoglycemia) : Increase to Grade 4	0	0	0	0
Potassium (Hyperkalemia) : Increase to Grade 3	0	0	1	0
Potassium (Hyperkalemia) : Increase to Grade 4	0	0	0	0
Potassium (Hypokalemia) : Increase to Grade 3	0	1	1	2
Potassium (Hypokalemia) : Increase to Grade 4	0	0	1	0
Lipase : Increase to Grade 3	0	0	0	0
Lipase : Increase to Grade 4	0	2	0	1
Magnesium (Hypermagnesemia) : Increase to Grade 3	0	0	0	0
Magnesium (Hypermagnesemia) : Increase to Grade 4	0	0	0	0
Magnesium (Hypomagnesemia) : Increase to Grade 3	0	0	1	0
Magnesium (Hypomagnesemia) : Increase to Grade 4	0	0	0	0

Sodium (Hypernatremia) : Increase to Grade 3	0	0	0	0
Sodium (Hypernatremia) : Increase to Grade 4	0	0	0	0
Sodium (Hyponatremia) : Increase to Grade 3	1	4	5	5
Sodium (Hyponatremia) : Increase to Grade 4	0	0	1	1
Phosphorus inorganic : Increase to Grade 3	0	0	3	2
Phosphorus inorganic : Increase to Grade 4	0	0	0	0
Triglycerides : Increase to Grade 3	0	0	0	0
Triglycerides : Increase to Grade 4	0	0	0	0
Uric acid : Increase to Grade 3	0	0	0	0
Uric acid : Increase to Grade 4	0	0	2	0

Part D: Number of participants with worst-case Chemistry Change from Baseline with respect to Normal Range

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 7 years))

	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrefinib 75 mg HPMC	Participants received dabrefinib 150 mg HPMC	Participants received dabrefinib 75 mg HPMC	Participants received dabrefinib 150 mg HPMC

	capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	capsules BID and trametinib 2 mg tablets QD.	capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	15	15	41	39
Part D: Number of participants with worst-case Chemistry Change from Baseline with respect to Normal Range (units: Participants) Count of Participants (Not Applicable)				
Direct Bilirubin : Decrease Low	0	0	0	0
Direct Bilirubin : Increase to High	0	0	0	0
Creatine Kinase MB mass : Decrease Low	0	0	0	0
Creatine Kinase MB mass : Increase to High	0	0	1	0
Chloride : Decrease Low	7	9	18	25

Chloride : Increase to High	2	2	7	9
Carbon dioxide content/Bicarbonate : Decrease Low	3	5	12	8
Carbon dioxide content/Bicarbonate : Increase to High	4	3	12	10
C-Reactive protein : Decrease Low	0	0	0	0
C-Reactive protein : Increase to High	2	0	3	3
Creatinine Clearance : Decrease Low	5	5	7	7
Creatinine Clearance : Increase to High	2	1	11	4
High Density Lipids cholesterol : Decrease Low	0	0	1	0
High Density Lipids cholesterol : Increase to High	0	0	0	0
Lactate Dehydrogenase : Decrease Low	2	3	1	4
Lactate Dehydrogenase : Increase to High	7	7	20	20
Low Density Lipids cholesterol : Decrease Low	0	0	0	0
Low Density Lipids cholesterol : Increase to High	0	0	1	0
Total Protein : Decrease Low	5	7	17	15

Total Protein : Increase to High	2	1	6	7
Troponin I : Decrease Low	0	0	0	0
Troponin I : Increase to High	0	0	1	0
Troponin T : Decrease Low	0	0	0	0
Troponin T : Increase to High	0	0	0	0
Urea/BUN : Decrease Low	2	2	10	5
Urea/BUN : Increase to High	4	5	12	13

Part D: Number of participants with worst-case Hematology Toxicity Grade Change from Baseline

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 7 years))

	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.

	allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.		
Number of Participants Analyzed [units: participants]	15	15	41	39
Part D: Number of participants with worst-case Hematology Toxicity Grade Change from Baseline (units: Participants) Count of Participants (Not Applicable)				
Hemoglobin (Increased) : Increase to Grade 3	0	0	0	0
Hemoglobin (Increased) : Increase to Grade 4	0	0	0	0
Hemoglobin (Anemia) : Increase to Grade 3	1	1	3	1
Hemoglobin (Anemia) : Increase to Grade 4	0	0	0	0
Lymphocytes (Increased) : Increase to Grade 3	0	0	0	0
Lymphocytes (Increased) : Increase to Grade 4	0	0	0	0
Lymphocytes (Decreased) : Increase to Grade 3	1	3	11	11
Lymphocytes (Decreased) : Increase to Grade 4	0	1	1	1

Total Neutrophils : Increase to Grade 3	0	1	2	4
Total Neutrophils : Increase to Grade 4	0	0	1	0
Platelet count : Increase to Grade 3	1	0	0	0
Platelet count : Increase to Grade 4	0	0	1	0
White Blood Cell count : Increase to Grade 3	0	0	1	3
White Blood Cell count : Increase to Grade 4	0	0	1	0

Part D: Number of participants with worst-case Hematology Change from Baseline with respect to Normal Range

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 7 years))

	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.

	continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.		
Number of Participants Analyzed [units: participants]	15	15	41	39
Part D: Number of participants with worst-case Hematology Change from Baseline with respect to Normal Range (units: Participants) Count of Participants (Not Applicable)				
Basophils : Decrease to Low	0	0	2	0
Basophils : Increase to High	1	2	8	2
Eosinophils : Decrease to Low	1	2	3	4
Eosinophils : Increase to High	4	2	6	5
Erythrocyte Sedimentation Rate : Decrease to Low	0	0	0	0
Erythrocyte Sedimentation Rate : Increase to High	0	0	0	1
Hematocrit : Decrease to Low	4	10	19	18
Hematocrit : Increase to High	1	0	2	2

Mean Corpuscle Hemoglobin concentration : Decrease to Low	3	4	10	6
Mean Corpuscle Hemoglobin concentration : Increase to High	6	3	8	6
Mean Corpuscle Hemoglobin : Decrease to Low	1	4	7	6
Mean Corpuscle Hemoglobin : Increase to High	1	1	8	3
Mean Corpuscle Volume : Decrease to Low	2	4	5	9
Mean Corpuscle Volume : Increase to High	2	0	5	2
Monocytes : Decrease to Low	4	2	12	12
Monocytes : Increase to High	7	8	17	13
Red Blood Cell count : Decrease to Low	5	8	26	17
Red Blood Cell count : Increase to High	0	0	5	1
Reticulocytes : Decrease to Low	0	0	3	1
Reticulocytes : Increase to High	0	0	2	1

Part D: Number of participants with the indicated worst-case change from Baseline in heart rate and blood pressure

(Time Frame: From Baseline (Day 1) until Follow-up visit (up to approximately 7 years))

	Part D: Dabrafenib (DAB) 75 mg	Part D: Dabrafenib 150 mg to	Part D: Dabrafenib 75 mg +	Part D: Dabrafenib 150 mg +

	to DAB 75 mg + Trametinib 2 mg	DAB 150 mg + Trametinib 2 mg	Trametinib 2 mg	Trametinib 2 mg
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	15	15	40	39
Part D: Number of participants with the indicated worst-case change from Baseline in heart rate and blood pressure (units: Participants)				
Heart rate, Decrease to <60 bpm	2	3	12	14

Heart rate, Change to normal or no change	9	8	18	17
Heart rate, Increase to >100 bpm	5	5	12	12
Systolic BP (mmHg) , increase to G3 or G4	3	1	5	6
Diastolic BP (mmHg), increase to G3 or G4	4	0	2	3

Secondary Outcome Result(s)

Part A: Steady state concentration of trametinib with concomitant administration of dabrafenib

(Time Frame: Day 15 and Day 16)

	Part A: Dabrafenib 75 mg + Trametinib 2 mg
Arm/Group Description	Participants received a single dose of dabrafenib 75 mg gelatin capsules with repeat dose trametinib (Day 15).
Number of Participants Analyzed [units: participants]	7
Part A: Steady state concentration of trametinib with concomitant administration of dabrafenib	

(units: ng/mL) Median (Full Range)	
Day 15	9.7 (6 to 18)
Day 16	10.2 (6 to 17)

Part B: AUC [0-tau] of dabrafenib (DAB) and its metabolite in combination with trametinib

(Time Frame: Day 15 and Day 21)

	Part B: Dabrafenib 75 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg	Part B: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants,	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose

	and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	escalation did not proceed beyond these doses of dabrafenib and trametinib.
Number of Participants Analyzed [units: participants]	6	8	12	8
Part B: AUC [0-tau] of dabrafenib (DAB) and its metabolite in combination with trametinib (units: ng*hr/mL) Geometric Mean (95% Confidence Interval)				
DAB, Day 15	2466 (1458 to 4171)	3539 (1634 to 7666)	5187 (3737 to 7199)	4114 (1560 to 10848)
DAB, Day 21		4656 (3901 to 5557)	4528 (3602 to 5692)	5518 (3732 to 8158)
GSK2285403, Day 15	2120 (1366 to 3290)	2163 (1267 to 3694)	3136 (2501 to 3932)	3180 (1389 to 7283)
GSK2285403, Day 21		3257 (2162 to 4907)	2989 (2545 to 3510)	3632 (2364 to 5581)
GSK2298683, Day 15	37159 (22389 to 61673)	40634 (30329 to 54441)	43727 (31486 to 60727)	68528 (42444 to 110642)

GSK2298683 , Day 21		47911 (30643 to 74909)	49939 (39219 to 63589)	59965 (45117 to 79699)
GSK2167542, Day 15	2859 (1568 to 5216)	2961 (1206 to 7270)	4156 (2802 to 6165)	3746 (1992 to 7043)
GSK2167542, Day 21		3609 (2279 to 5714)	2995 (1891 to 4743)	3961 (2361 to 6645)

Part B: Pre-dose (trough) concentration at the end of the dosing interval (Ctau) and maximum plasma concentration (Cmax) of dabrafenib and its metabolite in combination with trametinib

(Time Frame: Day 15 and Day 21)

	Part B: Dabrafenib 75 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg	Part B: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib

	(PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.
Number of Participants Analyzed [units: participants]	6	8	12	8
Part B: Pre-dose (trough) concentration at the end of the dosing interval (Ctau) and maximum plasma concentration (Cmax) of dabrafenib and its metabolite in combination with trametinib (units: ng/mL) Geometric Mean (95% Confidence Interval)				
DAB Ctau, Day 15	59.8 (19.1 to 187)	44.6 (17.1 to 117)	115 (27.8 to 472)	73.7 (10.3 to 528)
DAB Ctau, Day 21		185 (79.7 to 428)	102 (57.1 to 184)	79.9 (32.2 to 198)
DAB Cmax, Day 15	640 (390 to 1048)	906 (221 to 3717)	1306 (700 to 2437)	1046 (545 to 2011)
DAB Cmax, Day 21		1263 (863 to 1848)	1346 (997 to 1817)	1391 (1002 to 1932)

GSK2285403 Ctau, Day 15	72.9 (25.2 to 211)	47.8 (20.2 to 113)	97.9 (32.2 to 297)	74.4 (15.7 to 353)
GSK2285403 Ctau, Day 21		136 (62.4 to 299)	92.9 (60.2 to 143)	82.7 (37.6 to 182)
GSK2285403 Cmax, Day 15	399 (265 to 601)	418 (146 to 1201)	597 (300 to 1186)	630 (411 to 964)
GSK2285403 Cmax, Day 21		775 (441 to 1364)	668 (507 to 882)	722 (502 to 1039)
GSK2298683 Ctau, Day 15	2345 (1237 to 4447)	2360 (1134 to 4911)	2792 (2069 to 3768)	4372 (2589 to 7384)
GSK2298683 Ctau, Day 21		2920 (1674 to 5095)	3221 (2619 to 3962)	3740 (2564 to 5455)
GSK2298683 Cmax, Day 15	3757 (2385 to 5916)	4545 (3817 to 5411)	4636 (3258 to 6598)	7098 (4914 to 10254)
GSK2298683 Cmax, Day 21		5301 (3392 to 8286)	5416 (4163 to 7048)	6257 (4937 to 7931)
GSK2167542 Ctau, Day 15	257 (140 to 473)	249 (79.4 to 782)	331 (185 to 590)	318 (260 to 389)
GSK2167542 Ctau, Day 21		196 (90.8 to 425)	248 (140 to 439)	369 (191 to 714)
GSK2167542 Cmax, Day 15	300 (157 to 572)	355 (114 to 1108)	523 (251 to 1091)	460 (190 to 1113)
GSK2167542 Cmax, Day 21		543 (298 to 989)	373 (248 to 562)	430 (226 to 818)

Part B: tmax of dabrafenib and its metabolite in combination with trametinib

(Time Frame: Day 15 and Day 21)

	Part B: Dabrafenib 75 mg +	Part B: Dabrafenib 150 mg +	Part B: Dabrafenib 150 mg +	Part B: Dabrafenib 150 mg +

	Trametinib 1 mg	Trametinib 1 mg	Trametinib 1.5 mg	Trametinib 2 mg
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.

