Protocol Registration Receipt
04/24/2014

Grantor: CDER IND/IDE Number: 105,032 Serial Number:

A Study of GSK2118436 in BRAF Mutant Metastatic Melanoma to the Brain (Break MB)

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01266967

Purpose

This study is designed to assess the efficacy, pharmacokinetics, safety, and tolerability of an oral, twice daily dose of 150 mg GSK2118436 administered to subjects with BRAF V600E or V600K mutation-positive metastatic melanoma to the brain. Subjects in Cohort A will not have received any local brain therapy, and subjects in Cohort B will have received prior local therapy for brain metastases. Subjects will continue on treatment until disease progression, death, or unacceptable adverse event.

Condition	Intervention	Phase
Melanoma and Brain Metastases	Drug: GSK2118436	Phase 2

Study Type: Interventional
Study Design: Treatment, Single Group Assignment, Open Label, Non-Randomized
Official Title: BRF113929: An Open-Label, Two-Cohort, Multicentre Study of GSK2118436 as a Single Agent in Treatment Naïve and Previously Treated Subjects With BRAF Mutation-Positive Metastatic Melanoma to the Brain

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Number of Participants With BRAF V600E Mutation-positive Melanoma With Overall Intracranial Response (OIR), as Assessed by the Investigator [Time Frame: From the time of the Baseline assessment until disease progression or end of study treatment (average of 18.3 weeks)] [Designated as safety issue: No]

  OIR is defined as the number of participants whose intracranial response was a confirmed complete response (CR) or partial response (PR) assessed by investigators using modified Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. CR is defined as disappearance of all lesions. PR is defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters (e.g., percent change from Baseline). For the primary analysis, OIR was measured when all participants in both treatment arms had two post-Baseline disease assessments. Participants who had an intracranial response of not evaluable or a missing response were treated as non-responders. Confirmation assessments were to be performed no less than 4 weeks after the criteria for response were initially met and may have been performed at the next protocol scheduled assessment.

Secondary Outcome Measures:

- Number of Participants With V600E Mutation-positive Melanoma With a Best Overall Response (OR) of CR or PR, as Assessed by the Investigator [Time Frame: From the time of the Baseline assessment until disease progression or end of study treatment (average of 24 weeks)] [Designated as safety issue: No]

  OR is defined as the number of participants achieving either a CR (the disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]) per modified RECIST, version 1.1. To determine the OR, the extracranial response was combined with the intracranial response. Confirmation assessments were to be performed no less than 4 weeks after the criteria for response were initially met and may have been performed at the next protocol-scheduled assessment. Participants who had an overall response of not evaluable or a missing response were treated as non-responders.
- Number of Participants With V600K Mutation-positive Melanoma With a Best Overall Response (OR) of CR or PR, as Assessed by the Investigator [Time Frame: From the time of the Baseline assessment until disease progression or end of study treatment (average of 17 weeks)] [Designated as safety issue: No]

  OR is defined as the number of participants achieving either a CR (the disappearance of all target lesions) or PR (at least a 30% decrease in the sum of

the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]) per modified RECIST, version 1.1. To determine the OR, the extracranial response was combined with the intracranial response. Confirmation assessments were to be performed no less than 4 weeks after the criteria for response were initially met and may have been performed at the next protocol-scheduled assessment. Participants who had an overall response of not evaluable or a missing response were treated as non-responders.

- Number of Participants With V600K Mutation-positive Melanoma With OIR, as Assessed by the Investigator [Time Frame: From the time of the Baseline assessment until disease progression or end of study treatment (average of 16 weeks)] [Designated as safety issue: No]

  OIR is defined as the number of participants whose intracranial response was a confirmed complete response (CR) or partial response (PF) assessed by investigators using modified Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. CR is defined as disappearance of all target lesions. PR is defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters (e.g., percent change from Baseline). For the primary analysis, OIR was measured when all participants in both treatment arms had two post-Baseline disease assessments. Participants who had an intracranial response of not evaluable or a missing response were treated as non-responders. Confirmation assessments were to be performed no less than 4 weeks after the criteria for response were initially met and may have been performed at the next protocol scheduled assessment.

- Duration of Intracranial Response for the Subset of V600E Mutation-positive Participants [Time Frame: Time from the first documented evidence of intracranial CR or PR until the time of the first documented intracranial disease progression or death due to any cause (average of 27 weeks)] [Designated as safety issue: No]

  Duration of Intracranial Response is defined as the time from the first documented evidence of intracranial CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]) until the time of the first documented intracranial disease progression (PD) or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm).

- Duration of Intracranial Response for the Subset of V600K Mutation-positive Participants [Time Frame: Time from the first documented evidence of intracranial CR or PR until the time of the first documented intracranial disease progression or death due to any cause (average of 31 weeks)] [Designated as safety issue: No]

  Duration of Intracranial Response is defined as the time from the first documented evidence of intracranial CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]) until the time of the first documented intracranial disease progression (PD) or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm).

- Duration of Overall Response for the Subset of V600E Mutation-positive Participants [Time Frame: Time from the first documented evidence of CR or PR until the time of the first documented disease progression or death due to any cause (average of 28 weeks)] [Designated as safety issue: No]

  Duration of Overall Response is defined as the time from the first documented evidence of overall CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from

Baseline]) until the time of the first documented disease progression (PD) or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm).

- Duration of Overall Response for the Subset of V600K Mutation-positive Participants [Time Frame: Time from the first documented evidence of CR or PR until the time of the first documented disease progression or death due to any cause (average of 31 weeks)] [Designated as safety issue: No]

  Duration of Overall Response is defined as the time from the first documented evidence of overall CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]) until the time of the first documented disease progression (PD) or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm).

- Progression-free Survival in V600E Mutation-positive Participants [Time Frame: Time from the first dose of study medication to the earliest of death or progression (average of 23 weeks)] [Designated as safety issue: No]

  PFS is defined as the time from the first dose of study medication to the earliest of death or progression (at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm). If a participant received subsequent anti-cancer therapy prior to the date of documented PD/death, the participant was censored at the last adequate assessment and the visit level response was CR (disappearance of all target lesions), PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters [e.g., percent change from Baseline]), or stable disease (SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

- Progression-free Survival in V600K Mutation-positive Participants [Time Frame: Time from the first dose of study medication to the earliest of death or progression (average of 17 weeks)] [Designated as safety issue: No]

  PFS is defined as the time from the first dose of study medication to the earliest of death or progression (at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm). If a participant received subsequent anti-cancer therapy prior to the date of documented PD/death, the participant was censored at the last adequate assessment and the visit level response was CR (disappearance of all target lesions), PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters [e.g., percent change from Baseline]), or stable disease (SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

- Overall Survival of V600E Mutation-positive Participants [Time Frame: Time from the first dose of study medication until death due to any cause (average of 35 weeks)] [Designated as safety issue: No]

  Overall survival (OS) is defined as the time from the first dose of study medication until death due to any cause. OS was censored using the date of last known contact for those participants who were alive at the time of analysis.

- Overall Survival in V600K Mutation-positive Participants [Time Frame: Time from the first dose of study medication until death due to any cause (average

of 26 weeks)] [Designated as safety issue: No]

Overall survival (OS) is defined as the time from the first dose of study medication until death due to any cause. OS was censored using the date of last known contact for those participants who were alive at the time of analysis.

