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A study to evaluate the safety, tolerability, processing by the body and effectiveness against BRAF-mutated solid tumours or melanoma of RO7276389 by itself or in combination with cobimetinib

Submission date	**Recruitment status**	[X] Prospectively registered
19/11/2021	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
03/12/2021	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
04/12/2023	Cancer	[_] Record updated in last year

Plain English summary of protocol

Background and study aims:
The purpose of the study is to test an experimental drug called RO7276389 when given by itself or in combination with another drug called cobimetinib in participants with solid tumours. Some solid tumours will have a change in a gene which in turn causes an abnormal change (mutation) in a protein called the BRAF protein. This changed BRAF protein will change the communication within the cells and hence can cause cancer. The existing cancer medicines that block the changed BRAF protein are less effective in cancers that spread to the brain. RO7276389 is an experimental drug that by itself, or in combination with cobimetinib, has been approved by health authorities for the treatment of BRAF-mutant advanced cancer in participants in a clinical study. Cobimetinib is an anticancer medicine that blocks a protein called MEK which helps cancer cells to grow.

The aims of the study are:
1. To find out the highest dose that a participant can tolerate and/or the recommended dose of RO7276389 by itself or in combination with cobimetinib.
2. To find out how safe RO7276389 by itself or in combination with cobimetinib at different doses will be and to find out what side-effects this treatment may cause
3. To find out if RO7276389 by itself or in combination with cobimetinib is effective against BRAF-mutated solid tumours or melanoma (a type of skin cancer).
4. To find out how RO7276389 by itself or in combination with cobimetinib will be distributed and eliminated from the body.
5. To find out the effect of food on the distribution and elimination of RO7276389 alone or in combination with cobimetinib from the body.

Who can participate?
Participants who are over 18 years of age and have BRAF-mutated solid tumours.

What does the study involve?
Participants may be asked to be in the study for up to 24 months. This includes:
1. A Screening period of up to 28 days before the start of the study where tests will be done to check if the participants are eligible to take part in the study.
2. Treatment period where participants will receive RO7276389 alone or in combination with cobimetinib daily in 4-week cycles. Participants will get the study treatments both at the clinic under the guidance of a doctor and at the participant's preferred location.
3. Safety follow-up period where participants will have a check-up 28 days after receiving the last dose of RO7276389 and cobimetinib.

The study will be conducted in 2 parts:
1. Dose escalation, where the participants in one group will receive study treatment at a certain dose and once this dose is considered tolerable, the next group of participants will receive a higher dose. A participant's dose will be increased if the doctors think that the treatment is beneficial and decreased if there are side effects. The effect of food on distribution and elimination of the study treatment will also be studied.
2. Dose Expansion where a larger group of participants will be included. All participants will get the same dose of study treatment. The dose for Part 2 will be based on the findings from Part 1.

Participants will be placed in one of the following treatment groups:
1. RO7276389 group: Initially, the 25 mg dose of RO7276389 was explored in the first two participants, to see how the drug is distributed and then eliminated from the body. The data from these participants showed that this dose was safe but not high enough, so the following participants will start with a dose of 200 mg. The dose for new participants joining the study will be adjusted according to the test results of previous participants. The maximum daily dose (MDD) that a participant can receive is 4000 mg. Participants joining the study at later stages will get higher doses of the study drug. They will receive the study drug once a day or twice daily (BID) or three times daily (TID), given as a tablet, by mouth with a full glass of water and every day.
2. RO7276389 and cobimetinib group: Participants will get RO7276389 tablets to be taken by mouth once a day or BID or TID for 28 consecutive days (or 1 cycle) along with cobimetinib tablets, also to be taken by mouth once a day for 21 consecutive days. Cobimetinib will not be given from Day 21 to 28 of the treatment cycle.

Participants will continue to take RO7276389 alone or in combination with cobimetinib on a regular basis unless their cancer worsens, they experience severe side effects, or they decide that they no longer want to participate in the study. Treatment may also be stopped earlier than planned if the study doctor feels that the participant is not benefitting from the treatment. After the final dose of study treatment, the study doctor will follow-up participants every 3 months for as long as they agree to it.