		3 weeks of treatment.		
Number of Participants Analyzed [units: participants]	6	8	12	8
Part B: tmax of dabrafenib and its metabolite in combination with trametinib (units: Hours) Median (Full Range)				
DAB Day 15	2.00 (1.03 to 2.00)	2.00 (1.03 to 6.00)	2.00 (1.00 to 2.10)	1.50 (1.00 to 2.00)
DAB Day 21		1.54 (1.00 to 2.00)	1.53 (1.00 to 2.03)	2.04 (1.00 to 4.03)
GSK2285403 Day 15	2.00 (2.00 to 2.03)	2.00 (1.03 to 8.00)	2.00 (2.00 to 4.03)	2.00 (2.00 to 2.00)
GSK2285403 Day 21		1.97 (0.00 to 2.00)	2.00 (1.00 to 2.03)	2.07 (1.00 to 6.00)
GSK2298683 Day 15	6.00 (4.00 to 8.00)	4.96 (0.00 to 6.30)	4.17 (1.00 to 8.02)	4.10 (4.00 to 8.00)
GSK2298683 Day 21		4.00 (1.00 to 6.00)	4.00 (1.00 to 6.00)	4.02 (2.00 to 8.07)
GSK2167542 Day 15	0.00 (0.00 to 4.17)	2.94 (0.00 to 8.00)	4.17 (1.00 to 8.02)	1.52 (0.00 to 2.00)
GSK2167542 Day 21		2.00 (1.00 to 2.32)	1.01 (0.00 to 8.00)	1.50 (0.00 to 8.15)

Part B (Analyte=GSK1120212): AUC (0-tau) assessment of trametinib in combination with dabrafenib

(Time Frame: Day 15 and Day 21)

	Part B: Dabrafenib 75 mg + Trametinib 1 mg	**Part B: Dabrafenib 150 mg + Trametinib 1 mg**	**Part B: Dabrafenib 150 mg + Trametinib 1.5 mg**	**Part B: Dabrafenib 150 mg + Trametinib 2 mg**
Arm/Group Description	Melanoma BRAF-positive	Melanoma BRAF-positive	Melanoma BRAF-positive	Melanoma BRAF-positive

participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.

Number of Participants Analyzed [units: participants]	6	8	12	8
Part B (Analyte=GSK1120212): AUC (0-tau) assessment of trametinib in combination with dabrafenib (units: ng*hr/mL) Geometric Mean (95% Confidence Interval)				
Day 15	169 (113 to 252)	147 (101 to 212)	217 (139 to 338)	394 (229 to 679)
Day 21		169 (146 to 194)	269 (238 to 304)	351 (284 to 432)

Part B (Analyte=GSK1120212): Ctau and Cmax assessments of trametinib in combination with dabrafenib

(Time Frame: Day 15 and Day 21)

	Part B: Dabrafenib 75 mg + Trametinib 1 mg	**Part B: Dabrafenib 150 mg + Trametinib 1 mg**	**Part B: Dabrafenib 150 mg + Trametinib 1.5 mg**	**Part B: Dabrafenib 150 mg + Trametinib 2 mg**
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID

	pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.
Number of Participants Analyzed [units: participants]	6	8	12	8
Part B (Analyte=GSK1120212): Ctau and Cmax assessments of trametinib in combination with dabrafenib (units: ng/mL) Geometric Mean (95% Confidence Interval)				
Ctau, Day 15	5.56 (3.74 to 8.28)	5.05 (3.81 to 6.69)	7.62 (5.38 to 10.8)	12.4 (6.50 to 23.6)
Ctau, Day 21		5.57 (4.80 to 6.45)	8.51 (7.65 to 9.48)	10.8 (8.75 to 13.3)
Cmax, Day 15	10.2 (7.18 to 14.4)	8.08 (5.06 to 12.9)	11.5 (6.16 to 21.5)	22.4 (14.0 to 35.6)
Cmax, Day 21		10.2 (8.50 to 12.1)	18.0 (14.9 to 21.7)	22.6 (18.1 to 28.2)

Part B (Analyte=GSK1120212): tmax assessment of trametinib in combination with dabrafenib

(Time Frame: Day 15 and Day 21)

	Part B: Dabrafenib 75 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg	Part B: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.

	the first 3 weeks of treatment.	and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	DLTs occurring during the first 3 weeks of treatment.	
Number of Participants Analyzed [units: participants]	6	8	12	8
Part B (Analyte=GSK1120212): tmax assessment of trametinib in combination with dabrafenib (units: Hours) Median (Full Range)				
Day 15	2.00 (1.03 to 4.00)	2.00 (1.00 to 8.00)	2.00 (1.00 to 8.00)	1.52 (1.00 to 2.00)
Day 21		2.00 (0.93 to 8.00)	2.00 (1.00 to 2.00)	2.00 (1.00 to 8.15)

Part B: Number of participants with BRAFi-naïve mutant metastatic melanoma with the best overall response as assessed by investigator

(Time Frame: From the first dose of study medication to the first documented evidence of a confirmed complete response or partial response (up to approximately 8 years))

	Part B: Dabrafenib 75 mg + Trametinib 1 mg	**Part B: Dabrafenib 150 mg + Trametinib 1 mg**	**Part B: Dabrafenib 150 mg + Trametinib 1.5 mg**	**Part B: Dabrafenib 150 mg + Trametinib 2 mg**
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF	Melanoma BRAF-positive participants who received prior treatment with BRAF

	received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.
Number of Participants Analyzed [units: participants]	6	22	25	24

Part B: Number of participants with BRAFi-naïve mutant metastatic melanoma with the best overall response as assessed by investigator

(units: Participants)
Count of Participants (Not Applicable)

CR	0	4	3	4
PR	4	10	8	11

Part B: Duration of response as assessed by the investigator in participants with BRAFi-naïve mutant metastatic melanoma

(Time Frame: First documented evidence of PR or CR until the earlier of date of disease progression or date of death due to any cause (up to approximately 8 years))

	Part B: Dabrafenib 75 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1 mg	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg	Part B: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did

	participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	not proceed beyond these doses of dabrafenib and trametinib.
Number of Participants Analyzed [units: participants]	6	22	25	24
Part B: Duration of response as assessed by the investigator in participants with BRAFi-naïve mutant metastatic melanoma (units: Months) Median (95% Confidence Interval)				
	12.4 (3.7 to NA)[123]	8.4 (3.9 to 27.4)	12.6 (5.1 to NA)[123]	16.9 (7.4 to NA)[123]

[1] NA: Not estimable
[2] NA: Not estimable
[3] NA: Not estimable

Part B: Progression-free Survival (PFS) as assessed by the investigator in participants with BRAFi-naïve mutant metastatic melanoma

(Time Frame: From the date of first dose to the earliest date of disease progression (PD) or death due to any cause (up to approximately 8 years))

Part B: Dabrafenib 75	Part B: Dabrafenib	Part B: Dabrafenib	Part B: Dabrafenib

	mg + Trametinib 1 mg	150 mg + Trametinib 1 mg	150 mg + Trametinib 1.5 mg	150 mg + Trametinib 2 mg
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.

		during the first 3 weeks of treatment.		
Number of Participants Analyzed [units: participants]	6	22	25	24
Part B: Progression-free Survival (PFS) as assessed by the investigator in participants with BRAFi-naïve mutant metastatic melanoma (units: Months) Median (95% Confidence Interval)				
	8.7 (3.4 to NA)[1]	8.2 (4.3 to 11.0)	5.4 (3.5 to 12.8)	10.8 (3.6 to 18.6)

[1] NA: Not estimable

Part B: Overall survival (OS) in BRAFi Naïve Melanoma participants

(Time Frame: From the date of first dose until date of death due to any cause (up to approximately 8 years))

	Part B: Dabrafenib 75 mg + Trametinib 1 mg	**Part B: Dabrafenib 150 mg + Trametinib 1 mg**	**Part B: Dabrafenib 150 mg + Trametinib 1.5 mg**	**Part B: Dabrafenib 150 mg + Trametinib 2 mg**
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal

	and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.
Number of Participants Analyzed [units: participants]	6	22	25	24
Part B: Overall survival (OS) in BRAFi Naïve Melanoma participants (units: Months) Median (95% Confidence Interval)				

	17.4 (8.0 to NA)[12]	23.5 (12.9 to 33.7)	13.3 (6.3 to 23.4)	41.5 (12.9 to NA)[12]

[1] NA: Not estimable
[2] NA: Not estimable

Part B: Pre- and post-dose H-scores for individual participants

(Time Frame: Screening and at disease progression (up to approximately 8 years))

	Part B: Dabrafenib + Trametinib
Arm/Group Description	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib (75 mg or 150 mg) gelatin capsules BID and trametinib (1 mg, 1.5 mg, or 2 mg) tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants

	were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.
Number of Participants Analyzed [units: participants]	10
Part B: Pre- and post-dose H-scores for individual participants (units: scores on a scale)	
p-ERK: Participant 1, pre-dose score	135
p-ERK: Participant 1, post-dose score	109
p-ERK: Participant 2, pre-dose score	193
p-ERK: Participant 2, post-dose score	138
p-ERK: Participant 3, pre-dose score	148
p-ERK: Participant 3, post-dose score	65
p-ERK: Participant 4, pre-dose score	80
p-ERK: Participant 4, post-dose score	20
p-ERK: Participant 5, pre-dose score	130
p-ERK: Participant 5, post-dose score	99

p-ERK: Participant 6, pre-dose score	68
p-ERK: Participant 6, post-dose score	7
p-ERK: Participant 7, pre-dose score	128
p-ERK: Participant 7, post-dose score	81
p-ERK: Participant 8, pre-dose score	196
p-ERK: Participant 8, post-dose score	75
p-ERK: Participant 9, pre-dose score	164
p-ERK: Participant 9, post-dose score	109
p-ERK: Participant 10, pre-dose score	239
p-ERK: Participant 10, post-dose score	78
p-AKT: Participant 1, pre-dose score	130
p-AKT, Participant 1, post-dose score	180
p-AKT: Participant 2, pre-dose score	76
p-AKT, Participant 2, post-dose score	50
p-AKT: Participant 3, pre-dose score	192
p-AKT, Participant 3, post-dose score	277

p-AKT: Participant 4, pre-dose score	25
p-AKT, Participant 4, post-dose score	135
p-AKT: Participant 5, pre-dose score	55
p-AKT, Participant 5, post-dose score	2
p-AKT: Participant 6, pre-dose score	145
p-AKT, Participant 6, post-dose score	20
p-AKT: Participant 7, pre-dose score	22
p-AKT, Participant 7, post-dose score	7
p-AKT: Participant 8, pre-dose score	183
p-AKT, Participant 8, post-dose score	123
p-AKT: Participant 9, pre-dose score	278
p-AKT, Participant 9, post-dose score	289
p-AKT: Participant 10, pre-dose score	73
p-AKT, Participant 10, post-dose score	0

Part C (randomized): Overall survival (OS)

(Time Frame: From the date of randomization until date of death due to any cause (up to approximately 7 years))

	Part C: Dabrafenib 150 mg	Part C: Dabrafenib 150 mg + Trametinib 1 mg	Part C: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	54	54	54
Part C (randomized): Overall survival (OS) (units: Months) Median (95% Confidence Interval)			
	20.2 (14.0 to 27.1)	18.7 (13.7 to 35.3)	25.0 (17.5 to 36.5)

Part C: Plasma concentrations of dabrafenib and its metabolites

(Time Frame: Day 15, Week 8, Week 16, Week 24, Week 32, Week 40, Week 48, and Week 56)

	Part C: Dabrafenib 150 mg	Part C: Dabrafenib 150 mg + Trametinib 1 mg	Part C: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrafenib 150 mg	Participants received dabrafenib 150 mg gelatin	Participants received dabrafenib 150 mg gelatin

	gelatin capsules BID.	capsules BID and trametinib 1 mg tablets QD.	capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	49	53	50
Part C: Plasma concentrations of dabrafenib and its metabolites (units: ng/mL) Median (Full Range)			
Day 15, GSK2118436	59.3 (9 to 2420)	68.2 (0 to 1555)	66.3 (7 to 1804)
Week 8, GSK2118436	45.6 (3 to 1841)	69.8 (0 to 946)	50.5 (0 to 1696)
Week 16, GSK2118436	84.4 (0 to 1865)	66.7 (0 to 1774)	82.9 (2 to 3033)
Week 24, GSK2118436	66.3 (4 to 594)	66.2 (1 to 2684)	93.3 (7 to 741)
Week 32, GSK2118436	40.6 (1 to 500)	57.1 (0 to 1424)	66.4 (0 to 2042)
Week 40, GSK2118436	229 (5 to 714)	97.6 (19 to 2597)	150.9 (0 to 1624)
Week 48, GSK2118436	44.7 (13 to 132)	105.6 (0 to 1322)	107.7 (3 to 806)
Week 56, GSK2118436	46.4 (25 to 68)	44.5 (0 to 6646)	193.8 (3 to 413)
Day 15, GSK2285403	92.7 (14 to 1337)	71.8 (2 to 1220)	90.5 (10 to 995)
Week 8, GSK2285403	65.2 (3 to 2041)	80.4 (0 to 769)	90.6 (0 to 757)
Week 16, GSK2285403	113.4 (0 to 2090)	81.9 (0 to 995)	114.7 (3 to 2563)
Week 24, GSK2285403	95.0 (4 to 616)	88.1 (0 to 1689)	130.2 (9 to 529)

Week 32, GSK2285403	62.5 (3 to 890)	86.7 (0 to 808)	87.4 (0 to 973)
Week 40, GSK2285403	263.8 (7 to 693)	143.5 (16 to 870)	136.2 (0 to 1665)
Week 48, GSK2285403	43.3 (32 to 241)	93.6 (0 to 898)	146.4 (2 to 418)
Week 56, GSK2285403	48.3 (45 to 51)	92.9 (0 to 1841)	141.5 (7 to 755)
Day 15, GSK2298683	3493 (1381 to 16820)	3043.3 (199 to 8562)	3145.8 (428 to 16240)
Week 8, GSK2298683	3149.7 (238 to 13330)	3238.4 (20 to 7686)	3010 (31 to 13130)
Week 16, GSK2298683	3497.9 (21 to 9952)	2946.1 (0 to 8782)	2756.5 (44 to 14004)
Week 24, GSK2298683	2876.5 (500 to 8635)	3365.4 (25 to 7482)	3193.7 (133 to 6531)
Week 32, GSK2298683	2699.9 (447 to 14341)	3267.1 (0 to 9278)	3046.8 (50 to 9077)
Week 40, GSK2298683	4410.6 (1023 to 14258)	3694.7 (1900 to 7663)	3492.8 (0 to 12550)
Week 48, GSK2298683	3554.9 (1889 to 7148)	4146.9 (0 to 8351)	3936.1 (464 to 12239)
Week 56, GSK2298683	2032.2 (1102 to 2963)	3843.5 (374 to 6866)	2904.9 (1305 to 4673)
Day 15, GSK2167542	247.9 (95 to 955)	288 (49 to 1164)	289.3 (72 to 1140)
Week 8, GSK2167542	239.5 (19 to 1092)	275.2 (3 to 983)	262.4 (0 to 9876)