- Number of Participants With Any Adverse Event (AE) or Serious Adverse Event (SAE) [Time Frame: From Screening until the conclusion of the study (up to 103 weeks)] [Designated as safety issue: No]

  An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury.
- Number of Participants With a Worst-case on Therapy Change to Grade 3 and Grade 4, or With Any Grade Increase (AGI), From Baseline Grade for Clinical Chemistry Parameters [Time Frame: From Screening until the conclusion of the study (up to 103 weeks)] [Designated as safety issue: No]

  Clinical chemistry data were summarized at each scheduled assessment according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.0). Grade refers to the severity of the toxicity. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each toxicity based on this general guideline: Grade (G) 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, life threatening; Grade 5, death related to toxicity. Blood sample was collected for the assessment of glucose, potassium, magnesium, sodium, phosphorus, potassium. aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatinine, total bilirubin, albumin, amylase, cholesterol, creatine kinase, gamma glutamyl transferase (GGT), lipase, blood pH, and triglycerides.
- Number of Participants With the Indicated Hepatobiliary Laboratory Abnormalities [Time Frame: From Screening until the conclusion of the study (up to 103 weeks)] [Designated as safety issue: No]

  Blood samples were collected for the assessment of hepatobiliary parameters. ALT=alanine aminotranserase; AST=aspartate aminotransferase; ALP=alkaline phosphatase; BIL=total bilirubin; INR=international normalized ratio; ULN=upper limit of normal. Hepato-cellular injury is defined as (ALT/ULN)/(ALP/ULN) >=5.
- Number of Participants With a Worst-case on Therapy Change to Grade 3 and Grade 4, or With Any Grade Increase (AGI), From Baseline Grade for Hematology Parameters [Time Frame: From Screening until the conclusion of the study (up to 103 weeks)] [Designated as safety issue: No]

  Hematology data were summarized at each scheduled assessment according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.0). Grade refers to the severity of the toxicity. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each toxicity based on this general guideline: Grade 1, mild; Grade 2, moderate; Grade 3, severe, Grade 4, life threatening, Grade 5, death related to toxicity. Blood sample was collected for the assessment of hemoglobin, white blood cells, and platelet count.
- Mean Blood Pressure at Baseline and Weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36 [Time Frame: Baseline; Weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36] [Designated as safety issue: No]

  Systolic and diastolic blood pressure were measured for all treated participants.
- Number of Participants With a Worst-case On-therapy Increase From Baseline in Bazett's QTc Reading in the 12-lead Electrocardiogram (ECG) [Time Frame: Baseline; Weeks 4, 12, 20, 28, 40, 52, and 64] [Designated as safety issue: No]

  An increase in the QTc interval corrected using Bazett's formula (Bazett's QTc) was recorded for all treated participants. Grade 1 (450-480 milliseconds

[msec]), Grade 2 (481-500 msec), Grade 3/4 (>=501 msec). An increase is defined as an increase in CTCAE grade relative to Baseline grade.

- Number of Participants With Abnormal Echocardiograms (ECHO) at Weeks 4 and 12 [Time Frame: Weeks (W) 4 and 12] [Designated as safety issue: No]
  Echocardiograms (ECHO) were measured for all treated participants. An echocardiogram test gives information about the structure and function of the heart. LLN=lower limit of normal (determined by the institution).
- Median Concentrations of GSK2118436 and Its Metabolites Including GSK2285403, GSK2298683, and GSK2167542 [Time Frame: Week 4 (pre-dose and 1-3 hours post-dose) and Weeks 8, 16, 24, and 32 (either pre-dose in the morning or in the afternoon at 4-8 hours post-dose)] [Designated as safety issue: No]
  Summary statistics were calculated for each time point by cohort. The population pharmacokinetics were determined using a non-linear mixed effects modeling approach after pooling the data with other studies. These results are reported separately.
- Composite of Pharmacokinetic Parameters of GSK2118436 in a Subset of Participants Receiving Dexamethasone [Time Frame: Day 15] [Designated as safety issue: No]
  This outcome measure could not be analyzed because too few participants participated in the dexamethasone study.
- Number of Response Genetics Incorporated (RGI) Investigational Use Only (IUO) Assay Mutation Positive Participants and THxID BRAF Assay Mutation Positive Participants With the Indicated Best Intracranial Response [Time Frame: Screening] [Designated as safety issue: No]
  The BRAF screening assay determines the specific BRAF mutational status (V600 E and K) in participants with metastatic melanoma who may benefit from treatment with GSK2118436. Per RECIST, version 1.1, CR is defined as the disappearance of all lesions. PR is defined as a >=30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline (BL) sum of the diameters (e.g., percent change from BL). Stable disease is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD). PD is defined as a >=20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir [smallest sum of diameters recorded since treatment start]). In addition, the sum must have an absolute increase from nadir of 5 millimeters. Not evaluable: cannot be classified by a preceding definition.

Enrollment: 172
Study Start Date: February 2011
Study Completion Date: November 2012
Primary Completion Date: November 2011

Arms	Assigned Interventions
Experimental: Single Arm Single arm with 2 cohorts; Cohort A no previous brain therapy and Cohort B previous brain therapy	Drug: GSK2118436 Subjects in this study receive 150 mg of GSK2118436 twice daily and continue on treatment until disease progression, death, or unacceptable adverse event. Other Names: Dabrafenib

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both

Inclusion Criteria:

- Cohort A:
- No prior local therapy for brain metastases.
- Subjects who are receiving concomitant corticosteroids must be on a stable or decreasing dose for at least 3 weeks prior to first dose of study treatment.
- No prophylactic or preventive anti-epileptic therapy. Exception: anti-epileptic therapy indicated in order to prevent neurologic symptoms caused by a pre-existing condition and not related to brain metastasis is allowed.
- Cohort B:
- Subjects must have received at least one local therapy for brain metastases including but not restricted to brain surgery, Whole Brain Radiotherapy or Stereotactic Radiosurgery (e.g. gamma knife, linear-accelerated-based radiosurgery, charged particles, and CyberKnife). Multiple local therapies or combinations of local therapies are allowed. For subjects receiving local therapy to all brain lesions (including WBRT), progression of pre-existing lesions based on RECIST 1.1 (> 20% increase in longest diameter on baseline scan) or new measurable lesions are required. For subjects receiving local therapy for some but not all lesions, disease progression based on RECIST 1.1 is not required as long as there are remaining brain lesions that are measurable and not previously treated.
- Subjects who are receiving concomitant corticosteroids must be on a stable or decreasing dose for at least 2 weeks prior to first dose of study treatment.
- Prophylactic or preventive anti-epileptic therapy is allowed.
- General:
- Must sign written informed consent.
- Must be at least 18 years of age.
- Histologically confirmed metastatic melanoma (Stage IV), carrying BRAF V600E- or V600K-mutation.
- Up to two previous treatment regimens for extracranial metastatic melanoma including chemo-, cytokine-, immuno-, biological- and vaccine-therapy.
- At least one measurable intracranial target lesion for which all of the following criteria have to be met:
- previously untreated or progressive according to RECIST 1.1 (greater than or equal to 20% increase in longest diameter on baseline scan) after previous local therapy
- immediate local therapy clinically not indicated or patient is not a suitable candidate to receive immediate local therapy
- largest diameter of greater than or equal to 0.5cm but less than or equal to 4 cm as determined by contrast-enhanced MRI
- for target lesions (for definition see Section 6.1.1) with diameter of greater than 0.5 cm but less than or equal to 1 cm documented measurement by a neuroradiologist is required.
- for all lesions with diameter of greater than or equal to 3 cm but less than or equal to 4 cm documented measurement by a neuroradiologist is required.
- Time interval between last day of previous anti-tumour systemic treatment and first dose of GSK2118436:

- 14 days elapsed from last treatment with surgery, SRS or gamma knife
- 28 days elapsed from last treatment with WBRT
- Greater than or equal to 28 days or five half-lives (whichever is longer) have elapsed from last dose of approved or investigational chemo-, cytokine-, immune-, biological-, or vaccine-therapy.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1.
- Adequate organ function.
- Women with child-bearing potential and men with reproductive potential must be willing to practice acceptable methods of birth control during the study.
- Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to the first dose of study treatment.