What are the possible benefits and risks of participating?
Participants will not receive any benefit from participating in this study, but the information that is learned may help people with certain cancers in the future.

Participants may have side effects from the drugs or procedures used in this study that are mild to severe and even life-threatening, and they can vary from person to person. The potential side effects related to the study drug, based on laboratory studies or knowledge of similar drugs, are listed below:
1. Skin problems like rash, dry skin, hair loss, and skin cancer
2. Diarrhoea or loose stools

3. Joint pain
4. Kidney problems causing side-effects such as dehydration, urinating less than usual, feeling sick, diarrhoea, confusion, and drowsiness
5. Heart problems causing symptoms like dizziness, feeling faint, or palpitations (an irregular heartbeat).

The following are the additional risks associated with cobimetinib (for participants receiving RO7276389 in combination with cobimetinib):
1. Increased risk of bleeding. Types of bleeding associated with cobimetinib include nosebleeds, bleeding of the gums, blood in the urine, rectal bleeding, unusual vaginal bleeding, and bleeding within the brain.
2. Disturbances in vision caused by swelling and redness of the middle layer of the eye. Other visual changes that can occur are because of the separation of the layers of tissue on the back of the eye that are responsible for sight. This causes symptoms like blurred vision, seeing halos, distorted vision, areas of missing vision, etc.
3. Heart problems that can lead to inadequate pumping of the blood
4. Serious muscle problem called rhabdomyolysis which may lead to life-threatening complications of chemical imbalances in the blood and kidney injury
5. Increase in liver enzymes, which may indicate liver damage or infection
6. Swelling in the lungs that can decrease the level of oxygen in the blood

There may be a risk in exposing an unborn child to a study drug, and all risks are not known at this time. Women and men must take precautions to avoid exposing an unborn child to study drugs. If participants are pregnant, become pregnant, or are currently breastfeeding, participants cannot take part in this study.

Where is the study run from?
F. Hoffmann-La Roche (Switzerland)

When is the study starting and how long is it expected to run for?
September 2021 to March 2025

Who is funding the study?
F. Hoffmann-La Roche (Switzerland)

Who is the main contact?
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Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-003426-77

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
WP43295

Study information

Scientific Title
A phase IA/B open-label study to evaluate safety, pharmacokinetics, and preliminary clinical activity of RO7276389 alone and in combination with cobimetinib in participants with Braf-V600 mutation-positive advanced solid tumor or Braf-V600 mutation-positive melanoma with central nervous system metastases

Study objectives
To determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) for RO7276389 alone and in combination with cobimetinib in one or more schedules

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 09/12/2021, Northern B Health and Disability Ethics Committee (Ministry of Health, 133 Molesworth Street, PO Box 5013, Wellington 6011 New Zealand; no telephone contact available ;hdecs@health.govt.nz), ref: 2021 FULL 11468

Study design
Phase IA/B, open-label, multicentre, dose-escalation, and cohort expansion study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Brain metastases, Braf-V600 mutation-positive advanced solid tumor, Braf-V600 mutation-positive melanoma with central nervous system metastases

Interventions

Current intervention as of 01/08/2022:
Participants will be allocated to receive either:
1. RO7276389 tablet orally (PO) alone once daily (QD) or twice daily (BID) or three times daily (TID) on every day of each 28-day cycle
2. RO7276389 tablets PO in a combination of 60 milligrams (mg) cobimetinib PO QD on Day 1 to 21 of each 28-day cycle, followed by a 7-day break after Day 21
The first two participants got a single dose of RO7276389, to see how the drug is distributed and then eliminated from the body. The following participants will receive the study drug, QD or BID or TID, given as a tablet, by mouth with a full glass of water. The dose for new participants joining the study will be adjusted according to the test results of previous participants. Participants joining the study at later stages will get higher doses of the study drug.
The total duration of treatment and follow-up for all treatment arms would be approximately 24 months.