Week 16, GSK2167542	244 (1 to 772)	204.4 (0 to 922)	243.8 (3 to 1049)
Week 24, GSK2167542	225.6 (48 to 899)	247.2 (4 to 990)	254.6 (3 to 846)
Week 32, GSK2167542	171 (19 to 544)	255.4 (0 to 698)	289.3 (2 to 962)
Week 40, GSK2167542	222.2 (95 to 639)	249.3 (55 to 674)	268.9 (0 to 910)
Week 48, GSK2167542	204.5 (145 to 286)	232 (0 to 915)	260.9 (81 to 886)
Week 56, GSK2167542	171.8 (116 to 228)	250 (28 to 851)	462.1 (107 to 663)

Part C: Plasma concentrations of trametinib

(Time Frame: Day 15, Week 8, Week 16, Week 24, Week 32, Week 40, Week 48, and Week 56)

	Part C: Dabrafenib 150 mg	**Part C: Dabrafenib 150 mg + Trametinib 1 mg**	**Part C: Dabrafenib 150 mg + Trametinib 2 mg**
Arm/Group Description	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	59	53	50
Part C: Plasma concentrations of trametinib (units: ng/mL) Median (Full Range)			

Day 15	0 (0 to 0)	5.86 (3.4 to 11.3)	9.35 (4.8 to 26.00)
Week 8	0 (0 to 13.9)	6.70 (2.0 to 9.6)	10.3 (0 to 25.8)
Week 16	0 (0 to 9.8)	6.99 (0 to 20.7)	9.87 (1.1 to 25.4)
Week 24	0 (0 to 19.7)	5.99 (0 to 11.2)	9.54 (0.5 to 27.4)
Week 32	0 (0 to 0)	5.77 (0.7 to 11.6)	9.74 (0 to 51.5)
Week 40	0 (0 to 0)	7.11 (2.2 to 16.7)	10.1 (0 to 26.4)
Week 48	0 (0 to 0)	5.62 (0 to 14.3)	10.3 (0 to 35.6)
Week 56	0 (0 to 0)	9.90 (3.4 to 16.9)	8.60 (0 to 15.4)

Part C: Oral clearance (CL/F) of dabrafenib and trametinib

(Time Frame: Day 15, Week 8, Week 16, Week 24, Week 32, Week 40, and Week 48)

	Part C: Dabrafenib 150 mg	**Part C: Trametinib**
Arm/Group Description	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received Trametinib 1 mg or 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	53	109

Part C: Oral clearance (CL/F) of dabrafenib and trametinib

(units: Liters per hour (L/hr)) Mean (95% Confidence Interval)		
Non-inducible	19.4 (17.6 to 21.2)	5.07 (4.83 to 5.31)
Inducible	20.0 (19.2 to 20.8)	

Part C: Oral volume of distribution (V/F) of dabrafenib and trametinib

(Time Frame: Day 15, Week 8, Week 16, Week 24, Week 32, Week 40, and Week 48)

	Part C: Dabrafenib 150 mg	**Part C: Trametinib**
Arm/Group Description	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received Trametinib 1 mg or 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	53	109
Part C: Oral volume of distribution (V/F) of dabrafenib and trametinib (units: Liters (L)) Mean (95% Confidence Interval)		
	80.8 (73.9 to 87.7)	184 (158 to 210)

Part D: Cmax of dabrafenib metabolites

(Time Frame: Day 1: pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hours post dose. Day 21: pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hours post-dose)

Part D: Dabrafenib	**Part D: Dabrafenib**	**Part D: Dabrafenib**	**Part D: Dabrafenib**

	(DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	150 mg to DAB 150 mg + Trametinib 2 mg	75 mg + Trametinib 2 mg	150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	15	14	15	15
Part D: Cmax of dabrafenib metabolites (units: ng/mL) Geometric Mean (95% Confidence Interval)				
GSK2285403, Day 1	525 (429 to 643)	1055 (705 to 1579)	597 (474 to 752)	1363 (300 to 2066)

GSK2285403, Day 21	596 (501 to 709)	1203 (906 to 1599)	696 (551 to 880)	1120 (725 to 1730)
GSK2298683, Day 1	1475 (1249 to 1741)	2268 (1595 to 3223)	1478 (1197 to 1824)	2551 (1756 to 3707)
GSK2298683, Day 21	3637 (3119 to 4242)	6743 (5133 to 8859)	4158 (3136 to 5514)	6319 (4725 to 8450)
GSK2167542, Day 1	50.1 (30 to 84)	68.6 (36 to 129)	61.2 (41 to 91)	86.3 (48 to 155)
GSK2167542, Day 21	210 (154 to 285)	355 (268 to 470)	289 (201 to 416)	440 (303 to 637)

Part D: tmax of dabrafenib metabolites

(Time Frame: Day 1: pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hours post dose. Day 21: pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hours post-dose)

	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.

	continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.		
Number of Participants Analyzed [units: participants]	15	14	15	15
Part D: tmax of dabrafenib metabolites (units: Hours) Median (Full Range)				
GSK2285403, Day 1	3.00 (1.50 to 4.00)	3.51 (2.00 to 6.18)	3.00 (2.00 to 6.02)	2.07 (1.50 to 10.00)
GSK2285403, Day 21	2.00 (1.50 to 3.00)	2.00 (1.42 to 3.00)	2.00 (1.47 to 4.00)	2.00 (1.00 to 3.98)
GSK2298683, Day 1	10.0 (5.98 to 10.1)	8.93 (4.00 to 24.0)	10.0 (6.00 to 24.0)	8.00 (4.07 to 24.0)
GSK2298683, Day 21	5.00 (3.00 to 8.00)	4.00 (3.00 to 6.00)	5.98 (2.00 to 10.00)	4.00 (3.00 to 6.08)
GSK2167542, Day 1	24.0 (8.00 to 24.1)	24.0 (6.00 to 24.6)	24.0 (23.5 to 25.0)	24.0 (10.0 to 24.3)
GSK2167542, Day 21	0.75 (0 to 10.0)	2.00 (0.50 to 10.0)	2.00 (1.00 to 10.00)	1.75 (0 to 9.92)

Part D: Area under the concentration-time curve (AUC) of dabrafenib metabolites

(Time Frame: Day 1: pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hours post dose. Day 21: pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hours post-dose)

	Part D: Dabrafenib	**Part D: Dabrafenib**	**Part D: Dabrafenib**	**Part D: Dabrafenib**

	(DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	150 mg to DAB 150 mg + Trametinib 2 mg	75 mg + Trametinib 2 mg	150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	15	14	15	15
Part D: Area under the concentration-time curve (AUC) of dabrafenib metabolites (units: ng*hr/mL) Geometric Mean (95% Confidence Interval)				
GSK2285403, AUC(0-tau), Day 1	3134 (2533 to 3877)	5950 (4045 to 8753)	3694 (2903 to 4700)	6524 (4520 to 9416)

GSK2285403, AUC(0-inf), Day 1	3963 (3147 to 4990)	7415 (4991 to 11015)	5026 (3934 to 6422)	7907 (5434 to 11506)
GSK2285403, AUC (0-tau), Day 21	2568 (2099 to 3143)	4262 (3007 to 6040)	2919 (2296 to 3711)	4216 (2986 to 5951)
GSK2298683, AUC, (0-tau), Day 1	10396 (8388 to 12885)	15952 (10532 to 24160)	9575 (7143 to 12835)	20935 (12430 to 35259)
GSK2298683, AUC (0-t), Day 1	20047 (15384 to 26125)	35206 (24970 to 49639)	22692 (18398 to 27988)	31666 (18474 to 54277)
GSK2298683, AUC (0-tau), Day 21	34283 (29189 to 40266)	59340 (44595 to 78960)	39672 (29504 to 53343)	52712 (40084 to 69318)
GSK2167542, AUC(0-tau), Day 1	132 (79 to 219)	190 (101 to 356)	88.8 (56 to 139)	354 (228 to 549)
GSK2167542, AUC(0-t) Day 1	500 (271 to 925)	737 (385 to 1410)	614 (415 to 906)	1316 (824 to 2103)
GSK2167542, AUC(0-tau), Day 21	1775 (1225 to 2570)	2707 (2106 to 3481)	2508 (1793 to 3507)	3632 (2529 to 5216)

Part D: Cmax assessment of trametinib

(Time Frame: Day 1: pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hours post dose. Day 21: pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hours post-dose)

	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	**Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg**	**Part D: Dabrafenib 75 mg + Trametinib 2 mg**	**Part D: Dabrafenib 150 mg + Trametinib 2 mg**
Arm/Group Description	Participants received dabrefinib 75	Participants received dabrefinib 150	Participants received dabrefinib 75	Participants received dabrefinib 150

	mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	mg HPMC capsules BID and trametinib 2 mg tablets QD.	mg HPMC capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	0	0	15	14
Part D: Cmax assessment of trametinib (units: ng/mL) Geometric Mean (95% Confidence Interval)				
Day 1			6.8 (5 to 10)	6.6 (4 to 10)
Day 21			24.1 (20 to 29)	22.6 (20 to 26)

Part D: tmax assessment of trametinib

(Time Frame: Day 1: pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hours post dose. Day 21: pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hours post-dose)

	Part D: Dabrafenib (DAB) 75 mg	**Part D: Dabrafenib 150 mg to**	**Part D: Dabrafenib 75 mg +**	**Part D: Dabrafenib 150 mg +**

	to DAB 75 mg + Trametinib 2 mg	DAB 150 mg + Trametinib 2 mg	Trametinib 2 mg	Trametinib 2 mg
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	0	0	15	14
Part D: tmax assessment of trametinib (units: Hours) Median (Full Range)				
Day 1			2.00 (1.00 to 3.00)	1.50 (1.00 to 8.00)
Day 21			2.00 (1.00 to 4.00)	2.00 (1.50 to 3.98)

Part D: Area under the concentration-time curve assessment of trametinib

(Time Frame: Day 1: pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hours post dose. Day 21: pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hours post-dose)

	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	0	0	15	14

Part D: Area under the concentration-time curve assessment of trametinib (units: ng*h/mL) Geometric Mean (95% Confidence Interval)		
Day 1	53.4 (40 to 72)	50.7 (39 to 66)
Day 21	366 (305 to 439)	356 (318 to 400)

Part D: Number of participants with the best overall response as assessed by the investigator in participants

(Time Frame: From the date of first dose of study medication to the first documented evidence of a confirmed complete response or partial response (up to approximately 7 years))

	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg	Part D: Dabrafenib 75 mg + Trametinib 2 mg	Part D: Dabrafenib 150 mg + Trametinib 2 mg
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.

	combination dosing starting on Day 29.	combination dosing starting on Day 29.		
Number of Participants Analyzed [units: participants]	12	16	43	39
Part D: Number of participants with the best overall response as assessed by the investigator in participants (units: Participants) Count of Participants (Not Applicable)				
CR	0	2	5	7
PR	8	10	28	21

Part D: Duration of response as assessed by the investigator

(Time Frame: First documented evidence of PR or CR until the earlier of date of disease progression or date of death due to any cause (up to approximately 7 years))

	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	**Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg**	**Part D: Dabrafenib 75 mg + Trametinib 2 mg**	**Part D: Dabrafenib 150 mg + Trametinib 2 mg**
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.

	allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.		
Number of Participants Analyzed [units: participants]	12	16	43	39
Part D: Duration of response as assessed by the investigator (units: Months) Median (95% Confidence Interval)				
	8.2 (3.5 to 14.8)	10.1 (5.6 to NA)[1]	5.9 (3.7 to 9.0)	14.3 (8.8 to 67.8)

[1] NA: Not estimable

Part D: Progression-free Survival (PFS) as assessed by the investigator

(Time Frame: From the date of randomization to the earliest date of disease progression (PD) or death due to any cause (up to approximately 7 years))

	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg	**Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg**	**Part D: Dabrafenib 75 mg + Trametinib 2 mg**	**Part D: Dabrafenib 150 mg + Trametinib 2 mg**
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID.	Participants received dabrefinib 150 mg HPMC capsules BID.	Participants received dabrefinib 75 mg HPMC capsules BID	Participants received dabrefinib 150 mg HPMC capsules BID

	These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	and trametinib 2 mg tablets QD.	and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	12	16	43	39
Part D: Progression-free Survival (PFS) as assessed by the investigator (units: Months) Median (95% Confidence Interval)				
	7.9 (3.4 to 11.4)	9.3 (3.7 to 28.6)	7.4 (5.6 to 10.7)	11.1 (7.0 to 28.5)

Part D: Overall survival (OS)

(Time Frame: From the date of first dose until date of death due to any cause (up to approximately 7 years))

Part D: Dabrafenib (DAB) 75 mg to DAB 75	**Part D: Dabrafenib 150 mg to DAB 150 mg**	**Part D: Dabrafenib 75 mg +**	**Part D: Dabrafenib 150 mg +**

	mg + Trametinib 2 mg	+ Trametinib 2 mg	Trametinib 2 mg	Trametinib 2 mg
Arm/Group Description	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.
Number of Participants Analyzed [units: participants]	12	16	43	39
Part D: Overall survival (OS) (units: Months) Median (95% Confidence Interval)				
	19.5 (12.4 to 28.0)	15.5 (10.4 to 60.0)	15.3 (13.0 to 37.2)	40.3 (15.7 to 69.6)

Summary of Safety

Safety Results

All-Cause Mortality

	Part A: Dabrafenib 75 mg + Trametinib 2 mg N = 8	Part B: Dabrafenib 75 mg + Trametinib 1 mg N = 6	Part B: Dabrafenib 150 mg + Trametinib 1 mg N = 23	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg N = 27	Part B: Dabrafenib 150 mg + Trametinib 2 mg N = 94	Part C (randomized): Dabrafenib 150 mg N = 53	Part C (randomized): Dabrafenib 150 mg + Trametinib 1 mg N = 54	Part C (randomized): Dabrafenib 150 mg + Trametinib 2 mg N = 55	Part C (crossover): Dabrafenib 150 mg + Trametinib 2 mg N = 45	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg N = 15	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg N = 15	Part D: Dabrafenib 75 mg + Trametinib 2 mg N = 41	Part D: Dabrafenib 150 mg + Trametinib 2 mg N = 39
Arm/Group Description	Participants received a single dose of dabrafenib 75 mg gelatin capsules with repeat dose trametinib	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafe	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.	Participants who received dabrafenib 150 mg capsules BID alone in the Randomized Phase were given the opportunity to receive combination dosing of dabrafenib	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.