Exclusion Criteria:

- Neurological symptoms related to brain metastasis.
- Previous treatment with a BRAF or MEK inhibitor.
- Current or expected use of a prohibited medication during treatment with GSK2118436.
- Presence of leptomeningeal disease or primary dural metastases.
- Known allergies against contrast agents required for magnetic resonance imaging (MRI) of intracranial lesions.
- Current use of therapeutic warfarin. NOTE: Low molecular weight heparin and prophylactic low-dose warfarin are permitted.
- Unresolved toxicity of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI v4.0) Grade 2 or higher from previous anti-cancer therapy, except alopecia.
- Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption of drugs.
- A history of known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection.
- Acute infection requiring intravenous antibiotics
- History of another malignancy. Exception: (a) Subjects who have been disease-free for 5 years, (b) a history of completely resected non-melanoma skin cancer, (c) successfully treated in situ carcinoma, (d) CLL in stable remission, or (e) indolent prostate cancer requiring no or only anti-hormonal therapy with histologically confirmed tumour lesions that can be clearly differentiated from melanoma target and non-target lesions are eligible.
- Certain cardiac abnormalities.

Contacts and Locations

Locations

United States, California

GSK Investigational Site

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San Francisco, California, United States, 94115

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Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Publications:

G.V.Long, U.Trefzer, M.A.Davies, R.Kefford, P.A.Ascierto, P.B.Chapman, I.Puzanov, A.Hauschild, C.Robert, A.Algazi, L.Mortier, H.Tawbi, T.Wilhelm, L.Zimmer, J.Switzky, S.Swann, A-M.Martin, M.Guckert, V.Goodman, M.Streit, J.M.Kirkwood, D.Schadendorf. Dabrafenib is effective therapy for

BRAFV600E/K mutation-positive melanoma metastatic to the brain. [Lancet Oncol]. 2012;13(11):1087-95.

Responsible Party: GlaxoSmithKline
Study ID Numbers: 113929
Health Authority: Italy: Agenzia Italiana del Farmaco
United States: Food and Drug Administration
Germany: Bundesinstitut für Arzneimittel und Medizinprodukte
France: Agence Française de Sécurité Sanitaire des Produits de Santé
European Union: European Medicines Agency
Canada: Health Canada
Australia: Therapeutic Goods Administration

Study Results

Participant Flow

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 milligram (mg) capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Overall Study

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Started	89	83
Completed	0	0
Not Completed	89	83
Death	69	61
Study Closed/Terminated	15	17
Lost to Follow-up	2	1
Physician Decision	0	1
Withdrawal by Subject	3	3

Baseline Characteristics

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 milligram (mg) capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Baseline Measures

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy	Total
Number of Participants	89	83	172
Age, Continuous [units: Years] Mean (Standard Deviation)	52.3 (13.35)	52.7 (13.83)	52.5 (13.55)
Gender, Male/Female [units: Participants]			
Female	24	28	52
Male	65	55	120
Race/Ethnicity, Customized [1] [units: participants]			
White	89	82	171
Not reported	0	1	1

[1] Race was not reported for one participant who recevied prior local therapy.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants With BRAF V600E Mutation-positive Melanoma With Overall Intracranial Response (OIR), as Assessed by the Investigator
Measure Description	OIR is defined as the number of participants whose intracranial response was a confirmed complete response (CR) or partial response

	(PR) assessed by investigators using modified Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. CR is defined as disappearance of all lesions. PR is defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters (e.g., percent change from Baseline). For the primary analysis, OIR was measured when all participants in both treatment arms had two post-Baseline disease assessments. Participants who had an intracranial response of not evaluable or a missing response were treated as non-responders. Confirmation assessments were to be performed no less than 4 weeks after the criteria for response were initially met and may have been performed at the next protocol scheduled assessment.
Time Frame	From the time of the Baseline assessment until disease progression or end of study treatment (average of 18.3 weeks)
Safety Issue?	No

Analysis Population Description

V600E Population: all participants with BRAF V600E mutation-positive melanoma who received at least one dose of study treatment

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	74	65
Number of Participants With BRAF V600E Mutation-positive Melanoma With Overall Intracranial Response (OIR), as Assessed by the Investigator [units: participants]		
CR	4	1
PR	26	23

Statistical Analysis 1 for Number of Participants With BRAF V600E Mutation-positive Melanoma With Overall Intracranial Response (OIR), as Assessed by the Investigator

Groups	GSK2118436 150 mg: No Prior Local Therapy
Method	Other [Exact Test]
P-Value	<0.0001
Other Estimated Parameter [percentage of participants]	41
95% Confidence Interval	29.3 to 52.6

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

Other relevant estimation information:

The estimated value represents the percentage of participants with OIR.

Statistical Analysis 2 for Number of Participants With BRAF V600E Mutation-positive Melanoma With Overall Intracranial Response (OIR), as Assessed by the Investigator

Groups	GSK2118436 150 mg: Prior Local Therapy
Method	Other [Exact Test]
P-Value	<0.0001
Other Estimated Parameter [percentage of participants]	37
95% Confidence Interval	25.3 to 49.8

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

Other relevant estimation information:

The estimated value represents the percentage of participants with OIR.

2. Secondary Outcome Measure:

Measure Title	Number of Participants With V600E Mutation-positive Melanoma With a Best Overall Response (OR) of CR or PR, as Assessed by the Investigator
Measure Description	OR is defined as the number of participants achieving either a CR (the

	disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]) per modified RECIST, version 1.1. To determine the OR, the extracranial response was combined with the intracranial response. Confirmation assessments were to be performed no less than 4 weeks after the criteria for response were initially met and may have been performed at the next protocol-scheduled assessment. Participants who had an overall response of not evaluable or a missing response were treated as non-responders.
Time Frame	From the time of the Baseline assessment until disease progression or end of study treatment (average of 24 weeks)
Safety Issue?	No

Analysis Population Description

V600E Population

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	74	65
Number of Participants With V600E Mutation-positive Melanoma With a Best Overall Response (OR) of CR or PR, as Assessed by the Investigator [units: participants]		
CR	2	0
PR	28	23

3. Secondary Outcome Measure:

Measure Title	Number of Participants With V600K Mutation-positive Melanoma With a Best Overall Response (OR) of CR or PR, as Assessed by the Investigator
Measure Description	OR is defined as the number of participants achieving either a CR (the disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]) per modified RECIST, version 1.1. To determine the OR, the extracranial response was combined with the intracranial response. Confirmation assessments were to be performed no less than 4 weeks after the criteria for response were initially met and may have been performed at the next protocol-scheduled assessment. Participants who had an overall response of not evaluable or a missing response were treated as non-responders.
Time Frame	From the time of the Baseline assessment until disease progression or

	end of study treatment (average of 17 weeks)
Safety Issue?	No

Analysis Population Description

V600K Population: all participants with BRAF V600K mutation-positive melanoma who received at least one dose of study treatment

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	15	18
Number of Participants With V600K Mutation-positive Melanoma With a Best Overall Response (OR) of CR or PR, as Assessed by the Investigator [units: participants]		
CR	0	0

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
PR	0	5

4. Secondary Outcome Measure:

Measure Title	Number of Participants With V600K Mutation-positive Melanoma With OIR, as Assessed by the Investigator
Measure Description	OIR is defined as the number of participants whose intracranial response was a confirmed complete response (CR) or partial response (PF) assessed by investigators using modified Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. CR is defined as disappearance of all target lesions. PR is defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters (e.g., percent change from Baseline). For the primary analysis, OIR was measured when all participants in both treatment arms had two post-Baseline disease assessments. Participants who had an intracranial response of not evaluable or a missing response were treated as non-responders. Confirmation assessments were to be performed no less than 4 weeks after the criteria for response were initially met and may have been performed at the next protocol scheduled assessment.
Time Frame	From the time of the Baseline assessment until disease progression or end of study treatment (average of 16 weeks)
Safety Issue?	No

Analysis Population Description

V600K Population

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	15	18
Number of Participants With V600K Mutation-positive Melanoma With OIR, as Assessed by the Investigator [units: participants]		
CR	0	0
PR	1	4

5. Secondary Outcome Measure:

Measure Title	Duration of Intracranial Response for the Subset of V600E Mutation-positive Participants

Measure Description	Duration of Intracranial Response is defined as the time from the first documented evidence of intracranial CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]) until the time of the first documented intracranial disease progression (PD) or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm).
Time Frame	Time from the first documented evidence of intracranial CR or PR until the time of the first documented intracranial disease progression or death due to any cause (average of 27 weeks)
Safety Issue?	No

Analysis Population Description

V600E Population. Only the subset of participants who had a complete or partial intracranial response was included in this analysis.