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Previous intervention:
Participants will be allocated to receive either:
1. RO7276389 tablet orally (PO) alone once daily (QD) on every day of each 28-day cycle
2. RO7276389 tablets PO in a combination of 60 milligrams (mg) cobimetinib PO QD on Day 1 to 21 of each 28-day cycle, followed by a 7-day break after Day 21
The first few participants (up to 3 in number) will get a single dose of RO7276389, to see how the drug is distributed and then eliminated from the body. After three days, participants will receive the study drug, given as a tablet, every morning by mouth with a full glass of water. The dose for new participants joining the study will be adjusted according to the test results of previous participants. Participants joining the study at later stages will get higher doses of the study drug.
The total duration of treatment and follow-up for all treatment arms would be approximately 24 months.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
RO7276389, cobimetinib

Primary outcome(s)
1. Percentage of participants with Dose-Limiting Toxicities (DLTs) measured using the National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE V5.0) between Day 1 Cycle 1 and Day 14 Cycle 1 (cycle length = 28 days)
2. Percentage of participants with adverse events measured using the NCI-CTCAE V5.0 between Day 1 Cycle 1 and Day 14 Cycle 1 (cycle length = 28 days)

Key secondary outcome(s))
1. Percentage of participants with adverse events measured using the NCI-CTCAE V5.0 between Day 1 Cycle 1 and up to 28 days after the last dose (approximately 24 months)
2. Number of participants with a clinically significant change from baseline in vital signs measured using vital signs recorded between baseline and up to 28 days after the last dose (approximately 24 months)

3. Number of participants with a clinically significant change from baseline in physical and neurological findings measured using physical and neurological examinations undertaken between baseline and up to 28 days after the last dose (approximately 24 months)
4. Number of participants with a clinically significant change from baseline in ECG readings measured using ECGs undertaken between baseline and up to 28 days after the last dose (approximately 24 months)
5. Number of participants with a clinically significant change from baseline in Left Ventricular Ejection Fraction (LVEF) safety parameter measured using descriptive statistics (individual listings) using echocardiogram, or Multiple-gated acquisition (MUGA) on Day 1 Cycle 2, Day 1 Cycle 5, and thereafter every 3 months on subsequent cycles (up to approximately 24 months)
6. Number of participants with a clinically significant change from baseline in laboratory test results measured using laboratory tests undertaken between baseline and up to 28 days after the last dose (approximately 24 months)
7. Objective Response Rate (ORR) measured using the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (extracranial disease) at baseline, Day 1 Cycle 2, Day 1 Cycle 3, Day 1 Cycle 5, Day 1 Cycle 7, and thereafter every 8 weeks on subsequent cycles (up to approximately 24 months)
8. ORR as determined by the investigator using the Modified Response Assessment in Neuro-Oncology for Brain Metastases (mRECIST-BM; intra-cranial disease) criteria measured at baseline, Day 1 Cycle 2, Day 1 Cycle 3, Day 1 Cycle 5, Day 1 Cycle 7, and thereafter every 8 weeks on subsequent cycles (up to approximately 24 months)
9. Disease Control Rate (DCR) measured using the RECIST v1.1 (extracranial disease) at baseline, Day 1 Cycle 2, Day 1 Cycle 3, Day 1 Cycle 5, Day 1 Cycle 7, and thereafter every 8 weeks on subsequent cycles (up to approximately 24 months)
10. DCR measured using the mRECIST-BM (intra-cranial disease) criteria at baseline, Day 1 Cycle 2, Day 1 Cycle 3, Day 1 Cycle 5, Day 1 Cycle 7, and thereafter every 8 weeks on subsequent cycles (up to approximately 24 months)
11. Duration of Response (DOR) measured using the RECIST v1.1 (extracranial disease) at baseline, Day 1 Cycle 2, Day 1 Cycle 3, Day 1 Cycle 5, Day 1 Cycle 7, and thereafter every 8 weeks on subsequent cycles (up to approximately 24 months)
12. DOR measured using the mRECIST-BM (intra-cranial disease) criteria at baseline, Day 1 Cycle 2, Day 1 Cycle 3, Day 1 Cycle 5, Day 1 Cycle 7, and thereafter every 8 weeks on subsequent cycles (up to approximately 24 months)
13. Estimation of pharmacokinetics parameters (to Area Under the Curve (AUC), Maximum Concentration (Cmax), Time of Maximum Concentration Observed [Tmax] and, Apparent Oral Clearance [CL/F], Volume of Distribution at Steady-State [Vss/F], and Terminal Half-Life [t1/2]) may be performed using standard non-compartmental methods and/or population PK modelling at multiple timepoints in every 28-day cycle (up to approximately 24 months)