(Day 15).	1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants were enrolled	nib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled	colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.	150 mg gelatin capsules BID and trametinib 2 mg tablets QD upon disease progression with approval of the GlaxoSmithKline (GSK) Medical Monitor.	collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.

			ants and additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	based on DLTs occurring during the first 3 weeks of treatment.								
Total participants affected	2 (25.00%)	0 (0.00%)	1 (4.35%)	6 (22.22%)	12 (12.77%)	1 (1.89%)	4 (7.41%)	7 (12.73%)	7 (15.56%)	1 (6.67%)	4 (26.67%)	7 (17.07%)	2 (5.13%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events and Serious Adverse Events were collected for the maximum actual duration of treatment exposure and follow up for a participant per the protocol for approximately 90 months.
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment

	Part A: Dabrafenib 75 mg + Trametinib 2 mg N = 8	Part B: Dabrafenib 75 mg + Trametinib 1 mg N = 6	Part B: Dabrafenib 150 mg + Trametinib 1 mg N = 23	Part B: Dabrafenib 150 mg + Trametinib 1.5 mg N = 27	Part B: Dabrafenib 150 mg + Trametinib 2 mg N = 94	Part C (randomized): Dabrafenib 150 mg N = 53	Part C (randomized): Dabrafenib 150 mg + Trametinib 1 mg N = 54	Part C (randomized): Dabrafenib 150 mg + Trametinib 2 mg N = 55	Part C (crossover): Dabrafenib 150 mg + Trametinib 2 mg N = 45	Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg N = 15	Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg N = 15	Part D: Dabrafenib 75 mg + Trametinib 2 mg N = 41	Part D: Dabrafenib 150 mg + Trametinib 2 mg N = 39
Arm/Group Description	Participants received a single dose of dabrafenib 75 mg gelatin capsules with repeat dose trametinib (Day 15).	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who had salivary ductal cancer received dabrafenib	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 150 mg gelatin capsules BID and trametinib 1.5 mg	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants who had colorectal cancer and BRAFi naïve melanoma receive	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.	Participants who received dabrafenib 150 mg capsules BID alone in the Randomized Phase were given the opportunity to receive combination dosing of dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD upon disease progressi	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK collection in the first treatment period, were allowed to continue with	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.

made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and additional participants were enrolle	tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on DLTs occurring during the first	d dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and trametinib.
on with approval of the GlaxoSmithKline (GSK) Medical Monitor.	dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	

			d based on DLTs occurring during the first 3 weeks of treatment.	3 weeks of treatment.									
Total participants affected	5 (62.50%)	1 (16.67%)	15 (65.22%)	14 (51.85%)	55 (58.51%)	15 (28.30%)	24 (44.44%)	39 (70.91%)	24 (53.33%)	8 (53.33%)	11 (73.33%)	29 (70.73%)	30 (76.92%)
Blood and lymphatic system disorders													
Anaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.19%)	1 (1.89%)	2 (3.70%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	0 (0.00%)
Febrile neutropenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.06%)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Immune thrombocytopenic purpura	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	0 (0.00%)
Leukocytosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Leukopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (1.06%)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neutropenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.41%)	1 (1.06%)	0 (0.00%)	0 (0.00%)	2 (3.64%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	0 (0.00%)
Thrombocytopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	0 (0.00%)

Cardiac disorders													
Atrial fibrillation	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Atrial thrombosis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Cardiac failure	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Cardiogenic shock	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Left ventricular dysfunction	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Pericarditis	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Sinus tachycardia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Tachycardia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Ventricular arrhythmia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Endocrine disorders													
Addison's disease	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Adrenal insufficiency	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Eye disorders													
Chorioretinopathy	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Diplopia	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

Optic ischaemic neuropathy	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Uveitis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Vision blurred	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Gastrointestinal disorders													
Abdominal distension	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Abdominal pain	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	0 (0.00 %)	1 (1.89%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Abdominal pain upper	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Abdominal wall haematoma	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Ascites	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Colitis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Constipation	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Diarrhoea	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Duodenal stenosis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Dysphagia	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Gastric ulcer haemorrhage	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

Gastrointestinal haemorrhage	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	2 (3.64%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Haemorrhoids	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Intestinal obstruction	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Intestinal perforation	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Large intestinal obstruction	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (2.13 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Large intestine perforation	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Melaena	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Nausea	2 (25.0 0%)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	3 (3.19 %)	0 (0.00%)	3 (5.56%)	1 (1.82%)	2 (4.44%)	0 (0.00 %)	0 (0.00 %)	2 (4.88 %)	1 (2.56 %)
Obstructive pancreatitis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Pancreatitis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	1 (2.56 %)
Pancreatitis acute	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Rectal haemorrhage	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Small intestinal obstruction	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Vomiting	1 (12.5 0%)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	3 (3.19 %)	0 (0.00%)	4 (7.41%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	2 (4.88 %)	1 (2.56 %)

General disorders and administration site conditions													
Asthenia	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Chills	0 (0.00 %)	0 (0.00%)	3 (13.0 4%)	2 (7.41 %)	18 (19. 15%)	1 (1.89%)	7 (12.96 %)	12 (21.8 2%)	5 (11.11%)	6 (40.0 0%)	5 (33.3 3%)	14 (34. 15%)	15 (38. 46%)
Fatigue	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Hernia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Influenza like illness	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	2 (13.3 3%)	0 (0.00 %)	1 (2.56 %)
Non-cardiac chest pain	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (4.88 %)	0 (0.00 %)
Oedema peripheral	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Pain	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Peripheral swelling	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Pyrexia	0 (0.00 %)	0 (0.00%)	6 (26.0 9%)	6 (22.2 2%)	25 (26. 60%)	1 (1.89%)	10 (18.5 2%)	16 (29.0 9%)	7 (15.56%)	6 (40.0 0%)	6 (40.0 0%)	16 (39. 02%)	16 (41. 03%)
Hepatobiliary disorders													
Cholangitis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Gallbladder enlargement	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Hyperbilirubi naemia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (2.13 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

Immune system disorders													
Allergy to immunoglobulin therapy	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Cytokine release syndrome	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	5 (12.8 2%)
Drug hypersensitivity	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Sarcoidosis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Infections and infestations													
Abdominal abscess	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Abscess neck	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Appendicitis	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Bacteraemia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Bacterial sepsis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Cardiac infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Cellulitis	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	1 (2.44 %)	0 (0.00 %)
Device related infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)

Device related sepsis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Diverticulitis	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Endocarditis bacterial	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Escherichia sepsis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Gastroenteritis viral	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Hepatic infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Influenza	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Kidney infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Lower respiratory tract infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Pelvic infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Peritonitis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Pharyngitis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Pneumonia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	1 (1.89%)	1 (1.85%)	3 (5.45%)	1 (2.22%)	1 (6.67 %)	0 (0.00 %)	1 (2.44 %)	2 (5.13 %)
Pneumonia necrotising	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Prostate infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

Pseudomonal sepsis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Pyelonephritis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Sepsis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	1 (1.82%)	1 (2.22%)	1 (6.67 %)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Skin infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Staphylococcal sepsis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Streptococcal infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Streptococcal sepsis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Systemic infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Upper respiratory tract infection	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Urinary tract infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	1 (1.89%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Urosepsis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (1.89%)	1 (1.85%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Viral infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Wound infection	1 (12.50%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Wound infection staphylococcal	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Injury, poisoning and													

procedural complications													
Clavicle fracture	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Laceration	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Pelvic fracture	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Rib fracture	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Spinal compression fracture	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Wound dehiscence	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Wound haemorrhage	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Investigations													
Alanine aminotransferase increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (20.0 0%)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Aspartate aminotransferase increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (20.0 0%)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Blood alkaline phosphatase increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (20.0 0%)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Blood bilirubin increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (13.3 3%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

Blood calcium increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Blood creatine phosphokinase increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Blood creatinine increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Ejection fraction	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Ejection fraction decreased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	8 (8.51 %)	0 (0.00%)	3 (5.56%)	4 (7.27%)	5 (11.11%)	1 (6.67 %)	0 (0.00 %)	3 (7.32 %)	3 (7.69 %)
Gamma-glutamyltransferase increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	2 (5.13 %)
Hepatic enzyme increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Liver function test increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
White blood cell count decreased	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
White blood cell count increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Metabolism and nutrition disorders													

Decreased appetite	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Dehydration	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	2 (7.41 %)	4 (4.26 %)	0 (0.00%)	1 (1.85%)	2 (3.64%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	2 (4.88 %)	3 (7.69 %)
Failure to thrive	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (2.13 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Hypercalcaemia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Hypocalcaemia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Hypoglycaemia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Hypokalaemia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Hyponatraemia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	2 (7.41 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	1 (1.82%)	1 (2.22%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Hypophosphataemia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Musculoskeletal and connective tissue disorders													
Back pain	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Flank pain	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Muscle spasms	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Muscular weakness	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	2 (5.13 %)

Musculoskeletal chest pain	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Myalgia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Neck pain	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Pain in jaw	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Pathological fracture	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)													
Adenocarcinoma pancreas	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Basal cell carcinoma	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	5 (5.32 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	4 (8.89%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	3 (7.69 %)
Bowen's disease	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	2 (2.13 %)	2 (3.77%)	0 (0.00%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Breast cancer	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Clear cell renal cell carcinoma	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Colorectal adenocarcinoma	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Glioblastoma	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)

Intracranial tumour haemorrhage	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Keratoacanthoma	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	2 (3.77%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Lentigo maligna	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Lip squamous cell carcinoma	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Lymphoma	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Malignant ascites	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Malignant melanoma	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Malignant melanoma in situ	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Metastases to meninges	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Metastases to spine	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Metastatic squamous cell carcinoma	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Pericardial neoplasm	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Squamous cell carcinoma	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	2 (3.64%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)

Squamous cell carcinoma of head and neck	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Squamous cell carcinoma of skin	1 (12.5 0%)	0 (0.00%)	3 (13.0 4%)	3 (11.1 1%)	2 (2.13 %)	6 (11.32 %)	0 (0.00%)	2 (3.64%)	4 (8.89%)	0 (0.00 %)	1 (6.67 %)	2 (4.88 %)	4 (10.2 6%)
Squamous cell carcinoma of the tongue	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Superficial spreading melanoma stage unspecified	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Transitional cell carcinoma	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Tumour haemorrhage	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Nervous system disorders													
Brain stem haemorrhage	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Cerebral haemorrhage	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Cerebrospinal fluid leakage	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Cerebrovascular accident	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)

Cervical cord compression	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Chronic inflammatory demyelinating polyradiculoneuropathy	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Dizziness	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	2 (7.41 %)	2 (2.13 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	2 (4.88 %)	2 (5.13 %)
Facial paralysis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Facial paresis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Focal dyscognitive seizures	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Haemorrhage intracranial	1 (12.50%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Head discomfort	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Headache	1 (12.50%)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Hemiparesis	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Intracranial pressure increased	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Multiple sclerosis relapse	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Parkinson's disease	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

Partial seizures	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Presyncope	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	2 (7.41 %)	0 (0.00 %)	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Seizure	1 (12.5 0%)	1 (16.67 %)	0 (0.00 %)	1 (3.70 %)	2 (2.13 %)	0 (0.00%)	1 (1.85%)	1 (1.82%)	2 (4.44%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Sensory ganglionitis	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Syncope	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	2 (2.13 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	3 (7.32 %)	0 (0.00 %)
Transient ischaemic attack	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Tremor	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Psychiatric disorders													
Completed suicide	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Confusional state	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	2 (7.41 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	3 (7.32 %)	0 (0.00 %)
Mania	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Mental disorder	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Mental status changes	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	1 (2.56 %)
Renal and urinary disorders													
Acute kidney injury	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	2 (2.13 %)	0 (0.00%)	1 (1.85%)	2 (3.64%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (4.88 %)	0 (0.00 %)

Dysuria	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Nephrolithiasis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Renal disorder	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Renal failure	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Respiratory, thoracic and mediastinal disorders													
Cough	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Dyspnoea	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (2.13 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Haemoptysis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Hypoxia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Obstructive airways disorder	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Pleural effusion	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (1.89%)	0 (0.00%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Pneumonia aspiration	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Pneumothorax	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Pulmonary embolism	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	2 (2.13 %)	0 (0.00%)	0 (0.00%)	3 (5.45%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	2 (4.88 %)	0 (0.00 %)
Respiratory failure	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

Upper airway obstruction	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders													
Actinic keratosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.89%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Granulomatous dermatitis	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperhidrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Night sweats	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	1 (2.44%)	0 (0.00%)
Rash	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Rash generalised	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.85%)	0 (0.00%)	1 (2.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash maculo-papular	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vascular disorders													
Deep vein thrombosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypotension	0 (0.00%)	0 (0.00%)	1 (4.35%)	3 (11.11%)	7 (7.45%)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	2 (4.88%)	3 (7.69%)
Orthostatic hypotension	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Vena cava thrombosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events and Serious Adverse Events were collected for the maximum actual duration of treatment exposure and follow up for a participant per the protocol for approximately 90 months.
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Part A: Dabrafenib 75 mg + Trametinib 2 mg N = 8	**Part B: Dabrafenib 75 mg + Trametinib 1 mg N = 6**	**Part B: Dabrafenib 150 mg + Trametinib 1 mg N = 23**	**Part B: Dabrafenib 150 mg + Trametinib 1.5 mg N = 27**	**Part B: Dabrafenib 150 mg + Trametinib 2 mg N = 94**	**Part C (randomized): Dabrafenib 150 mg N = 53**	**Part C (randomized): Dabrafenib 150 mg + Trametinib 1 mg N = 54**	**Part C (randomized): Dabrafenib 150 mg + Trametinib 2 mg N = 55**	**Part C (crossover): Dabrafenib 150 mg + Trametinib 2 mg N = 45**	**Part D: Dabrafenib (DAB) 75 mg to DAB 75 mg + Trametinib 2 mg N = 15**	**Part D: Dabrafenib 150 mg to DAB 150 mg + Trametinib 2 mg N = 15**	**Part D: Dabrafenib 75 mg + Trametinib 2 mg N = 41**	**Part D: Dabrafenib 150 mg + Trametinib 2 mg N = 39**
Arm/Group Description	Participants received a single dose of dabrafenib 75 mg gelatin capsules with repeat dose trametinib (Day 15).	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafenib 75 mg gelatin capsules BID and	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors and participants who	Melanoma BRAF-positive participants who did not receive prior treatment with BRAF inhibitors received dabrafe	Melanoma BRAF-positive participants who received prior treatment with BRAF inhibitors and participants	Participants received dabrafenib 150 mg gelatin capsules BID.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD.	Participants received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD.	Participants who received dabrafenib 150 mg capsules BID alone in the Randomized Phase were given the opportunity to receive combination dosing	Participants received dabrefinib 75 mg HPMC capsules BID. These participants, after completion of serial PK	Participants received dabrefinib 150 mg HPMC capsules BID. These participants, after completion of serial PK	Participants received dabrefinib 75 mg HPMC capsules BID and trametinib 2 mg tablets QD.	Participants received dabrefinib 150 mg HPMC capsules BID and trametinib 2 mg tablets QD.

trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available pharmacokinetic (PK), safety, and other data from the first 4 evaluable participants, and additional participants were enrolled based on dose-limiting toxicities (DLTs) occurring during the first 3 weeks of treatment.	had salivary ductal cancer received dabrafenib 150 mg gelatin capsules BID and trametinib 1 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants and	nib 150 mg gelatin capsules BID and trametinib 1.5 mg tablets QD as continuous daily dosing. Dose escalation decisions were made based on all available PK, safety, and other data from the first 4 evaluable participants, and additional participants were enrolled	who had colorectal cancer and BRAFi naïve melanoma received dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD as continuous daily dosing. Dose escalation did not proceed beyond these doses of dabrafenib and	of dabrafenib 150 mg gelatin capsules BID and trametinib 2 mg tablets QD upon disease progression with approval of the GlaxoSmithKline (GSK) Medical Monitor.	collection in the first treatment period, were allowed to continue with dabrafenib 75 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.	collection in the first treatment period, were allowed to continue with dabrafenib 150 mg BID and trametinib 2 mg tablets QD as combination dosing starting on Day 29.

			additional participants were enrolled based on DLTs occurring during the first 3 weeks of treatment.	based on DLTs occurring during the first 3 weeks of treatment.	trametinib.								
Total participants affected	8 (100.00%)	6 (100.00%)	23 (100.00%)	27 (100.00%)	91 (96.81%)	53 (100.00%)	53 (98.15%)	55 (100.00%)	44 (97.78%)	15 (100.00%)	15 (100.00%)	41 (100.00%)	37 (94.87%)
Blood and lymphatic system disorders													
Anaemia	1 (12.50%)	1 (16.67%)	4 (17.39%)	3 (11.11%)	21 (22.34%)	3 (5.66%)	10 (18.52%)	12 (21.82%)	9 (20.00%)	0 (0.00%)	6 (40.00%)	8 (19.51%)	8 (20.51%)
Leukopenia	1 (12.50%)	0 (0.00%)	5 (21.74%)	3 (11.11%)	8 (8.51%)	2 (3.77%)	2 (3.70%)	2 (3.64%)	3 (6.67%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	1 (2.56%)
Lymph node pain	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lymphadenopathy	1 (12.50%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.89%)	1 (1.85%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)
Lymphopenia	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	3 (3.19%)	1 (1.89%)	1 (1.85%)	3 (5.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.88%)	1 (2.56%)
Neutropenia	0 (0.00%)	0 (0.00%)	3 (13.04%)	6 (22.22%)	11 (11.70%)	1 (1.89%)	8 (14.81%)	4 (7.27%)	2 (4.44%)	1 (6.67%)	2 (13.33%)	3 (7.32%)	4 (10.26%)

Thrombocytopenia	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	3 (11.11%)	10 (10.64%)	0 (0.00%)	2 (3.70%)	3 (5.45%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Cardiac disorders													
Intracardiac mass	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Palpitations	0 (0.00 %)	1 (16.67 %)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	3 (5.66%)	3 (5.56%)	1 (1.82%)	2 (4.44%)	0 (0.00 %)	0 (0.00 %)	3 (7.32 %)	1 (2.56 %)
Tachycardia	1 (12.50%)	1 (16.67 %)	1 (4.35 %)	2 (7.41 %)	7 (7.45 %)	0 (0.00%)	1 (1.85%)	3 (5.45%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (4.88 %)	1 (2.56 %)
Congenital, familial and genetic disorders													
Dermoid cyst	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Ear and labyrinth disorders													
Ear congestion	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	3 (5.45%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Ear pain	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	1 (3.70 %)	2 (2.13 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Tinnitus	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	2 (3.70%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (4.88 %)	1 (2.56 %)
Vertigo	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	2 (2.13 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (4.88 %)	2 (5.13 %)
Endocrine disorders													
Hypothyroidism	1 (12.50%)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	4 (4.26 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Eye disorders													

Asthenopia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Chalazion	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Chorioretin opathy	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	2 (7.41 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Diplopia	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	2 (4.88 %)	1 (2.56 %)
Dry eye	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	4 (4.26 %)	2 (3.77%)	4 (7.41%)	3 (5.45%)	2 (4.44%)	0 (0.00 %)	2 (13.3 3%)	2 (4.88 %)	2 (5.13 %)
Eye haemorrha ge	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Eye pain	1 (12.5 0%)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	2 (3.70%)	2 (3.64%)	1 (2.22%)	1 (6.67 %)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Eye pruritus	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Keratopath y	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Lacrimation decreased	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Ocular hyperaemi a	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	2 (3.70%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	1 (2.44 %)	1 (2.56 %)
Photophobi a	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	1 (1.82%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Photopsia	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	2 (3.70%)	1 (1.82%)	2 (4.44%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Retinal detachmen t	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Vision blurred	1 (12.5 0%)	2 (33.33 %)	3 (13.0 4%)	2 (7.41 %)	5 (5.32 %)	5 (9.43%)	10 (18.5 2%)	5 (9.09%)	4 (8.89%)	3 (20.0 0%)	4 (26.6 7%)	6 (14.6 3%)	5 (12.8 2%)

Visual acuity reduced	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Visual impairment	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	5 (5.32 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Vitreous detachmen t	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	1 (1.89%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Vitreous floaters	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	2 (3.77%)	5 (9.26%)	0 (0.00%)	3 (6.67%)	3 (20.0 0%)	0 (0.00 %)	0 (0.00 %)	2 (5.13 %)
Gastrointesti nal disorders													
Abdominal discomfort	0 (0.00 %)	1 (16.67 %)	2 (8.70 %)	0 (0.00 %)	2 (2.13 %)	1 (1.89%)	2 (3.70%)	2 (3.64%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Abdominal distension	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	4 (4.26 %)	1 (1.89%)	3 (5.56%)	3 (5.45%)	2 (4.44%)	2 (13.3 3%)	1 (6.67 %)	1 (2.44 %)	1 (2.56 %)
Abdominal pain	1 (12.5 0%)	2 (33.33 %)	4 (17.3 9%)	1 (3.70 %)	15 (15. 96%)	6 (11.32 %)	11 (20.3 7%)	12 (21.8 2%)	4 (8.89%)	5 (33.3 3%)	5 (33.3 3%)	10 (24. 39%)	1 (2.56 %)
Abdominal pain upper	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	3 (11.1 1%)	7 (7.45 %)	4 (7.55%)	4 (7.41%)	10 (18.1 8%)	1 (2.22%)	1 (6.67 %)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Anal fissure	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	1 (2.44 %)	0 (0.00 %)
Aphthous ulcer	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	1 (2.56 %)
Cheilitis	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Constipatio n	1 (12.5 0%)	1 (16.67 %)	9 (39.1 3%)	6 (22.2 2%)	26 (27. 66%)	6 (11.32 %)	15 (27.7 8%)	15 (27.2 7%)	7 (15.56 %)	1 (6.67 %)	6 (40.0 0%)	11 (26. 83%)	7 (17.9 5%)
Dental caries	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Diarrhoea	3 (37.5 0%)	2 (33.33 %)	9 (39.1 3%)	8 (29.6 3%)	32 (34. 04%)	15 (28.3 0%)	18 (33.3 3%)	27 (49.0 9%)	10 (22.22 %)	5 (33.3 3%)	6 (40.0 0%)	18 (43. 90%)	12 (30. 77%)

Diverticulum	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	0 (0.00%)
Dry mouth	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.41%)	9 (9.57%)	3 (5.66%)	8 (14.81%)	7 (12.73%)	6 (13.33%)	0 (0.00%)	2 (13.33%)	6 (14.63%)	4 (10.26%)
Dyspepsia	0 (0.00%)	1 (16.67%)	2 (8.70%)	4 (14.81%)	5 (5.32%)	3 (5.66%)	7 (12.96%)	7 (12.73%)	2 (4.44%)	1 (6.67%)	0 (0.00%)	6 (14.63%)	1 (2.56%)
Flatulence	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.41%)	4 (4.26%)	3 (5.66%)	0 (0.00%)	1 (1.82%)	1 (2.22%)	1 (6.67%)	1 (6.67%)	1 (2.44%)	3 (7.69%)
Gastritis	0 (0.00%)	0 (0.00%)	2 (8.70%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (3.64%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	0 (0.00%)
Gastrooesophageal reflux disease	1 (12.50%)	0 (0.00%)	1 (4.35%)	1 (3.70%)	6 (6.38%)	1 (1.89%)	4 (7.41%)	4 (7.27%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	4 (10.26%)
Haematochezia	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	3 (3.19%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (6.67%)	2 (4.88%)	1 (2.56%)
Haemorrhoids	1 (12.50%)	0 (0.00%)	1 (4.35%)	1 (3.70%)	1 (1.06%)	2 (3.77%)	0 (0.00%)	2 (3.64%)	1 (2.22%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	1 (2.56%)
Intestinal obstruction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)
Large intestine perforation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)
Mesenteric artery thrombosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Mouth ulceration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.13%)	0 (0.00%)	1 (1.85%)	1 (1.82%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	2 (5.13%)
Nausea	4 (50.00%)	2 (33.33%)	11 (47.83%)	12 (44.44%)	49 (52.13%)	11 (20.75%)	30 (55.56%)	26 (47.27%)	11 (24.44%)	5 (33.33%)	10 (66.67%)	26 (63.41%)	21 (53.85%)
Oral mucosa erosion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Oral pain	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	3 (3.19%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Retching	1 (12.50%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (1.06%)	2 (3.77%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	0 (0.00%)
Small intestinal obstruction	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	
Stomatitis	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (1.06%)	0 (0.00%)	2 (3.70%)	2 (3.64%)	1 (2.22%)	0 (0.00%)	0 (0.00%)	2 (4.88%)	2 (5.13%)
Tongue ulceration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.13%)
Toothache	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.82%)	1 (2.22%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	2 (5.13%)
Vomiting	4 (50.00%)	2 (33.33%)	6 (26.09%)	12 (44.44%)	39 (41.49%)	8 (15.09%)	23 (42.59%)	26 (47.27%)	13 (28.89%)	3 (20.00%)	8 (53.33%)	20 (48.78%)	21 (53.85%)
General disorders and administration site conditions													
Asthenia	0 (0.00%)	0 (0.00%)	8 (34.78%)	3 (11.11%)	12 (12.77%)	3 (5.66%)	2 (3.70%)	6 (10.91%)	1 (2.22%)	1 (6.67%)	0 (0.00%)	6 (14.63%)	3 (7.69%)
Axillary pain	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (1.06%)	4 (7.55%)	2 (3.70%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chest discomfort	1 (12.50%)	0 (0.00%)	3 (13.04%)	1 (3.70%)	1 (1.06%)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	2 (5.13%)
Chills	3 (37.50%)	3 (50.00%)	9 (39.13%)	11 (40.74%)	38 (40.43%)	8 (15.09%)	24 (44.44%)	29 (52.73%)	6 (13.33%)	2 (13.33%)	5 (33.33%)	15 (36.59%)	13 (33.33%)
Face oedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	3 (7.69%)
Fatigue	5 (62.50%)	4 (66.67%)	13 (56.52%)	12 (44.44%)	50 (53.19%)	22 (41.51%)	35 (64.81%)	32 (58.18%)	12 (26.67%)	7 (46.67%)	4 (26.67%)	29 (70.73%)	16 (41.03%)

Gait disturbance	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	3 (3.19 %)	0 (0.00%)	2 (3.70%)	2 (3.64%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	2 (4.88 %)	1 (2.56 %)
Influenza like illness	0 (0.00 %)	0 (0.00%)	3 (13.0 4%)	2 (7.41 %)	3 (3.19 %)	4 (7.55%)	12 (22.2 2%)	6 (10.91 %)	5 (11.11 %)	2 (13.3 3%)	3 (20.0 0%)	3 (7.32 %)	6 (15.3 8%)
Malaise	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	2 (7.41 %)	7 (7.45 %)	0 (0.00%)	2 (3.70%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (4.88 %)	1 (2.56 %)
Mass	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Mucosal inflammatio n	0 (0.00 %)	1 (16.67 %)	1 (4.35 %)	4 (14.8 1%)	2 (2.13 %)	0 (0.00%)	3 (5.56%)	2 (3.64%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Nodule	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	2 (7.41 %)	1 (1.06 %)	1 (1.89%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (4.88 %)	0 (0.00 %)
Non-cardiac chest pain	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	2 (7.41 %)	3 (3.19 %)	2 (3.77%)	2 (3.70%)	3 (5.45%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	2 (5.13 %)
Oedema peripheral	1 (12.5 0%)	0 (0.00%)	6 (26.0 9%)	5 (18.5 2%)	18 (19. 15%)	9 (16.98 %)	13 (24.0 7%)	14 (25.4 5%)	7 (15.56 %)	3 (20.0 0%)	2 (13.3 3%)	10 (24. 39%)	11 (28. 21%)
Pain	2 (25.0 0%)	2 (33.33 %)	4 (17.3 9%)	4 (14.8 1%)	8 (8.51 %)	4 (7.55%)	6 (11.11 %)	4 (7.27%)	0 (0.00%)	2 (13.3 3%)	0 (0.00 %)	3 (7.32 %)	3 (7.69 %)
Peripheral swelling	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	4 (4.26 %)	1 (1.89%)	4 (7.41%)	3 (5.45%)	1 (2.22%)	1 (6.67 %)	2 (13.3 3%)	1 (2.44 %)	1 (2.56 %)
Pyrexia	3 (37.5 0%)	4 (66.67 %)	10 (43. 48%)	13 (48. 15%)	58 (61. 70%)	13 (24.5 3%)	39 (72.2 2%)	37 (67.2 7%)	12 (26.67 %)	7 (46.6 7%)	7 (46.6 7%)	19 (46. 34%)	19 (48. 72%)
Swelling	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	1 (6.67 %)	1 (2.44 %)	0 (0.00 %)
Systemic inflammato ry response syndrome	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Tendernes s	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (2.13 %)	0 (0.00%)	2 (3.70%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)

Xerosis	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	2 (7.41 %)	1 (1.06 %)	2 (3.77%)	3 (5.56%)	2 (3.64%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	1 (2.44 %)	0 (0.00 %)
Immune system disorders													
Contrast media allergy	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	1 (2.44 %)	1 (2.56 %)
Cytokine release syndrome	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	4 (4.26 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	2 (5.13 %)
Seasonal allergy	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	2 (5.13 %)
Infections and infestations													
Anorectal infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Bronchitis	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	1 (3.70 %)	4 (4.26 %)	1 (1.89%)	1 (1.85%)	2 (3.64%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Candida infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	1 (1.89%)	0 (0.00%)	2 (3.64%)	2 (4.44%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	2 (5.13 %)
Cellulitis	1 (12.5 0%)	0 (0.00%)	1 (4.35 %)	2 (7.41 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	4 (7.27%)	1 (2.22%)	1 (6.67 %)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Conjunctivitis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	2 (4.44%)	1 (6.67 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Cystitis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	3 (3.19 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Ear infection	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	3 (3.19 %)	0 (0.00%)	1 (1.85%)	3 (5.45%)	1 (2.22%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Eye infection	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)

Folliculitis	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	2 (7.41 %)	3 (3.19 %)	1 (1.89%)	3 (5.56%)	4 (7.27%)	3 (6.67%)	1 (6.67 %)	0 (0.00 %)	4 (9.76 %)	1 (2.56 %)
Fungal infection	0 (0.00 %)	0 (0.00%)	3 (13.0 4%)	0 (0.00 %)	0 (0.00 %)	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Fungal skin infection	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	2 (3.64%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Gastroente ritis viral	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	3 (5.56%)	2 (3.64%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Groin abscess	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Herpes zoster	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	2 (5.13 %)
Hordeolum	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	2 (3.77%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	1 (2.44 %)	0 (0.00 %)
Infected bite	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Influenza	0 (0.00 %)	0 (0.00%)	3 (13.0 4%)	3 (11.1 1%)	0 (0.00 %)	0 (0.00%)	3 (5.56%)	2 (3.64%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Localised infection	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	2 (3.64%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	2 (4.88 %)	1 (2.56 %)
Lower respiratory tract infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	1 (1.89%)	0 (0.00%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	2 (5.13 %)
Mastitis	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Nasophary ngitis	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	1 (3.70 %)	4 (4.26 %)	0 (0.00%)	3 (5.56%)	5 (9.09%)	0 (0.00%)	1 (6.67 %)	3 (20.0 0%)	5 (12.2 0%)	0 (0.00 %)
Oral candidiasis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	2 (3.64%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	5 (12.2 0%)	0 (0.00 %)
Oral herpes	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	2 (2.13 %)	2 (3.77%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	2 (4.88 %)	0 (0.00 %)

Paronychia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	2 (13.3 3%)	1 (2.44 %)	1 (2.56 %)
Periorbital infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Pharyngitis	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Pneumonia	1 (12.5 0%)	0 (0.00%)	2 (8.70 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	2 (4.44%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Rash pustular	1 (12.5 0%)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	2 (3.64%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	1 (2.44 %)	1 (2.56 %)
Rhinitis	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (2.13 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Sepsis	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Sinusitis	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	5 (18.5 2%)	7 (7.45 %)	0 (0.00%)	2 (3.70%)	4 (7.27%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	3 (7.32 %)	6 (15.3 8%)
Skin infection	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	2 (3.77%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	2 (4.88 %)	0 (0.00 %)
Staphyloco ccal infection	2 (25.0 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Tinea pedis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	1 (1.89%)	1 (1.85%)	1 (1.82%)	0 (0.00%)	1 (6.67 %)	1 (6.67 %)	1 (2.44 %)	1 (2.56 %)
Upper respiratory tract infection	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	1 (3.70 %)	10 (10. 64%)	5 (9.43%)	10 (18.5 2%)	5 (9.09%)	5 (11.11 %)	2 (13.3 3%)	3 (20.0 0%)	4 (9.76 %)	6 (15.3 8%)
Urinary tract infection	1 (12.5 0%)	0 (0.00%)	5 (21.7 4%)	4 (14.8 1%)	18 (19. 15%)	3 (5.66%)	3 (5.56%)	8 (14.55 %)	6 (13.33 %)	2 (13.3 3%)	2 (13.3 3%)	5 (12.2 0%)	10 (25. 64%)
Wound infection staphyloco ccal	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

Injury, poisoning and procedural complications													
Arthropod bite	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	1 (1.06 %)	1 (1.89%)	1 (1.85%)	2 (3.64%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	1 (2.44 %)	0 (0.00 %)
Contusion	0 (0.00 %)	1 (16.67 %)	1 (4.35 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	3 (5.56%)	3 (5.45%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	5 (12.8 2%)
Fall	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	4 (7.41%)	0 (0.00%)	0 (0.00%)	3 (20.0 0%)	0 (0.00 %)	3 (7.32 %)	3 (7.69 %)
Infusion related reaction	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Laceration	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (2.13 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	2 (5.13 %)
Ligament sprain	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	4 (7.27%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Limb injury	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	1 (1.89%)	1 (1.85%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Procedural pain	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (2.13 %)	1 (1.89%)	0 (0.00%)	1 (1.82%)	2 (4.44%)	1 (6.67 %)	0 (0.00 %)	2 (4.88 %)	2 (5.13 %)
Spinal compression fracture	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	2 (5.13 %)
Sunburn	1 (12.5 0%)	0 (0.00%)	2 (8.70 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (4.88 %)	0 (0.00 %)
Tooth fracture	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Wound haemorrhage	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

Wrist fracture	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Investigations													
Alanine aminotransferase increased	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	3 (11.11%)	7 (7.45 %)	1 (1.89%)	11 (20.37%)	6 (10.91 %)	2 (4.44%)	1 (6.67 %)	3 (20.00%)	8 (19.51%)	5 (12.82%)
Aspartate aminotransferase increased	0 (0.00 %)	1 (16.67 %)	2 (8.70 %)	4 (14.81%)	12 (12.77%)	1 (1.89%)	10 (18.52%)	10 (18.18%)	3 (6.67%)	0 (0.00 %)	3 (20.00%)	6 (14.63%)	6 (15.38%)
Blood alkaline phosphatase increased	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	2 (7.41 %)	14 (14.89%)	2 (3.77%)	11 (20.37%)	7 (12.73 %)	2 (4.44%)	0 (0.00 %)	5 (33.33%)	5 (12.20%)	4 (10.26%)
Blood creatine phosphokinase increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	3 (7.32 %)	1 (2.56 %)
Blood creatinine increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	2 (7.41 %)	5 (5.32 %)	2 (3.77%)	4 (7.41%)	1 (1.82%)	1 (2.22%)	1 (6.67 %)	0 (0.00 %)	4 (9.76 %)	5 (12.82%)
Blood iron decreased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Blood magnesium decreased	1 (12.50%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (2.13 %)	0 (0.00%)	1 (1.85%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Blood potassium decreased	1 (12.50%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Blood pressure increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

Blood testosterone decreased	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Blood thyroid stimulating hormone increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Carbon dioxide increased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	3 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Ejection fraction decreased	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	6 (6.38 %)	0 (0.00%)	1 (1.85%)	5 (9.09%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	2 (4.88 %)	0 (0.00 %)
Gamma-glutamyltransferase increased	0 (0.00 %)	0 (0.00%)	3 (13.04%)	3 (11.11%)	12 (12.77%)	1 (1.89%)	11 (20.37%)	6 (10.91 %)	6 (13.33 %)	0 (0.00 %)	3 (20.00%)	6 (14.63%)	6 (15.38%)
Liver function test abnormal	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Lymphocyte count decreased	1 (12.50%)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	2 (2.13 %)	1 (1.89%)	5 (9.26%)	2 (3.64%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	2 (4.88 %)	2 (5.13 %)
Mean cell volume decreased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Neutrophil count decreased	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	2 (7.41 %)	0 (0.00 %)	1 (1.89%)	3 (5.56%)	1 (1.82%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	2 (4.88 %)	2 (5.13 %)
Platelet count decreased	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	1 (1.82%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	3 (7.32 %)	3 (7.69 %)

Protein urine present	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Thyroxine free decreased	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	2 (2.13%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)
Transaminases increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.13%)	0 (0.00%)	4 (7.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (13.33%)	1 (2.44%)	1 (2.56%)
Weight decreased	0 (0.00%)	0 (0.00%)	3 (13.04%)	0 (0.00%)	5 (5.32%)	4 (7.55%)	8 (14.81%)	6 (10.91%)	3 (6.67%)	1 (6.67%)	2 (13.33%)	4 (9.76%)	3 (7.69%)
Weight increased	0 (0.00%)	1 (16.67%)	5 (21.74%)	2 (7.41%)	3 (3.19%)	0 (0.00%)	1 (1.85%)	4 (7.27%)	2 (4.44%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	1 (2.56%)
White blood cell count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (3.70%)	2 (3.64%)	0 (0.00%)	1 (6.67%)	1 (6.67%)	5 (12.20%)	3 (7.69%)
Metabolism and nutrition disorders													
Decreased appetite	4 (50.00%)	3 (50.00%)	2 (8.70%)	7 (25.93%)	23 (24.47%)	11 (20.75%)	18 (33.33%)	16 (29.09%)	7 (15.56%)	2 (13.33%)	3 (20.00%)	12 (29.27%)	14 (35.90%)
Dehydration	0 (0.00%)	0 (0.00%)	3 (13.04%)	2 (7.41%)	12 (12.77%)	1 (1.89%)	4 (7.41%)	5 (9.09%)	2 (4.44%)	1 (6.67%)	1 (6.67%)	5 (12.20%)	6 (15.38%)
Diabetes mellitus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Hypercalcaemia	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	2 (2.13%)	1 (1.89%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	0 (0.00%)
Hyperglycaemia	0 (0.00%)	0 (0.00%)	3 (13.04%)	0 (0.00%)	8 (8.51%)	3 (5.66%)	6 (11.11%)	5 (9.09%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	4 (9.76%)	3 (7.69%)
Hyperkalaemia	0 (0.00%)	0 (0.00%)	2 (8.70%)	1 (3.70%)	4 (4.26%)	4 (7.55%)	0 (0.00%)	2 (3.64%)	0 (0.00%)	0 (0.00%)	2 (13.33%)	0 (0.00%)	1 (2.56%)
Hypermagnesaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.44%)	0 (0.00%)

Hyperuricaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (3.70%)	2 (3.64%)	1 (2.22%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypoalbuminaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (6.38%)	1 (1.89%)	4 (7.41%)	3 (5.45%)	1 (2.22%)	0 (0.00%)	2 (13.33%)	5 (12.20%)	2 (5.13%)
Hypokalaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.41%)	13 (13.83%)	3 (5.66%)	1 (1.85%)	5 (9.09%)	1 (2.22%)	1 (6.67%)	3 (20.00%)	5 (12.20%)	3 (7.69%)
Hypomagnesaemia	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	7 (7.45%)	1 (1.89%)	1 (1.85%)	3 (5.45%)	1 (2.22%)	0 (0.00%)	1 (6.67%)	2 (4.88%)	0 (0.00%)
Hyponatraemia	0 (0.00%)	0 (0.00%)	2 (8.70%)	2 (7.41%)	11 (11.70%)	1 (1.89%)	5 (9.26%)	7 (12.73%)	1 (2.22%)	0 (0.00%)	2 (13.33%)	5 (12.20%)	4 (10.26%)
Hypophosphataemia	0 (0.00%)	0 (0.00%)	2 (8.70%)	1 (3.70%)	8 (8.51%)	4 (7.55%)	5 (9.26%)	2 (3.64%)	1 (2.22%)	0 (0.00%)	0 (0.00%)	6 (14.63%)	2 (5.13%)
Impaired fasting glucose	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Increased appetite	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	2 (5.13%)
Lactic acidosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)
Vitamin D deficiency	1 (12.50%)	0 (0.00%)	1 (4.35%)	1 (3.70%)	1 (1.06%)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders													
Arthralgia	2 (25.00%)	2 (33.33%)	6 (26.09%)	6 (22.22%)	18 (19.15%)	18 (33.96%)	28 (51.85%)	19 (34.55%)	12 (26.67%)	9 (60.00%)	8 (53.33%)	17 (41.46%)	17 (43.59%)
Arthritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (3.70%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.13%)
Back pain	0 (0.00%)	0 (0.00%)	1 (4.35%)	6 (22.22%)	13 (13.83%)	6 (11.32%)	7 (12.96%)	12 (21.82%)	8 (17.78%)	1 (6.67%)	4 (26.67%)	4 (9.76%)	4 (10.26%)

Bone pain	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	1 (3.70 %)	3 (3.19 %)	0 (0.00%)	0 (0.00%)	3 (5.45%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Costochon dritis	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Flank pain	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	0 (0.00 %)	7 (7.45 %)	2 (3.77%)	0 (0.00%)	3 (5.45%)	0 (0.00%)	0 (0.00 %)	3 (20.0 0%)	0 (0.00 %)	1 (2.56 %)
Intervertebr al disc protrusion	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Joint swelling	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	5 (5.32 %)	1 (1.89%)	1 (1.85%)	3 (5.45%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Limb discomfort	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (2.13 %)	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Limb mass	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Muscle spasms	1 (12.5 0%)	1 (16.67 %)	5 (21.7 4%)	2 (7.41 %)	13 (13. 83%)	2 (3.77%)	3 (5.56%)	11 (20.0 0%)	2 (4.44%)	1 (6.67 %)	0 (0.00 %)	7 (17.0 7%)	5 (12.8 2%)
Muscle tightness	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Muscular weakness	1 (12.5 0%)	0 (0.00%)	2 (8.70 %)	3 (11.1 1%)	6 (6.38 %)	0 (0.00%)	7 (12.96 %)	7 (12.73 %)	4 (8.89%)	1 (6.67 %)	2 (13.3 3%)	2 (4.88 %)	3 (7.69 %)
Musculosk eletal chest pain	1 (12.5 0%)	1 (16.67 %)	2 (8.70 %)	1 (3.70 %)	3 (3.19 %)	1 (1.89%)	3 (5.56%)	2 (3.64%)	2 (4.44%)	0 (0.00 %)	0 (0.00 %)	2 (4.88 %)	4 (10.2 6%)
Musculosk eletal pain	1 (12.5 0%)	0 (0.00%)	2 (8.70 %)	2 (7.41 %)	8 (8.51 %)	6 (11.32 %)	4 (7.41%)	6 (10.91 %)	0 (0.00%)	1 (6.67 %)	1 (6.67 %)	4 (9.76 %)	2 (5.13 %)
Musculosk eletal stiffness	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	2 (7.41 %)	1 (1.06 %)	2 (3.77%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	1 (2.44 %)	2 (5.13 %)
Myalgia	2 (25.0 0%)	1 (16.67 %)	2 (8.70 %)	6 (22.2 2%)	17 (18. 09%)	12 (22.6 4%)	16 (29.6 3%)	12 (21.8 2%)	2 (4.44%)	1 (6.67 %)	3 (20.0 0%)	12 (29. 27%)	8 (20.5 1%)
Neck pain	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	2 (7.41 %)	5 (5.32 %)	5 (9.43%)	4 (7.41%)	7 (12.73 %)	2 (4.44%)	2 (13.3 3%)	0 (0.00 %)	2 (4.88 %)	2 (5.13 %)

Osteoarthritis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Pain in extremity	0 (0.00 %)	1 (16.67 %)	4 (17.39%)	5 (18.52%)	16 (17.02%)	11 (20.75%)	11 (20.37%)	13 (23.64%)	5 (11.11 %)	4 (26.67%)	2 (13.33%)	5 (12.20%)	4 (10.26%)
Pain in jaw	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	3 (3.19 %)	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	2 (5.13 %)
Plantar fasciitis	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Rhabdomyolysis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	1 (2.56 %)
Rheumatoid arthritis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	1 (2.56 %)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)													
Acrochordon	1 (12.50%)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	3 (3.19 %)	5 (9.43%)	3 (5.56%)	5 (9.09%)	0 (0.00%)	3 (20.00%)	3 (20.00%)	1 (2.44 %)	4 (10.26%)
Basal cell carcinoma	0 (0.00 %)	0 (0.00%)	3 (13.04%)	1 (3.70 %)	3 (3.19 %)	0 (0.00%)	3 (5.56%)	7 (12.73 %)	0 (0.00%)	2 (13.33%)	0 (0.00 %)	0 (0.00 %)	2 (5.13 %)
Cancer pain	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Fibrous histiocytoma	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	3 (5.45%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Haemangioma of skin	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	2 (2.13 %)	0 (0.00%)	3 (5.56%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Juvenile melanoma benign	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

Keratoacanthoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.06%)	3 (5.66%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lipoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.13%)
Melanocytic naevus	1 (12.50%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (1.06%)	3 (5.66%)	4 (7.41%)	5 (9.09%)	0 (0.00%)	1 (6.67%)	1 (6.67%)	0 (0.00%)	0 (0.00%)
Seborrhoeic keratosis	0 (0.00%)	0 (0.00%)	2 (8.70%)	2 (7.41%)	4 (4.26%)	5 (9.43%)	7 (12.96%)	6 (10.91%)	0 (0.00%)	4 (26.67%)	1 (6.67%)	4 (9.76%)	6 (15.38%)
Skin papilloma	3 (37.50%)	1 (16.67%)	1 (4.35%)	2 (7.41%)	2 (2.13%)	8 (15.09%)	4 (7.41%)	2 (3.64%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	1 (2.44%)	0 (0.00%)
Tumour pain	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (3.70%)	0 (0.00%)	1 (1.89%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	1 (2.56%)
Nervous system disorders													
Amnesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.85%)	3 (5.45%)	1 (2.22%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Aphasia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.85%)	0 (0.00%)	2 (4.44%)	1 (6.67%)	0 (0.00%)	1 (2.44%)	1 (2.56%)
Ataxia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.85%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	1 (2.56%)
Balance disorder	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (3.70%)	2 (2.13%)	1 (1.89%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Burning sensation	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.89%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Disturbance in attention	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	1 (1.06%)	0 (0.00%)	2 (3.70%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	1 (2.44%)	0 (0.00%)
Dizziness	1 (12.50%)	1 (16.67%)	4 (17.39%)	5 (18.52%)	24 (25.53%)	5 (9.43%)	12 (22.22%)	10 (18.18%)	7 (15.56%)	4 (26.67%)	1 (6.67%)	14 (34.15%)	4 (10.26%)
Dysarthria	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.06%)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)

Dysgeusia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	5 (5.32 %)	0 (0.00%)	5 (9.26%)	5 (9.09%)	1 (2.22%)	1 (6.67 %)	1 (6.67 %)	2 (4.88 %)	3 (7.69 %)
Dyskinesia	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Facial paralysis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	1 (6.67 %)	2 (4.88 %)	0 (0.00 %)
Headache	0 (0.00 %)	3 (50.00 %)	12 (52. 17%)	8 (29.6 3%)	32 (34. 04%)	17 (32.0 8%)	25 (46.3 0%)	18 (32.7 3%)	9 (20.00 %)	5 (33.3 3%)	4 (26.6 7%)	13 (31. 71%)	16 (41. 03%)
Hemiparesis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	1 (1.82%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Hyperaesthesia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	3 (3.19 %)	0 (0.00%)	0 (0.00%)	2 (3.64%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	2 (5.13 %)
Hypoaesthesia	1 (12.5 0%)	1 (16.67 %)	1 (4.35 %)	1 (3.70 %)	4 (4.26 %)	1 (1.89%)	3 (5.56%)	4 (7.27%)	1 (2.22%)	2 (13.3 3%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Lethargy	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	1 (1.89%)	1 (1.85%)	4 (7.27%)	1 (2.22%)	2 (13.3 3%)	0 (0.00 %)	2 (4.88 %)	0 (0.00 %)
Memory impairment	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	0 (0.00 %)	5 (5.32 %)	0 (0.00%)	2 (3.70%)	1 (1.82%)	2 (4.44%)	0 (0.00 %)	1 (6.67 %)	2 (4.88 %)	0 (0.00 %)
Motor dysfunction	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Neuralgia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	1 (2.22%)	1 (6.67 %)	1 (6.67 %)	0 (0.00 %)	1 (2.56 %)
Neuropathy peripheral	0 (0.00 %)	1 (16.67 %)	3 (13.0 4%)	1 (3.70 %)	6 (6.38 %)	4 (7.55%)	4 (7.41%)	4 (7.27%)	1 (2.22%)	2 (13.3 3%)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Noninfective encephalitis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	2 (3.70%)	0 (0.00%)	0 (0.00%)	2 (13.3 3%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Nystagmus	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Paraesthesia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	6 (6.38 %)	6 (11.32 %)	0 (0.00%)	4 (7.27%)	3 (6.67%)	2 (13.3 3%)	1 (6.67 %)	1 (2.44 %)	1 (2.56 %)

Partial seizures	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Presyncope	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (2.13 %)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	3 (7.32 %)	1 (2.56 %)
Sedation	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Seizure	1 (12.50%)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	4 (7.41%)	1 (1.82%)	1 (2.22%)	1 (6.67 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Sinus headache	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Somnolence	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	2 (2.13 %)	0 (0.00%)	0 (0.00%)	3 (5.45%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	1 (2.44 %)	0 (0.00 %)
Syncope	0 (0.00 %)	1 (16.67 %)	1 (4.35 %)	0 (0.00 %)	3 (3.19 %)	1 (1.89%)	3 (5.56%)	3 (5.45%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	4 (9.76 %)	3 (7.69 %)
Tremor	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	5 (5.32 %)	0 (0.00%)	1 (1.85%)	2 (3.64%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Psychiatric disorders													
Anxiety	0 (0.00 %)	1 (16.67 %)	5 (21.74%)	1 (3.70 %)	10 (10.64%)	5 (9.43%)	5 (9.26%)	4 (7.27%)	2 (4.44%)	0 (0.00 %)	2 (13.33%)	0 (0.00 %)	2 (5.13 %)
Confusional state	1 (12.50%)	1 (16.67 %)	2 (8.70 %)	0 (0.00 %)	5 (5.32 %)	1 (1.89%)	3 (5.56%)	6 (10.91 %)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	4 (9.76 %)	2 (5.13 %)
Depression	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	4 (14.81%)	6 (6.38 %)	2 (3.77%)	5 (9.26%)	4 (7.27%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	2 (4.88 %)	3 (7.69 %)
Emotional disorder	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Insomnia	1 (12.50%)	0 (0.00%)	1 (4.35 %)	6 (22.22%)	6 (6.38 %)	4 (7.55%)	7 (12.96 %)	10 (18.18%)	0 (0.00%)	2 (13.33%)	2 (13.33%)	3 (7.32 %)	4 (10.26%)
Irritability	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	3 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Mental status changes	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	2 (7.41 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

Mood altered	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Thinking abnormal	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Renal and urinary disorders													
Dysuria	1 (12.5 0%)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	4 (4.26 %)	0 (0.00%)	1 (1.85%)	4 (7.27%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	2 (4.88 %)	2 (5.13 %)
Haematuria	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	1 (1.89%)	1 (1.85%)	2 (3.64%)	0 (0.00%)	1 (6.67 %)	2 (13.3 3%)	1 (2.44 %)	4 (10.2 6%)
Micturition urgency	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (13.3 3%)	0 (0.00 %)	1 (2.44 %)	1 (2.56 %)
Nephrolithiasis	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Pollakiuria	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	2 (2.13 %)	4 (7.55%)	1 (1.85%)	1 (1.82%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	3 (7.32 %)	2 (5.13 %)
Polyuria	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	3 (5.45%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Renal injury	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Reproductive system and breast disorders													
Breast pain	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	2 (5.13 %)
Menorrhagia	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Menstruation irregular	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	1 (1.89%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Ovarian cyst	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	3 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)

Pelvic pain	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	2 (4.88 %)	0 (0.00 %)
Testicular pain	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	2 (7.41 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Respiratory, thoracic and mediastinal disorders													
Asthma	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Cough	3 (37.5 0%)	3 (50.00 %)	5 (21.7 4%)	9 (33.3 3%)	22 (23. 40%)	11 (20.7 5%)	10 (18.5 2%)	19 (34.5 5%)	5 (11.11 %)	5 (33.3 3%)	4 (26.6 7%)	14 (34. 15%)	12 (30. 77%)
Dysphonia	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	3 (5.45%)	1 (2.22%)	1 (6.67 %)	1 (6.67 %)	3 (7.32 %)	2 (5.13 %)
Dyspnoea	1 (12.5 0%)	1 (16.67 %)	5 (21.7 4%)	3 (11.1 1%)	12 (12. 77%)	4 (7.55%)	7 (12.96 %)	7 (12.73 %)	5 (11.11 %)	1 (6.67 %)	2 (13.3 3%)	5 (12.2 0%)	6 (15.3 8%)
Dyspnoea exertional	0 (0.00 %)	2 (33.33 %)	1 (4.35 %)	0 (0.00 %)	5 (5.32 %)	1 (1.89%)	0 (0.00%)	1 (1.82%)	2 (4.44%)	0 (0.00 %)	1 (6.67 %)	2 (4.88 %)	2 (5.13 %)
Epistaxis	1 (12.5 0%)	1 (16.67 %)	1 (4.35 %)	2 (7.41 %)	6 (6.38 %)	0 (0.00%)	2 (3.70%)	5 (9.09%)	1 (2.22%)	1 (6.67 %)	1 (6.67 %)	3 (7.32 %)	1 (2.56 %)
Haemoptysis	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Hiccups	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Hypoxia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Laryngeal haemorrhage	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Nasal congestion	1 (12.5 0%)	1 (16.67 %)	0 (0.00 %)	3 (11.1 1%)	7 (7.45 %)	1 (1.89%)	6 (11.11 %)	6 (10.91 %)	2 (4.44%)	1 (6.67 %)	1 (6.67 %)	4 (9.76 %)	2 (5.13 %)
Nasal dryness	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	1 (2.44 %)	0 (0.00 %)