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	30	24
Duration of Intracranial Response for the Subset of V600E Mutation-positive Participants [units: weeks] Median (95% Confidence Interval)	24.1 (16.1 to 30.3)	28.1 (24.1 to 44.1)

6. Secondary Outcome Measure:

Measure Title	Duration of Intracranial Response for the Subset of V600K Mutation-positive Participants
Measure Description	Duration of Intracranial Response is defined as the time from the first documented evidence of intracranial CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]) until the time of the first documented intracranial disease progression (PD) or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm).
Time Frame	Time from the first documented evidence of intracranial CR or PR until the time of the first documented intracranial disease progression or death due to any cause (average of 31 weeks)

Safety Issue?	No

Analysis Population Description

V600K Population. Only the subset of participants who had a complete or partial intracranial response was included in this analysis.

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	1	4
Duration of Intracranial Response for the Subset of V600K Mutation-positive Participants [units: weeks] Median (95% Confidence Interval)	12.4 (NA to NA) [1]	NA (16.6 to NA) [2]

[1] The confidence interval cannot be calculated because too few participants were V600K mutation positive.

[2] The median and the upper limit of the confidence interval cannot be calculated because too few V600K participants had intracranial responses.

7. Secondary Outcome Measure:

Measure Title	Duration of Overall Response for the Subset of V600E Mutation-positive Participants
Measure Description	Duration of Overall Response is defined as the time from the first documented evidence of overall CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]) until the time of the first documented disease progression (PD) or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm).
Time Frame	Time from the first documented evidence of CR or PR until the time of the first documented disease progression or death due to any cause (average of 28 weeks)
Safety Issue?	No

Analysis Population Description

V600E Population. Only the subset of participants who had a complete or partial response was included in this analysis.

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

	Description
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	30	23
Duration of Overall Response for the Subset of V600E Mutation-positive Participants [units: weeks] Median (95% Confidence Interval)	27.6 (16.6 to 32.4)	23.7 (20.0 to 28.1)

8. Secondary Outcome Measure:

Measure Title	Duration of Overall Response for the Subset of V600K Mutation-positive Participants
Measure Description	Duration of Overall Response is defined as the time from the first documented evidence of overall CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline sum of the diameters [e.g., percent change from Baseline]) until the time of the first documented disease progression (PD) or death due to any cause. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir,

	where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm).
Time Frame	Time from the first documented evidence of CR or PR until the time of the first documented disease progression or death due to any cause (average of 31 weeks)
Safety Issue?	No

Analysis Population Description

V600K Population. Only the subset of participants who had a complete or partial response was included in this analysis.

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	0	5
Duration of Overall Response for the		36.1 (12.3 to

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Subset of V600K Mutation-positive Participants [units: weeks] Median (95% Confidence Interval)		NA) [1]

[1] The upper limit of the confidence interval cannot be calculated because too few V600K participants had intracranial responses.

9. Secondary Outcome Measure:

Measure Title	Progression-free Survival in V600E Mutation-positive Participants
Measure Description	PFS is defined as the time from the first dose of study medication to the earliest of death or progression (at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm). If a participant received subsequent anti-cancer therapy prior to the date of documented PD/death, the participant was censored at the last adequate assessment and the visit level response was CR (disappearance of all target lesions), PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters [e.g., percent change from Baseline]), or stable disease (SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Time Frame	Time from the first dose of study medication to the earliest of death or progression (average of 23 weeks)

Safety Issue?	No

Analysis Population Description

V600E Population

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	74	65
Progression-free Survival in V600E Mutation-positive Participants [units: weeks] Median (95% Confidence Interval)	16.1 (15.7 to 23.4)	16.0 (15.9 to 23.9)

10. Secondary Outcome Measure:

Measure Title	Progression-free Survival in V600K Mutation-positive

	Participants
Measure Description	PFS is defined as the time from the first dose of study medication to the earliest of death or progression (at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 millimeters (mm). If a participant received subsequent anti-cancer therapy prior to the date of documented PD/death, the participant was censored at the last adequate assessment and the visit level response was CR (disappearance of all target lesions), PR (at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters [e.g., percent change from Baseline]), or stable disease (SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Time Frame	Time from the first dose of study medication to the earliest of death or progression (average of 17 weeks)
Safety Issue?	No

Analysis Population Description

V600K Population

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2

	Description
	hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	15	18
Progression-free Survival in V600K Mutation-positive Participants [units: weeks] Median (95% Confidence Interval)	8.1 (3.1 to 16.1)	15.6 (7.9 to 17.6)

11. Secondary Outcome Measure:

Measure Title	Overall Survival of V600E Mutation-positive Participants
Measure Description	Overall survival (OS) is defined as the time from the first dose of study medication until death due to any cause. OS was censored using the date of last known contact for those participants who were alive at the time of analysis.
Time Frame	Time from the first dose of study medication until death due to any cause (average of 35 weeks)
Safety Issue?	No

Analysis Population Description

V600E Population

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	74	65
Overall Survival of V600E Mutation-positive Participants [units: months] Median (95% Confidence Interval)	6.8 (6.1 to 9.2)	7.6 (6.3 to 10.6)

12. Secondary Outcome Measure:

Measure Title	Overall Survival in V600K Mutation-positive Participants
Measure Description	Overall survival (OS) is defined as the time from the first dose of study medication until death due to any cause. OS was censored using the date of last known contact for those participants who were alive at the time of analysis.

Time Frame	Time from the first dose of study medication until death due to any cause (average of 26 weeks)
Safety Issue?	No

Analysis Population Description

V600K Population

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	15	18
Overall Survival in V600K Mutation-positive Participants [units: months] Median (95% Confidence Interval)	3.7 (1.6 to 5.2)	5.0 (3.1 to 11.9)

13. Secondary Outcome Measure:

Measure Title	Number of Participants With Any Adverse Event (AE) or Serious Adverse Event (SAE)
Measure Description	An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an event of possible drug-induced liver injury.
Time Frame	From Screening until the conclusion of the study (up to 103 weeks)
Safety Issue?	No

Analysis Population Description

All Treated Subjects (ATS) Population: all participants who received at least one dose of study treatment

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	89	83
Number of Participants With Any Adverse Event (AE) or Serious Adverse Event (SAE) [units: participants]		
Any AE	81	79
Any SAE	26	31

14. Secondary Outcome Measure:

Measure Title	Number of Participants With a Worst-case on Therapy Change to Grade 3 and Grade 4, or With Any Grade Increase (AGI), From Baseline Grade for Clinical Chemistry Parameters
Measure Description	Clinical chemistry data were summarized at each scheduled assessment according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.0). Grade refers to the severity of the toxicity. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each toxicity based on this general guideline: Grade (G) 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, life threatening; Grade 5, death related to toxicity. Blood sample was collected for the assessment of glucose, potassium, magnesium, sodium, phosphorus, potassium. aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatinine, total

	bilirubin, albumin, amylase, cholesterol, creatine kinase, gamma glutamyl transferase (GGT), lipase, blood pH, and triglycerides.
Time Frame	From Screening until the conclusion of the study (up to 103 weeks)
Safety Issue?	No

Analysis Population Description

ATS Population. Only those participants with data available for the indicated parameters were analyzed.

Reporting Groups

	Description
GSK2118436 150 mg	Participants with or without prior local therapy for brain metastasis received GSK2118436 50 mg and 75 mg capsules either one hour before or 2 hours after a meal twice daily.

Measured Values

	GSK2118436 150 mg
Number of Participants Analyzed	165
Number of Participants With a Worst-case on Therapy Change to Grade 3 and Grade 4, or With Any Grade Increase (AGI), From Baseline Grade for Clinical Chemistry Parameters [units: participants]	
Glucose (hyperglycemia), AGI, n=165	71
Glucose (hyperglycemia), Increase to G 3, n=165	8
Glucose (hyperglycemia), Increase to G 4, n=165	1

	GSK2118436 150 mg
Glucose (hypoglycemia), AGI, n=165	24
Glucose (hypoglycemia), Increase to G 3, n=165	0
Glucose (hypoglycemia), Increase to G 4, n=165	0
Magnesium (hypermagnesemia) AGI, n=165	2
Magnesium (hypermagnesemia), Increase to G 3,n=165	0
Magnesium (hypermagnesemia), Increase to G 4,n=165	0
Magnesium (hypomagnesemia), AGI, n=165	0
Magnesium (hypomagnesemia), Increase to G 3, n=165	0
Magnesium (hypomagnesemia), Increase to G 4, n=165	0
Sodium (hypernatremia), AGI, n=165	8
Sodium (hypernatremia), Increase to G 3, n=165	0
Sodium (hypernatremia), Increase to G 4, n=165	0
Sodium (hyponatremia), AGI, n=165	21
Sodium (hyponatremia), Increase to G 3, n=165	3

	GSK2118436 150 mg
Sodium (hyponatremia), Increase to G. 4, n=165	0
Phosphorus inorganic, AGI, n=165	53
Phosphorus inorganic, Increase to G 3, n=165	13
Phosphorus inorganic, Increase to G 4, n=165	0
Potassium (hyperkalemia), AGI, n=165	8
Potassium (hyperkalemia), Increase to G 3, n=165	0
Potassium (hyperkalemia), Increase to G 4, n=165	0
Potassium (hypokalemia), AGI, n=165	17
Potassium (hypokalemia), Increase to G 3, n=165	4
Potassium (hypokalemia), Increase to G 4, n=165	0
ALP, AGI, n=165	41
ALP, Increase to G 3, n=165	1
ALP, Increase to G 4, n=165	0
AST, AGI, n=165	26
AST, Increase to G 3, n=165	1
AST, Increase to G 4, n=165	0

	GSK2118436 150 mg
ALT, AGI, n=165	27
ALT, Increase to G 3, n=165	2
ALT, Increase to G 4, n=165	0
Creatinine, AGI, n=165	10
Creatinine, Increase to G 3, n=165	0
Creatinine, Increase to G 4, n=165	0
Total bilirubin, AGI, n=163	5
Total bilirubin, Increase to G 3 n=163	0
Total bilirubin, Increase to G 4 n=163	0
Albumin, AGI, n=27	9
Albumin, Increase to G 3, n=27	0
Albumin, Increase to G 4, n=27	0
Amylase, AGI, n=16	3
Amylase, Increase to G 3, n=16	1
Amylase, Increase to G 4, n=16	1
Cholesterol, AGI, n=2	1
Cholesterol, Increase to G 3, n=2	0
Cholesterol, Increase to G 4, n=2	0
Creatine kinase, AGI, n=6	1
Creatine kinase, Increase to G 3, n=6	0
Creatine kinase, Increase to G 4, n=6	1

	GSK2118436 150 mg
GGT, AGI, n=22	13
GGT, Increase to G 3, n=22	4
GGT, Increase to G 4, n=22	0
Lipase, AGI, n=19	10
Lipase, Increase to G 3, n=19	4
Lipase, Increase to G 4, n=19	2
Blood pH, AGI, n=1	0
Blood pH, Increase to G 3, n=1	0
Blood pH, Increase to G 4, n=1	0
Triglycerides, AGI, n=5	3
Triglycerides, Increase to G 3, n=5	0
Triglycerides, Increase to G 4, n=5	0

15. Secondary Outcome Measure:

Measure Title	Number of Participants With the Indicated Hepatobiliary Laboratory Abnormalities
Measure Description	Blood samples were collected for the assessment of hepatobiliary parameters. ALT=alanine aminotranserase; AST=aspartate aminotransferase; ALP=alkaline phosphatase; BIL=total bilirubin; INR=international normalized ratio; ULN=upper limit of normal. Hepato-cellular injury is defined as (ALT/ULN)/(ALP/ULN) >=5.
Time Frame	From Screening until the conclusion of the study (up to 103 weeks)

Safety Issue?	No

Analysis Population Description

ATS Population

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	89	83
Number of Participants With the Indicated Hepatobiliary Laboratory Abnormalities [units: participants]		
Possible HYs Law, >3x ULN ALT, >=2x ULN BIL	0	0
Possible HYs Law, >3x ULN ALT, >1.5x ULN INR	0	0

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Hepato-cellular injury	2	1
Bilirubin elevations, >=2x ULN BIL	0	1
Bilirubin elevations, >=2x ULN BIL and <2x ULN BIL	0	1
ALT or AST elevations, >3x ULN ALT or AST	2	4
ALT or AST elevations, >5x ULN ALT or AST	1	1
ALT or AST elevations, >8x ULN ALT or AST	1	1
ALT or AST elevations, >20x ULN ALT or AST	0	0
ALT elevations, >3x ULN ALT	2	4
ALT elevations, >5x ULN ALT	1	1
ALT elevations, >8x ULN ALT	1	1
ALT elevations, >20x ULN ALT	0	0
ALT elevations, >3x ULN ALT, <=3x ULN ALT Baseline	2	4
ALP elevations, >=3x ULN ALP	5	2
ALP elevations, >=3x ULN ALP and <3x ULN ALP	4	2

16. Secondary Outcome Measure:

Measure Title	Number of Participants With a Worst-case on Therapy Change to Grade 3 and Grade 4, or With Any Grade Increase (AGI), From Baseline Grade for Hematology Parameters
Measure Description	Hematology data were summarized at each scheduled assessment according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.0). Grade refers to the severity of the toxicity. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each toxicity based on this general guideline: Grade 1, mild; Grade 2, moderate; Grade 3, severe, Grade 4, life threatening, Grade 5, death related to toxicity. Blood sample was collected for the assessment of hemoglobin, white blood cells, and platelet count.
Time Frame	From Screening until the conclusion of the study (up to 103 weeks)
Safety Issue?	No

Analysis Population Description

ATS Population. Only those participants with data available for the indicated parameters were analyzed.

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2

	Description
	hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	84	81
Number of Participants With a Worst-case on Therapy Change to Grade 3 and Grade 4, or With Any Grade Increase (AGI), From Baseline Grade for Hematology Parameters [units: participants]		
Hemoglobin (anemia), AGI	25	81
Hemoglobin (anemia), Increase to Grade 3	2	3
Hemoglobin (anemia), Increase to Grade 4	0	0
Hemoglobin (increased), AGI	1	0
Hemoglobin (increased), Increase to Grade 3	0	0
Hemoglobin (increased), Increase to Grade 4	0	0
Lymphocyte count increased, AGI	0	0
Lymphocyte count increased, Increase	0	0

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
to Grade 3		
Lymphocyte count increased, Increase to Grade 4	0	0
Lymphocyte count decreased, AGI	18	81
Lymphocyte count decreased, Increase Grade 3	4	6
Lymphocyte count decreased, Increase Grade 4	1	0
Total neutrophils, AGI,	6	11
Total neutrophils, Increase to Grade 3	0	0
Total neutrophils, Increase to Grade 4	2	2
Platelet count, AGI	7	9
Platelet count, Increase to Grade 3	2	1
Platelet count, Increase to Grade 4	1	0
White blood cell count, AGI	9	16
White blood cell count, Increase to Grade 3	0	0
White blood cell count, Increase to Grade 4	1	1

17. Secondary Outcome Measure:

Measure Title	Mean Blood Pressure at Baseline and Weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36
Measure Description	Systolic and diastolic blood pressure were measured for all treated participants.
Time Frame	Baseline; Weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36
Safety Issue?	No

Analysis Population Description

ATS Population. Only those participants with data available at the indicated time points were analyzed.