Completion date
24/03/2025

Eligibility

Key inclusion criteria
1. Have Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2
2. Aged ≥18 years at the time of signing Informed consent form (ICF)
3. Life expectancy of >3 months
4. Documented BRAF-V600 mutation status of tumour tissue preferentially using an FDA-

approved or CE-IVD genetic test
5. Confirmation of availability of archival tumour tissue for submission to the sponsor/central laboratory

For Part 1 only:
1. Participants with histologically confirmed advanced/metastatic solid tumour or brain metastases with the measurable systemic disease per RECIST v1.1 (extracranial disease) or mRECIST-BM (intra-cranial disease)

For Part 2 only:
1. Participants with histologically confirmed cutaneous melanoma with radiologically confirmed asymptomatic brain metastases per mRECIST-BM
2. Stable or improved CNS disease symptoms for at least 14 days before the start of study treatment

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 01/08/2022:
1. For Part 2 only: History of or current leptomeningeal metastases
2. Any metastasis requiring immediate local intervention
3. Uncontrolled tumour-related pain
4. Participants requiring narcotic pain medication must be on a stable regimen at the start of study treatment
5. Ascites, pleural effusion, or pericardial effusion requiring medical intervention (including use of diuretics) within 6 months prior to study entry
6. Active malignancy (other than the one under investigation) or a prior malignancy within the past two years prior to enrolment with some exceptions
7. Active uveitis, or any history of serous retinopathy or retinal vein occlusion
8. Current or history of Central Nervous System (CNS) disease unrelated to the malignancy under investigation, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease
9. Active autoimmune disease, or quiescent autoimmune disease with exacerbations/flares within 1 year prior to enrolment
10. Systemic anti-cancer therapy or small-molecular therapeutic(s), including but not limited to chemotherapy, investigational drugs, hormonal therapy and radiotherapy, and antibody-based agents all within 2 weeks or at least 5 half-lives, whichever is shorter, prior to start of study treatment
11. Treatment with stereotactic radiosurgery or craniotomy within 1 week prior to study

treatment or treatment with whole brain radiotherapy within 3 months prior study treatment. Participants with local therapy should have a complete recovery with no neurological sequelae.
12. Radiation therapy to visceral metastases within 1 week prior to study treatment. Palliative radiotherapy is allowed.
13. Major surgical procedure other than for diagnosis within 2 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
14. Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥2 weeks prior to screening
15. Contraindication to cobimetinib or known hypersensitivity to any formulation component of cobimetinib (if applicable)
16. Participants with known hypersensitivity to BRAFi and/or MEK inhibitors (MEKi)
17. Increasing corticosteroid dose during the 14 days prior to initiation of study treatment or current dexamethasone or equivalent dose of >8 mg/day
18. Strong CYP3A inducers (including St. John's wort and hyperforin) are prohibited during study treatment and for 2 weeks after the last dose of cobimetinib or RO7276389 (whichever is later).
19. Concomitant treatment with anti-convulsants other than gabapentin, vigabatrin and levetiracetam are prohibited (e.g., carbamazepine, phenytoin, and phenobarbital due to strong CYP3A induction) during study treatment and for 2 weeks after the last dose of cobimetinib or RO7276389 (whichever is later)
20. For combination treatment with cobimetinib, moderate and strong CYP3A inducers and inhibitors are prohibited during study treatment and for 2 weeks after the last dose of cobimetinib or RO7276389 (whichever is later)
21. Concomitant treatment with drugs known to shorten the QT interval, e.g. rufinamide
22. Uncontrolled diabetes or symptomatic hyperglycemia
23. Any Grade ≥3 haemorrhage or bleeding event within 28 days of study treatment initiation
24. History of human immunodeficiency virus (HIV) positivity
25. Hepatitis B virus (HBV) infection (chronic or acute)
26. Hepatitis C virus (HCV) infection (chronic or acute)