Oropharyngeal pain	1 (12.50%)	0 (0.00%)	4 (17.39%)	1 (3.70%)	16 (17.02%)	0 (0.00%)	7 (12.96%)	9 (16.36%)	3 (6.67%)	1 (6.67%)	2 (13.33%)	3 (7.32%)	5 (12.82%)
Painful respiration	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Paranasal sinus hypersecretion	0 (0.00%)	1 (16.67%)	0 (0.00%)	2 (7.41%)	3 (3.19%)	0 (0.00%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	0 (0.00%)
Pleuritic pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)
Productive cough	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.19%)	2 (3.77%)	9 (16.67%)	3 (5.45%)	1 (2.22%)	2 (13.33%)	1 (6.67%)	2 (4.88%)	4 (10.26%)
Pulmonary congestion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)
Respiratory tract congestion	0 (0.00%)	0 (0.00%)	1 (4.35%)	1 (3.70%)	0 (0.00%)	1 (1.89%)	0 (0.00%)	3 (5.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	0 (0.00%)
Rhinitis allergic	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	2 (2.13%)	4 (7.55%)	4 (7.41%)	1 (1.82%)	1 (2.22%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	1 (2.56%)
Rhinorrhoea	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	4 (4.26%)	0 (0.00%)	1 (1.85%)	1 (1.82%)	1 (2.22%)	2 (13.33%)	0 (0.00%)	1 (2.44%)	2 (5.13%)
Sinus congestion	0 (0.00%)	0 (0.00%)	1 (4.35%)	2 (7.41%)	2 (2.13%)	1 (1.89%)	3 (5.56%)	4 (7.27%)	2 (4.44%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	1 (2.56%)
Sleep apnoea syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)
Throat irritation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	1 (2.44%)	0 (0.00%)
Upper-airway cough syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	0 (0.00%)	1 (1.89%)	3 (5.56%)	2 (3.64%)	2 (4.44%)	0 (0.00%)	1 (6.67%)	1 (2.44%)	0 (0.00%)
Wheezing	1 (12.50%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	2 (2.13%)	1 (1.89%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Skin and subcutaneous tissue disorders													
Acne	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	0 (0.00 %)	4 (4.26 %)	0 (0.00%)	3 (5.56%)	2 (3.64%)	1 (2.22%)	2 (13.3 3%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Actinic keratosis	0 (0.00 %)	1 (16.67 %)	4 (17.3 9%)	3 (11.1 1%)	11 (11. 70%)	6 (11.32 %)	6 (11.11 %)	12 (21.8 2%)	1 (2.22%)	0 (0.00 %)	2 (13.3 3%)	4 (9.76 %)	7 (17.9 5%)
Alopecia	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	2 (7.41 %)	8 (8.51 %)	19 (35.8 5%)	8 (14.81 %)	3 (5.45%)	5 (11.11 %)	4 (26.6 7%)	4 (26.6 7%)	5 (12.2 0%)	2 (5.13 %)
Blister	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Dermal cyst	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	2 (3.70%)	1 (1.82%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Dermatitis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	2 (7.41 %)	0 (0.00 %)	0 (0.00%)	2 (3.70%)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	2 (13.3 3%)	1 (2.44 %)	0 (0.00 %)
Dermatitis acneiform	2 (25.0 0%)	0 (0.00%)	3 (13.0 4%)	5 (18.5 2%)	12 (12. 77%)	2 (3.77%)	6 (11.11 %)	10 (18.1 8%)	0 (0.00%)	3 (20.0 0%)	4 (26.6 7%)	6 (14.6 3%)	6 (15.3 8%)
Dermatitis contact	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	1 (3.70 %)	2 (2.13 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Dry skin	1 (12.5 0%)	1 (16.67 %)	3 (13.0 4%)	2 (7.41 %)	5 (5.32 %)	2 (3.77%)	6 (11.11 %)	11 (20.0 0%)	3 (6.67%)	3 (20.0 0%)	1 (6.67 %)	6 (14.6 3%)	6 (15.3 8%)
Ecchymosis	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	2 (7.41 %)	0 (0.00 %)	0 (0.00%)	2 (3.70%)	2 (3.64%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Eczema	1 (12.5 0%)	0 (0.00%)	3 (13.0 4%)	1 (3.70 %)	3 (3.19 %)	0 (0.00%)	2 (3.70%)	4 (7.27%)	2 (4.44%)	2 (13.3 3%)	1 (6.67 %)	1 (2.44 %)	2 (5.13 %)
Eczema asteatotic	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)
Erythema	2 (25.0 0%)	1 (16.67 %)	2 (8.70 %)	7 (25.9 3%)	5 (5.32 %)	1 (1.89%)	5 (9.26%)	10 (18.1 8%)	2 (4.44%)	1 (6.67 %)	1 (6.67 %)	1 (2.44 %)	1 (2.56 %)
Erythema multiforme	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.67%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

Erythema nodosum	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	3 (3.19 %)	0 (0.00%)	1 (1.85%)	3 (5.45%)	1 (2.22%)	3 (20.0 0%)	0 (0.00 %)	2 (4.88 %)	2 (5.13 %)
Hair texture abnormal	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	4 (7.55%)	1 (1.85%)	0 (0.00%)	3 (6.67%)	1 (6.67 %)	1 (6.67 %)	0 (0.00 %)	1 (2.56 %)
Hyperhidrosis	0 (0.00 %)	1 (16.67 %)	4 (17.3 9%)	1 (3.70 %)	10 (10. 64%)	1 (1.89%)	5 (9.26%)	6 (10.91 %)	1 (2.22%)	2 (13.3 3%)	0 (0.00 %)	6 (14.6 3%)	4 (10.2 6%)
Hyperkeratosis	1 (12.5 0%)	0 (0.00%)	1 (4.35 %)	2 (7.41 %)	4 (4.26 %)	15 (28.3 0%)	5 (9.26%)	9 (16.36 %)	1 (2.22%)	3 (20.0 0%)	2 (13.3 3%)	4 (9.76 %)	1 (2.56 %)
Keratosis pilaris	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	2 (3.77%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (13.3 3%)	0 (0.00 %)	0 (0.00 %)	1 (2.56 %)
Macule	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	2 (2.13 %)	0 (0.00%)	2 (3.70%)	1 (1.82%)	1 (2.22%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Night sweats	1 (12.5 0%)	1 (16.67 %)	4 (17.3 9%)	7 (25.9 3%)	16 (17. 02%)	3 (5.66%)	11 (20.3 7%)	15 (27.2 7%)	3 (6.67%)	1 (6.67 %)	3 (20.0 0%)	8 (19.5 1%)	9 (23.0 8%)
Nodular rash	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	1 (3.70 %)	2 (2.13 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Onychoclasis	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	3 (3.19 %)	9 (16.98 %)	4 (7.41%)	4 (7.27%)	2 (4.44%)	0 (0.00 %)	2 (13.3 3%)	2 (4.88 %)	3 (7.69 %)
Papule	1 (12.5 0%)	0 (0.00%)	2 (8.70 %)	0 (0.00 %)	5 (5.32 %)	1 (1.89%)	2 (3.70%)	2 (3.64%)	0 (0.00%)	1 (6.67 %)	1 (6.67 %)	0 (0.00 %)	1 (2.56 %)
Petechiae	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	2 (3.64%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Photodermatosis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	2 (2.13 %)	0 (0.00%)	0 (0.00%)	3 (5.45%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Photosensitivity reaction	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	2 (2.13 %)	3 (5.66%)	3 (5.56%)	2 (3.64%)	1 (2.22%)	0 (0.00 %)	0 (0.00 %)	2 (4.88 %)	2 (5.13 %)

Pigmentation disorder	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pruritus	2 (25.00%)	1 (16.67%)	3 (13.04%)	1 (3.70%)	4 (4.26%)	8 (15.09%)	8 (14.81%)	8 (14.55%)	3 (6.67%)	3 (20.00%)	2 (13.33%)	4 (9.76%)	7 (17.95%)
Pruritus generalised	0 (0.00%)	0 (0.00%)	3 (13.04%)	4 (14.81%)	4 (4.26%)	7 (13.21%)	4 (7.41%)	2 (3.64%)	4 (8.89%)	2 (13.33%)	4 (26.67%)	6 (14.63%)	4 (10.26%)
Psoriasis	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (1.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (2.44%)	0 (0.00%)
Rash	6 (75.00%)	2 (33.33%)	6 (26.09%)	9 (33.33%)	21 (22.34%)	19 (35.85%)	13 (24.07%)	18 (32.73%)	8 (17.78%)	4 (26.67%)	6 (40.00%)	14 (34.15%)	18 (46.15%)
Rash erythematous	0 (0.00%)	1 (16.67%)	3 (13.04%)	1 (3.70%)	1 (1.06%)	0 (0.00%)	5 (9.26%)	1 (1.82%)	2 (4.44%)	1 (6.67%)	1 (6.67%)	2 (4.88%)	2 (5.13%)
Rash generalised	1 (12.50%)	2 (33.33%)	4 (17.39%)	0 (0.00%)	5 (5.32%)	3 (5.66%)	2 (3.70%)	6 (10.91%)	1 (2.22%)	1 (6.67%)	0 (0.00%)	1 (2.44%)	4 (10.26%)
Rash macular	0 (0.00%)	0 (0.00%)	3 (13.04%)	3 (11.11%)	2 (2.13%)	2 (3.77%)	5 (9.26%)	2 (3.64%)	0 (0.00%)	4 (26.67%)	0 (0.00%)	3 (7.32%)	3 (7.69%)
Rash maculo-papular	0 (0.00%)	0 (0.00%)	1 (4.35%)	2 (7.41%)	5 (5.32%)	3 (5.66%)	5 (9.26%)	4 (7.27%)	2 (4.44%)	3 (20.00%)	1 (6.67%)	5 (12.20%)	7 (17.95%)
Rash papular	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (3.77%)	3 (5.56%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	1 (6.67%)	2 (4.88%)	1 (2.56%)
Rash pruritic	0 (0.00%)	0 (0.00%)	2 (8.70%)	0 (0.00%)	4 (4.26%)	0 (0.00%)	3 (5.56%)	3 (5.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (7.69%)
Skin exfoliation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.89%)	1 (1.85%)	2 (3.64%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	0 (0.00%)	0 (0.00%)
Skin haemorrhage	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin hyperpigmentation	0 (0.00%)	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (1.06%)	2 (3.77%)	0 (0.00%)	1 (1.82%)	0 (0.00%)	1 (6.67%)	1 (6.67%)	0 (0.00%)	0 (0.00%)

Skin hypertrophy	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	2 (3.77%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Skin lesion	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	5 (5.32 %)	1 (1.89%)	2 (3.70%)	1 (1.82%)	0 (0.00%)	1 (6.67 %)	2 (13.3 3%)	2 (4.88 %)	4 (10.2 6%)
Solar lentigo	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	3 (5.56%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Swelling face	1 (12.5 0%)	0 (0.00%)	0 (0.00 %)	1 (3.70 %)	0 (0.00 %)	0 (0.00%)	1 (1.85%)	1 (1.82%)	0 (0.00%)	1 (6.67 %)	1 (6.67 %)	1 (2.44 %)	1 (2.56 %)
Transient acantholytic dermatosis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	1 (1.89%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	1 (2.44 %)	0 (0.00 %)
Urticaria	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	0 (0.00%)	0 (0.00%)	3 (5.45%)	0 (0.00%)	1 (6.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Vitiligo	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	2 (3.77%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (2.44 %)	3 (7.69 %)
Vascular disorders													
Flushing	1 (12.5 0%)	0 (0.00%)	1 (4.35 %)	0 (0.00 %)	7 (7.45 %)	4 (7.55%)	6 (11.11 %)	1 (1.82%)	1 (2.22%)	0 (0.00 %)	1 (6.67 %)	1 (2.44 %)	4 (10.2 6%)
Hot flush	1 (12.5 0%)	0 (0.00%)	2 (8.70 %)	0 (0.00 %)	2 (2.13 %)	1 (1.89%)	5 (9.26%)	4 (7.27%)	0 (0.00%)	2 (13.3 3%)	0 (0.00 %)	1 (2.44 %)	5 (12.8 2%)
Hypertension	0 (0.00 %)	0 (0.00%)	2 (8.70 %)	3 (11.1 1%)	6 (6.38 %)	2 (3.77%)	4 (7.41%)	9 (16.36 %)	4 (8.89%)	0 (0.00 %)	0 (0.00 %)	7 (17.0 7%)	7 (17.9 5%)
Hypotension	1 (12.5 0%)	1 (16.67 %)	3 (13.0 4%)	2 (7.41 %)	9 (9.57 %)	0 (0.00%)	2 (3.70%)	4 (7.27%)	0 (0.00%)	2 (13.3 3%)	0 (0.00 %)	3 (7.32 %)	5 (12.8 2%)
Labile blood pressure	0 (0.00 %)	1 (16.67 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)
Lymphoedema	0 (0.00 %)	0 (0.00%)	1 (4.35 %)	1 (3.70 %)	1 (1.06 %)	0 (0.00%)	1 (1.85%)	4 (7.27%)	1 (2.22%)	1 (6.67 %)	2 (13.3 3%)	2 (4.88 %)	3 (7.69 %)

Thrombophlebitis superficial	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00 %)	1 (6.67 %)	1 (2.44 %)	0 (0.00 %)
Vasculitis	0 (0.00 %)	0 (0.00%)	0 (0.00 %)	0 (0.00 %)	1 (1.06 %)	1 (1.89%)	1 (1.85%)	0 (0.00%)	1 (2.22%)	0 (0.00 %)	2 (13.3 3%)	1 (2.44 %)	0 (0.00 %)

Other Relevant Findings

None

Conclusion:

Safety

The combination of dabrafenib and trametinib exhibited an acceptable safety profile with toxicities manageable with appropriate intervention. With the additional follow-up since the previous CSRs, the overall safety profile of the combination is consistent with the previously reported safety profile.

Efficacy

The combination of dabrafenib and trametinib demonstrated superior efficacy over the dabrafenib monotherapy in subjects with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Long-term survival is achievable with dabrafenib + trametinib in patients with BRAF V600–mutant metastatic melanoma, particularly those with favorable baseline factors.

Overall

Dabrafenib at 150 mg twice daily in combination with trametinib 2 mg once daily provided meaningful clinical benefit with a favorable benefit/risk ratio for subjects with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Date of Clinical Trial Report

17-Oct-2018