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	89	83
Mean Blood Pressure at Baseline and		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36 [units: millimeters of mercury (mmHg)] Mean (Standard Deviation)		
Diastolic BP, Baseline, n=89,83	77.7 (8.78)	77.1 (9.73)
Diastolic BP, Week 4, n=81, 78	74.0 (10.12)	74.6 (10.88)
Diastolic BP, Week 8, n=70, 73	74.6 (9.14)	72.7 (9.54)
Diastolic BP, Week 12, n=68, 62	75.2 (7.70)	74.3 (11.64)
Diastolic BP, Week 16, n=52, 52	73.2 (10.01)	71.4 (9.40)
Diastolic BP, Week 20, n=29, 34	73.6 (9.98)	71.7 (9.67)
Diastolic BP, Week 24, n=22, 25	74.7 (7.87)	72.7 (9.99)
Diastolic BP, Week 28, n=15, 17	73.9 (6.98)	76.5 (8.37)
Diastolic BP, Week 32, n=9, 7	73.1 (9.47)	73.6 (9.64)
Diastolic BP, Week 36, n=2, 1	75.5 (7.78)	93.0 (NA) [1]
Systolic BP, Baseline, n=89, 83	126.6 (16.73)	123.9 (14.17)
Systolic BP, Week 4, n=81, 78	122.2 (13.68)	121.9 (15.37)
Systolic BP, Week 8, n=70, 73	123.0 (12.71)	117.3 (14.53)
Systolic BP, Week 12, 68, 62	123.6 (14.74)	120.1 (14.21)
Systolic BP, Week 16, n=52, 52	124.7 (17.70)	119.9 (11.67)
Systolic BP, Week 20, n=29, 34	123.7 (16.02)	118.9 (13.51)
Systolic BP, Week 24, n=22, 25	126.3 (17.80)	120.9 (16.63)

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Systolic BP, Week 28, n=15, 17	122.2 (17.03)	120.8 (14.32)
Systolic BP, Week 32, n=9, 7	122.8 (14.84)	117.7 (10.01)
Systolic BP, Week 36, n=2, 1	119.5 (13.44)	128.0 (NA) [2]

[1] Standard deviation could not be calculated because only one participant was analyzed in this treatment group at this time point.

[2] Standard deviation could not be calculated because only one participant was analyzed in this treatment group at this time point.

18. Secondary Outcome Measure:

Measure Title	Number of Participants With a Worst-case On-therapy Increase From Baseline in Bazett's QTc Reading in the 12-lead Electrocardiogram (ECG)
Measure Description	An increase in the QTc interval corrected using Bazett's formula (Bazett's QTc) was recorded for all treated participants. Grade 1 (450-480 milliseconds [msec]), Grade 2 (481-500 msec), Grade 3/4 (>=501 msec). An increase is defined as an increase in CTCAE grade relative to Baseline grade.
Time Frame	Baseline; Weeks 4, 12, 20, 28, 40, 52, and 64
Safety Issue?	No

Analysis Population Description

ATS Population. Only those participants with data available at the indicated time points were analyzed.

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	75	74
Number of Participants With a Worst-case On-therapy Increase From Baseline in Bazett's QTc Reading in the 12-lead Electrocardiogram (ECG) [units: participants]		
Increase from Baseline to any grade	11	17
Increase from Baseline to Grade 2	1	2
Increase from Baseline to Grade 3/4	0	0

19. Secondary Outcome Measure:

Measure Title	Number of Participants With Abnormal Echocardiograms

	(ECHO) at Weeks 4 and 12
Measure Description	Echocardiograms (ECHO) were measured for all treated participants. An echocardiogram test gives information about the structure and function of the heart. LLN=lower limit of normal (determined by the institution).
Time Frame	Weeks (W) 4 and 12
Safety Issue?	No

Analysis Population Description

ATS Population

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	89	83
Number of Participants With Abnormal		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Echocardiograms (ECHO) at Weeks 4 and 12 [units: participants]		
W 4, Left ventricle (LV) ejection fraction < LLN	1	0
W 4, LV ejection fraction < normal	0	0
W 12, LV ejection fraction < LLN	0	0
W 12, LV ejection fraction < normal	1	0

20. Secondary Outcome Measure:

Measure Title	Median Concentrations of GSK2118436 and Its Metabolites Including GSK2285403, GSK2298683, and GSK2167542
Measure Description	Summary statistics were calculated for each time point by cohort. The population pharmacokinetics were determined using a non-linear mixed effects modeling approach after pooling the data with other studies. These results are reported separately.
Time Frame	Week 4 (pre-dose and 1-3 hours post-dose) and Weeks 8, 16, 24, and 32 (either pre-dose in the morning or in the afternoon at 4-8 hours post-dose)
Safety Issue?	No

Analysis Population Description

PK Population: participants in the ATS population for whom a PK sample was obtained and analyzed. Only those participants whose samples were available at the indicated time points were analyzed.

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	75	77
Median Concentrations of GSK2118436 and Its Metabolites Including GSK2285403, GSK2298683, and GSK2167542 [units: nanograms per milliliter (ng/mL)] Median (Full Range)		
GSK2118436, Week 4, predose, n=55, 58	31.6 (7 to 2995)	50.2 (0 to 4293)
GSK2118436, Week 4, 1-3 hours (hrs), n=63, 70	992.1 (5 to 4870)	810.7 (4 to 4995)

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
GSK2118436, Week 8, predose, n=36, 36	27.2 (8 to 1148)	37.5 (3 to 944)
GSK2118436, Week 8, 4-8 hrs, n=19, 25	274.7 (28 to 1062)	294.5 (15 to 2011)
GSK2118436, Week 16, predose, n=26, 23	27.8 (6 to 3390)	30.7 (3 to 203)
GSK2118436, Week 16, 4-8 hrs, n=11, 18	341.5 (33 to 1141)	295.8 (55 to 1808)
GSK2118436, Week 24, predose, n=14, 10	60.7 (1 to 597)	53.8 (14 to 211)
GSK2118436, Week 24, 4-8 hrs, n=5, 12	371.2 (0 to 1072)	226.1 (30 to 974)
GSK2118436, Week 32, predose, n=11, 7	38.6 (7 to 777126)	28.4 (2 to 87)
GSK2118436, Week 32, 4-8 hrs, n=2, 8	227.6 (90 to 365)	335.7 (94 to 1939)
GSK2285403, Week 4, predose, n=55, 58	62.7 (9 to 1495)	80.5 (0 to 2931)
GSK2285403, Week 4, 1-3 hrs, n=63, 70	688.9 (15 to 2499)	593.2 (8 to 2812)
GSK2285403, Week 8, predose, n=36, 36	46.5 (10 to 1743)	74.4 (6 to 553)
GSK2285403, Week 8, 4-8 hrs, n=19, 25	335.5 (55 to 1114)	310.5 (12 to 3160)

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
GSK2285403, Week 16, predose, n=26, 23	45.1 (10 to 824)	54.4 (5 to 354)
GSK2285403, Week 16, 4-8 hrs, n=11, 18	434.1 (44 to 976)	456.9 (148 to 1053)
GSK2285403, Week 24, predose, n=14, 10	97.3 (6 to 386)	103.3 (14 to 325)
GSK2285403, Week 24, 4-8 hrs, n=5, 12	617.1 (0 to 1057)	357.7 (79 to 959)
GSK2285403, Week 32, predose, n=11, 7	63.1 (8 to 934)	46.6 (4 to 88)
GSK2285403, Week 32, 4-8 hrs, n=2, 8	375.3 (118 to 633)	377.5 (117 to 1519)
GSK2298683, Week 4, predose, n=55, 58	3215.8 (1225 to 14064)	3877.4 (43 to 13435)
GSK2298683, Week 4, 1-3 hrs, n=63, 70	4272.5 (747 to 18161)	4500.3 (275 to 18196)
GSK2298683, Week 8, predose, n=36, 36	3152.0 (1564 to 10402)	3250.0 (667 to 12747)
GSK2298683, Week 8, 4-8 hrs, n=19, 25	4692.1 (2133 to 11320)	5447.5 (2015 to 15009)
GSK2298683, Week 16, predose, n=26, 23	3070.0 (1143 to 11414)	3561.2 (922 to 10204)
GSK2298683, Week 16, 4-8 hrs, n=11, 18	4865.5 (2670 to 11821)	6595.7 (1630 to 11380)

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
GSK2298683, Week 24, predose, n=14, 10	3026.8 (1532 to 14762)	4199.7 (2040 to 7504)
GSK2298683, Week 24, 4-8 hrs, n=5, 12	3825.9 (320 to 13056)	5659.9 (3225 to 11009)
GSK2298683, Week 32, predose, n=11, 7	2386.6 (1421 to 6528)	2451.7 (1253 to 5026)
GSK2298683, Week 32, 4-8 hrs, n=2, 8	11225.8 (5323 to 17129)	6547.4 (4578 to 8786)
GSK2167542, Week 4, predose, n=55, 58	317.9 (50 to 1338)	323.0 (3 to 2690)
GSK2167542, Week 4, 1-3 hrs, n=63, 70	351.6 (62 to 1505)	332.1 (46 to 1619)
GSK2167542, Week 8, predose, n=36, 36	324.1 (86 to 964)	298.6 (56 to 1272)
GSK2167542, Week 8, 4-8 hrs, n=19, 25	305.4 (91 to 899)	320.5 (78 to 960)
GSK2167542, Week 16, predose, n=26, 23	285.5 (93 to 1095)	310.8 (35 to 1200)
GSK2167542, Week 16, 4-8 hrs, n=11, 18	291.1 (69 to 769)	320.5 (81 to 652)
GSK2167542, Week 24, predose, n=14, 10	304.0 (94 to 875)	334.0 (63 to 795)
GSK2167542, Week 24, 4-8 hrs, n=5,	190.7 (19 to	287.9 (106 to

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
12	401)	599)
GSK2167542, Week 32, predose, n=11, 2	361.2 (113 to 960)	316.3 (69 to 690)
GSK2167542, Week 32, 4-8 hrs, n=2, 8	227.8 (225 to 231)	273.9 (231 to 1021)

21. Secondary Outcome Measure:

Measure Title	Composite of Pharmacokinetic Parameters of GSK2118436 in a Subset of Participants Receiving Dexamethasone
Measure Description	This outcome measure could not be analyzed because too few participants participated in the dexamethasone study.
Time Frame	Day 15
Safety Issue?	No

Analysis Population Description

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

	Description
GSK2118436 150 mg: Prior Local Therapy	Participants who received prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Measured Values

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

22. Secondary Outcome Measure:

Measure Title	Number of Response Genetics Incorporated (RGI) Investigational Use Only (IUO) Assay Mutation Positive Participants and THxID BRAF Assay Mutation Positive Participants With the Indicated Best Intracranial Response
Measure Description	The BRAF screening assay determines the specific BRAF mutational status (V600 E and K) in participants with metastatic melanoma who may benefit from treatment with GSK2118436. Per RECIST, version 1.1, CR is defined as the disappearance of all lesions. PR is defined as a >=30% decrease in the sum of the diameters of target lesions, taking as a reference, the Baseline (BL) sum of the diameters (e.g., percent change from BL). Stable disease is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD). PD is defined as a >=20% increase in the sum of the diameters of target lesions, taking as a reference, the

	smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir [smallest sum of diameters recorded since treatment start]). In addition, the sum must have an absolute increase from nadir of 5 millimeters. Not evaluable: cannot be classified by a preceding definition.
Time Frame	Screening
Safety Issue?	No

Analysis Population Description

V600EK and THIDEK Population: all enrolled participants who were V600E or V600K mutation positive by the RGI IUO assay

Reporting Groups

	Description
RGI IUO Mutation Positive Participants	Melanoma participants determined to be positive for the BRAF V600E and V600K mutations as determined by the RGI assay. The RGI assay is a BRAF mutation test developed by Response Genetics Incorporated, and was used to determine eligibility. It employs the allele-specific polymerase chain reaction (ASPCR) methodology, and was offered as an Investigational Use Only assay (only for pre-market investigational purposes).
ThxID BRAF Mutation Positive Participants	Melanoma participants determined to be positive for the BRAF V600E and V600K mutations as determined by the ThxID assay. The RGI test was further validated by BioMerieux (BMX THxID assay) for regulatory approval. The THxID IUO assay was used to retrospectively confirm the RGI test results.

Measured Values

	RGI IUO Mutation Positive Participants	ThxID BRAF Mutation Positive Participants
Number of Participants Analyzed	172	155
Number of Response Genetics Incorporated (RGI) Investigational Use Only (IUO) Assay Mutation Positive Participants and THxID BRAF Assay Mutation Positive Participants With the Indicated Best Intracranial Response [units: participants]		
Complete response	2	2
Partial response	52	49
Stable disease	78	69
Progressive disease	26	23
Not evaluable	14	12

Reported Adverse Events

Reporting Groups

	Description
GSK2118436 150 mg: No Prior Local Therapy	Participants who received no prior local therapy for brain metastasis received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.
GSK2118436 150 mg: Prior	Participants who received prior local therapy for brain metastasis

	Description
Local Therapy	received GSK2118436 150 mg capsules either one hour before or 2 hours after a meal twice daily until evidence of disease progression, death, or unacceptable adverse events.

Time Frame

Serious adverse events (SAEs) and non-serious AEs were collected from the time the first dose of study treatment was administered until 30 days following discontinuation of study treatment (up to 103 weeks).

Additional Description

SAEs and non-serious AEs were collected in the All Treated Subjects (ATS) Population, comprised of all participants who received at least one dose of study medication.

Serious Adverse Events

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Total # participants affected/at risk	26/89 (29.21%)	31/83 (37.35%)
Blood and lymphatic system disorders		
Agranulocytosis †[A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Anaemia †[A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
# events		
Disseminated intravascular coagulation † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Leukopenia † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Neutropenia † [A]		
# participants affected/at risk	2/89 (2.25%)	0/83 (0%)
# events		
Pancytopenia † [A]		
# participants affected/at risk	0/89 (0%)	2/83 (2.41%)
# events		
Thrombocytopenia † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Cardiac disorders		
Atrial fibrillation † [A]		
# participants affected/at risk	2/89 (2.25%)	0/83 (0%)
# events		
Atrial flutter † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Cardiac arrest † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Gastrointestinal disorders		
Nausea † [A]		
# participants affected/at risk	1/89 (1.12%)	1/83 (1.2%)
# events		
Pancreatitis † [A]		
# participants affected/at	1/89 (1.12%)	0/83 (0%)

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
risk		
# events		
Pyrexia † [A]		
# participants affected/at risk	4/89 (4.49%)	9/83 (10.84%)
# events		
Subileus † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Vomiting † [A]		
# participants affected/at risk	0/89 (0%)	2/83 (2.41%)
# events		
General disorders		
Chills † [A]		
# participants affected/at risk	1/89 (1.12%)	2/83 (2.41%)
# events		
Fatigue † [A]		
# participants affected/at	0/89 (0%)	2/83 (2.41%)

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
risk		
# events		
Influenza like illness † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Oedema peripheral † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Pain † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Hepatobiliary disorders		
Cholecystitis † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Infections and infestations		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Cellulitis † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Infection † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Pneumonia † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Urinary tract infection † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Viral pericarditis † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Injury, poisoning and		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
procedural complications		
Femoral neck fracture † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Investigations		
Ejection fraction decreased † [A]		
# participants affected/at risk	3/89 (3.37%)	0/83 (0%)
# events		
Metabolism and nutrition disorders		
Hyperglycaemia † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Musculoskeletal and connective tissue disorders		
Arthritis † [A]		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Bone pain †[A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Mobility decreased †[A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Muscular weakness †[A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Pain in extremity †[A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Neoplasms benign, malignant and unspecified (incl cysts		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
and polyps)		
Bowen's disease † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Metastases to meninges † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Squamous cell carcinoma † [A]		
# participants affected/at risk	6/89 (6.74%)	7/83 (8.43%)
# events		
Nervous system disorders		
Aphasia † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Cerebral haemorrhage † [A]		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
# participants affected/at risk	2/89 (2.25%)	1/83 (1.2%)
# events		
Cerebrovascular accident † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Convulsion † [A]		
# participants affected/at risk	0/89 (0%)	2/83 (2.41%)
# events		
Depressed level of consciousness † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Dizziness † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Haemorrhage intracranial †		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
[A]		
# participants affected/at risk	2/89 (2.25%)	3/83 (3.61%)
# events		
Headache † [A]		
# participants affected/at risk	2/89 (2.25%)	2/83 (2.41%)
# events		
Hemiparesis † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Intracranial tumour haemorrhage † [A]		
# participants affected/at risk	1/89 (1.12%)	1/83 (1.2%)
# events		
Lethargy † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Motor dysfunction † [A]		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Paraesthesia † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Partial seizures † [A]		
# participants affected/at risk	1/89 (1.12%)	1/83 (1.2%)
# events		
Somnolence † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Syncope † [A]		
# participants affected/at risk	1/89 (1.12%)	1/83 (1.2%)
# events		
Psychiatric disorders		
Mental status changes † [A]		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Renal and urinary disorders		
Renal failure † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Renal failure acute † [A]		
# participants affected/at risk	1/89 (1.12%)	1/83 (1.2%)
# events		
Respiratory, thoracic and mediastinal disorders		
Dyspnoea † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Pleural effusion † [A]		
# participants affected/at	1/89 (1.12%)	0/83 (0%)

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
risk		
# events		
Pulmonary embolism † [A]		
# participants affected/at risk	2/89 (2.25%)	0/83 (0%)
# events		
Vascular disorders		
Deep vein thrombosis † [A]		
# participants affected/at risk	0/89 (0%)	1/83 (1.2%)
# events		
Hypotension † [A]		
# participants affected/at risk	0/89 (0%)	3/83 (3.61%)
# events		
Phlebitis † [A]		
# participants affected/at risk	1/89 (1.12%)	0/83 (0%)
# events		
Thrombosis † [A]		
# participants affected/at	0/89 (0%)	1/83 (1.2%)

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
risk		
# events		

† Indicates events were collected by systematic assessment.

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Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Total # participants affected/at risk	79/89 (88.76%)	74/83 (89.16%)
Blood and lymphatic system disorders		
Anaemia † [A]		
# participants affected/at risk	6/89 (6.74%)	4/83 (4.82%)
# events		
Lymphopenia † [A]		
# participants affected/at risk	3/89 (3.37%)	5/83 (6.02%)
# events		
Gastrointestinal		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
disorders		
Abdominal pain † [A]		
# participants affected/at risk	6/89 (6.74%)	3/83 (3.61%)
# events		
Constipation † [A]		
# participants affected/at risk	3/89 (3.37%)	11/83 (13.25%)
# events		
Diarrhoea † [A]		
# participants affected/at risk	7/89 (7.87%)	15/83 (18.07%)
# events		
Nausea † [A]		
# participants affected/at risk	16/89 (17.98%)	26/83 (31.33%)
# events		
Vomiting † [A]		
# participants affected/at risk	18/89 (20.22%)	15/83 (18.07%)
# events		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
General disorders		
Asthenia † [A]		
# participants affected/at risk	2/89 (2.25%)	6/83 (7.23%)
# events		
Chills † [A]		
# participants affected/at risk	9/89 (10.11%)	8/83 (9.64%)
# events		
Fatigue † [A]		
# participants affected/at risk	18/89 (20.22%)	25/83 (30.12%)
# events		
Oedema peripheral † [A]		
# participants affected/at risk	5/89 (5.62%)	4/83 (4.82%)
# events		
Pyrexia † [A]		
# participants affected/at risk	23/89 (25.84%)	15/83 (18.07%)
# events		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Infections and infestations		
Nasopharyngitis † [A]		
# participants affected/at risk	5/89 (5.62%)	2/83 (2.41%)
# events		
Investigations		
Alanine aminotransferase increased † [A]		
# participants affected/at risk	6/89 (6.74%)	4/83 (4.82%)
# events		
Metabolism and nutrition disorders		
Decreased appetite † [A]		
# participants affected/at risk	8/89 (8.99%)	13/83 (15.66%)
# events		
Hyperglycaemia † [A]		
# participants affected/at risk	5/89 (5.62%)	3/83 (3.61%)

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
# events		
Hypophosphataemia † [A]		
# participants affected/at risk	5/89 (5.62%)	4/83 (4.82%)
# events		
Musculoskeletal and connective tissue disorders		
Arthralgia † [A]		
# participants affected/at risk	17/89 (19.1%)	13/83 (15.66%)
# events		
Back pain † [A]		
# participants affected/at risk	2/89 (2.25%)	5/83 (6.02%)
# events		
Muscular weakness † [A]		
# participants affected/at risk	4/89 (4.49%)	5/83 (6.02%)
# events		
Musculoskeletal pain † [A]		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
# participants affected/at risk	2/89 (2.25%)	5/83 (6.02%)
# events		
Myalgia †[A]		
# participants affected/at risk	12/89 (13.48%)	13/83 (15.66%)
# events		
Pain in extremity †[A]		
# participants affected/at risk	12/89 (13.48%)	8/83 (9.64%)
# events		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Acrochordon †[A]		
# participants affected/at risk	7/89 (7.87%)	4/83 (4.82%)
# events		
Dysplastic naevus †[A]		
# participants affected/at risk	5/89 (5.62%)	2/83 (2.41%)

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
# events		
Melanocytic naevus † [A]		
# participants affected/at risk	8/89 (8.99%)	4/83 (4.82%)
# events		
Seborrhoeic keratosis † [A]		
# participants affected/at risk	8/89 (8.99%)	7/83 (8.43%)
# events		
Skin papilloma † [A]		
# participants affected/at risk	17/89 (19.1%)	8/83 (9.64%)
# events		
Nervous system disorders		
Dizziness † [A]		
# participants affected/at risk	5/89 (5.62%)	3/83 (3.61%)
# events		
Headache † [A]		
# participants affected/at	24/89	20/83 (24.1%)

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
risk	(26.97%)	
# events		
Psychiatric disorders		
Confusional state † [A]		
# participants affected/at risk	0/89 (0%)	7/83 (8.43%)
# events		
Depression † [A]		
# participants affected/at risk	0/89 (0%)	5/83 (6.02%)
# events		
Insomnia † [A]		
# participants affected/at risk	6/89 (6.74%)	6/83 (7.23%)
# events		
Respiratory, thoracic and mediastinal disorders		
Cough † [A]		
# participants affected/at risk	13/89 (14.61%)	5/83 (6.02%)
# events		

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
Skin and subcutaneous tissue disorders		
Actinic keratosis † [A]		
# participants affected/at risk	3/89 (3.37%)	6/83 (7.23%)
# events		
Alopecia † [A]		
# participants affected/at risk	15/89 (16.85%)	10/83 (12.05%)
# events		
Dermatitis acneiform † [A]		
# participants affected/at risk	5/89 (5.62%)	3/83 (3.61%)
# events		
Dry skin † [A]		
# participants affected/at risk	9/89 (10.11%)	4/83 (4.82%)
# events		
Hyperkeratosis † [A]		
# participants affected/at risk	24/89 (26.97%)	20/83 (24.1%)

	GSK2118436 150 mg: No Prior Local Therapy	GSK2118436 150 mg: Prior Local Therapy
# events		
Palmar-plantar erythrodysaesthesia syndrome † [A]		
# participants affected/at risk	15/89 (16.85%)	10/83 (12.05%)
# events		
Pruritus † [A]		
# participants affected/at risk	7/89 (7.87%)	2/83 (2.41%)
# events		
Rash † [A]		
# participants affected/at risk	16/89 (17.98%)	14/83 (16.87%)
# events		
Transient acantholytic dermatosis † [A]		
# participants affected/at risk	1/89 (1.12%)	6/83 (7.23%)
# events		

† Indicates events were collected by systematic assessment.

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More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

GSK agreements may vary with individual investigators, but will not prohibit any investigator from publishing. GSK supports the publication of results from all centers of a multi-center trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

Limitations and Caveats:

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