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Previous exclusion criteria:
1. History of or current leptomeningeal metastases
2. Any metastasis requiring immediate local intervention
3. Uncontrolled tumour-related pain
4. Participants requiring narcotic pain medication must be on a stable regimen at the start of study treatment
5. Ascites, pleural effusion, or pericardial effusion requiring medical intervention (including use of diuretics) within 6 months prior to study entry
6. Active malignancy (other than the one under investigation) or a prior malignancy within the past two years prior to enrolment with some exceptions
7. Active uveitis, or any history of serous retinopathy or retinal vein occlusion
8. Current or history of Central Nervous System (CNS) disease unrelated to the malignancy under investigation, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease
9. Active autoimmune disease, or quiescent autoimmune disease with exacerbations/flares within 1 year prior to enrolment
10. Systemic anti-cancer therapy or small-molecular therapeutic(s), including but not limited to chemotherapy, investigational drugs, hormonal therapy and radiotherapy, and antibody-based agents all within 2 weeks or at least 5 half-lives, whichever is shorter, prior to start of study treatment
11. Treatment with stereotactic radiosurgery or craniotomy within 1 week prior to study

treatment or treatment with whole brain radiotherapy within 3 months prior study treatment. Participants with local therapy should have a complete recovery with no neurological sequelae.
12. Radiation therapy to visceral metastases within 1 week prior to study treatment. Palliative radiotherapy is allowed.
13. Major surgical procedure other than for diagnosis within 2 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
14. Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥2 weeks prior to screening
15. Contraindication to cobimetinib or known hypersensitivity to any formulation component of cobimetinib (if applicable)
16. Participants with known hypersensitivity to BRAFi and/or MEK inhibitors (MEKi)
17. Increasing corticosteroid dose during the 14 days prior to initiation of study treatment or current dexamethasone or equivalent dose of >8 mg/day
18. Concomitant treatment with CYP3A-inducing anti-epileptic drugs (such as carbamazepine, phenytoin, and phenobarbital due to strong CYP3A induction) during study treatment and for 2 weeks after the last dose of cobimetinib or RO7276389 (whichever is later)
19. St. John's wort and hyperforin being strong CYP3A inducers are prohibited during study treatment and for 2 weeks after the last dose of cobimetinib or RO7276389 (whichever is later)
20. Concomitant treatment with drugs known to shorten the QT interval, e.g. rufinamide
21. Uncontrolled diabetes or symptomatic hyperglycaemia
22. Any Grade ≥3 haemorrhage or bleeding event within 28 days of study treatment initiation
23. History of human immunodeficiency virus (HIV) positivity
24. Hepatitis B virus (HBV) infection (chronic or acute)
25. Hepatitis C virus (HCV) infection (chronic or acute)

Date of first enrolment
07/03/2022

Date of final enrolment
06/01/2025

Locations

Countries of recruitment
United Kingdom

Belgium

Brazil

Denmark

New Zealand

Poland

Spain

Switzerland

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Sponsor information

Organisation
Roche (United States)

ROR
https://ror.org/011qkaj49

Funder(s)

Funder type
Industry

Funder Name
F. Hoffmann-La Roche

Alternative Name(s)
Hoffman-La Roche, F. Hoffmann-La Roche Ltd.

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to participant-level data not being a regulatory requirement

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes