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A study to characterize the impact of dietary modification on inavolisib associated hyperglycaemia and to assess the CYP3A4 induction potential of inavolisib using midazolam as a probe substrate in participants with incurable metastatic solid tumours previously treated with multiple (≥2) lines of therapy

Submission date 24/08/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 24/08/2022	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 27/08/2024	**Condition category** Cancer	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
Cancer is a disease in which abnormal cells divide without control and can invade nearby tissues. Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) is a gene that controls a message telling cells to grow and multiply. This message is often involved in cancer when cells lose the ability to turn it off. This messaging system is called the PI3K cancer pathway. Inavolisib, the drug that is being studied, is designed to block the wrong messaging from the mutated PIK3CA gene and, therefore, block the PI3K cancer pathway described above.

The main purpose of this study is:
1. To investigate the effect of dietary modification, in the form of a low carbohydrate diet, on inavolisib associated hyperglycaemia (high levels of glucose [sugar] in the blood) in high-risk participants (BMI (body mass index) ≥ 30 and/or pre-diabetic) and low-risk participants (BMI < 30 and non-diabetic).
2. To determine the effect of morning (AM) dosing versus evening (PM) dosing of inavolisib in combination with a low carbohydrate diet on hyperglycaemia and changes in blood sugar levels in participants
3. To study the effect of multiple doses of inavolisib on how quickly and to what extent a dose of a mild sedative known as midazolam is absorbed and eliminated from the body, in Arm A

Who can participate?
People aged at least 18 years with PIK3CA-wild type or PIK3CA-mutated incurable metastatic solid tumours including breast cancer, endometrial cancer, ovarian cancer, head and neck squamous cell carcinoma, or colorectal cancer who have progressed after two or more prior lines of therapy.

What does the study involve?
The length of participation in the study depends on how long the participants continue to benefit from the treatment, which could range from one day up to a maximum of 2 years.
The study involves three parts:
1. Screening period of 21 days (to see if the participants are eligible for the study): The participants will be asked to complete some procedures and tests, including taking some blood and urine samples to check their eligibility. They might be asked to come back for further visits for confirmation.
2. Pre-treatment period of 6 days where participants will be started on a low carbohydrate diet.
3. Treatment Phase: The participants will receive the treatment drug(s) in 28-day cycles (each 28-day period is called a "cycle"). The participants will be expected to stay on a low carbohydrate diet in the first 3 cycles and thereafter it is recommended but not mandatory to follow the same. During this study, the participants will be confined to the clinical research unit for a few days and will also have to make a few clinic visits on certain other days. The glucose (sugar) levels in the blood will be monitored via a continuous glucose monitoring device and participants will also be asked to attend regular radiographic tumour assessments (every 8 weeks) where images of the tumour will be recorded.
4. Follow-up (to check on the participant after treatment is finished): Following study treatment discontinuation, participants will be followed for safety for 30 days after final study treatment (30-day safety follow-up, including a 30-day follow-up visit), or until the start of another anti-cancer therapy, whichever occurs first. There will be additional hyperglycaemia follow-up, if required, which will be monitored until resolution or for 90 days, whichever is sooner

Participants will be enrolled in two separate groups namely:
1. Arm A- Participants in this group will receive inavolisib tablets, to be taken by mouth, once daily either as morning or evening dose, starting on Day 2 of Cycle 1 through the discontinuation of study treatment. Participants will also receive midazolam syrup/solution, to be taken by mouth, once on Day 1 and 15 of Cycle 1.
2. Arm B1- Participants in this group will receive inavolisib tablets, to be taken by mouth, once daily either as morning or evening dose on Days 1-28 on each 28-day cycle.
3. Arm B2- Participants in this group will receive inavolisib tablets, to be taken by mouth, once daily as evening dose on Days 1-28 on each 28-day cycle.

The treatment will continue until the cancer worsens, the participants have medically unacceptable side effects, or if the participants decide to withdraw from the study.

What are the possible benefits and risks of participating?
Participants will not receive any direct medical benefit from participating in this study, but the information will other people who have a similar medical condition 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 very common side effects of inavolisib based on human and laboratory studies or knowledge of similar drugs, are listed below. There may be side effects that are not known at this time.
Hyperglycaemia (increased blood sugar levels)
Diarrhoea (loose stools)
Decreased appetite

Vomiting
Nausea
Dysgeusia/taste disorder (abnormal taste in mouth)
Fatigue
Alopecia (hair loss)
Decreased weight
Constipation
Flatulence (gas)
Rash
Mucosal inflammation/stomatitis (inflammation of the lining of the mouth or ulcers of the lip or mouth)
Asthenia (weakness)
Headache
Thrombocytopenia (low levels of cells called platelets)
Hyponatremia (low sodium)
Lymphopenia (low levels of a type of white blood cell)
Eye inflammatory disorder (eye pain or sensitivity to light)
Cataract (cloudiness of the eye)
Colitis (inflammation [swelling and redness] of the large bowel [colon])
Possible harm to a developing foetus, including birth defects and/or miscarriage
Pneumonitis (inflammation of the lungs that may cause difficulty breathing and can be life threatening)
Depressed immune function that may lead to increased risk of infections
In males, reduced fertility or permanent sterility

Midazolam is a sedative drug and is used before surgical procedures. The following are the side effects:

Tiredness, loss of memory, impaired attention, and impaired muscular function, which may adversely affect the ability to drive or use machines
Some other “unknown” side effects include euphoria, depression, restlessness, drug dependence, drowsiness, headache, transient loss of memory, cardiac arrest, reduced respiratory rate, gastrointestinal disorders, skin reactions, weakness of muscles, tiredness, hypersensitivity.

There may be some risks associated with the procedures performed during the study:

For blood samples - Discomfort due to swelling or bruising around the injection site, light-headedness, fainting (uncommon) and a small risk of infection at the injection site
For electrocardiogram (ECG) - The sticky pads placed on the chest may cause skin irritation
For magnetic resonance imaging (MRI) scans - If the participant doesn’t like confined spaces, it may make them feel uncomfortable being in the MRI scanner
For computed tomography (CT) scans - A CT scan is a source of radiation exposure. Although the radiation that would be received is minimal it may increase the risk of cell changes in the body or having cancerous tumours. The radiation received in this study is no more than the normal diagnosis and treatment of the illness and is not expected to greatly increase these risks, but the exact increase in such risks is unknown.

There may be a risk in exposing an unborn child to 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 drug. 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 Ltd (USA)

When is the study starting and how long is it expected to run for?
August 2021 to July 2024

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

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Protocol serial number
GP43040

Study information

Scientific Title
A Phase I, open-label, non-randomized study to characterize the impact of dietary modification on inavolisib associated hyperglycemia and to assess the CYP3A4 induction potential of inavolisib using midazolam as a probe substrate in patients with incurable metastatic solid tumors previously treated with multiple (≥2) lines of therapy

Study objectives
The purpose of the study is to investigate the impact of dietary modification (low carbohydrate diet) on hyperglycaemia associated with inavolisib when administered as a single oral agent and to assess the impact of inavolisib on the sensitive CYP3A4 substrate midazolam.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 23/02/2022, MINISTRY OF HEALTH OF THE REPUBLIC OF MOLDOVA (MD 2009, Chisinau City, 3, A. Cosmescu Street, Republic of Moldova; +373 22 20 54 14; comitetetica@msmps.gov.md), ref: 1249

2. Approved 21/03/2022, Medicines and Medical Devices Agency (2/1 Korolenko Street, MD-2028, Chisinau, Republic of Moldova; +373 22 884301; office@amdm.gov.md)

Primary study design
Interventional

Study design
Phase I open-label non-randomized parallel design study

Study type(s)
Other

Health condition(s) or problem(s) studied
Metastatic solid tumours

Interventions
Arm A: Participants will receive inavolisib, 9 milligrams (mg), orally, once daily (QD) starting on Day 2 of Cycle 1 through the discontinuation of study treatment due to adverse events, withdrawal of consent, or disease progression. Participants will receive the medication(s) as a morning (AM) dose, in Cycle 1 and from Day 8 of Cycle 2 until the end of study treatment. During Day 1 through Day 7 of Cycle 2, participants will receive the medication(s) as an evening (PM) dose. Participants will also receive midazolam, 5 mg, orally on Days 1 and 15 of Cycle 1.

Arm B1: Participants will receive inavolisib, 9 mg, orally, QD starting on Day 1 of Cycle 1 through the discontinuation of study treatment due to adverse events, withdrawal of consent, or disease progression. Participants will receive the medication as a morning (AM) dose, in Cycle 1 and from Day 8 of Cycle 2 until the end of study treatment. During Day 1 through Day 7 of Cycle 2, participants will receive the medication as an evening (PM) dose.

Arm B2: Participants will receive inavolisib, 9 mg, orally, QD, as an evening (PM) dose starting on Day 1 of Cycle 1 through the discontinuation of study treatment due to adverse events, withdrawal of consent, or disease progression.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Inavolisib, midazolam

Primary outcome(s)
1. Percentage of Participants with Severity of Inavolisib Associated Hyperglycaemia as Assessed as an Adverse Event (AE) per National Cancer Institute-Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0) from Pre-treatment till 30-days Post Final Dose of the Study Treatment (approximately up to 2 years)
2. Change in Blood Glucose Levels as Assessed by Laboratory Measurements at Multiple Timepoints from Pre-treatment till Day 1 of Cycle 3
3. Average Glucose over 24 hours Assessed Using Continuous Glucose Monitoring (CGM) of Participants Receiving Inavolisib in Arm A, Arm B1, and Arm B2 at Multiple Timepoints from Pre-

treatment till Day 1 of Cycle 3
4. Peak Glucose over 24 hours Assessed Using CGM of Participants receiving Inavolisib in Arm A, Arm B1, and Arm B2 at Multiple Timepoints from Pre-treatment till Day 1 of Cycle 3
5. Average Glucose over 24 hours Assessed Using CGM of Participants Receiving Morning (AM) Dosing of Inavolisib Versus Evening (PM) Dosing of Inavolisib in Arm A, Arm B1, and Arm B2 at Multiple Timepoints from Pre-treatment till Day 1 of Cycle 3
6. Peak Glucose over 24 hours Assessed Using CGM of Participants Receiving Morning (AM) Dosing of Inavolisib Versus Evening (PM) Dosing of Inavolisib in Arm A, Arm B1, and Arm B2 at Multiple Timepoints from Pre-treatment till Day 1 of Cycle 3
7. Percentage of Participants with AEs from Pre-treatment till 30-days Post Final Dose of the Study Treatment (approximately up to 2 years)
8. Percentage of Participants with Severity of AEs per NCI-CTCAE v5.0 from Pre-treatment till 30-days Post Final Dose of the Study Treatment (approximately up to 2 years)
9. Maximum Observed Concentration (Cmax) of Inavolisib at Multiple Timepoints from Day 1 (Day 2 for Arm A) of Cycle 1 till Day 1 of Cycle 3
10. Area under the Concentration-time Curve from Hour 0 to the Last Measurable Concentration (AUC0-t) of Inavolisib at Multiple Timepoints from Day 1 (Day 2 for Arm A) of Cycle 1 till Day 1 of Cycle 3
11. Cmax of Midazolam in Arm A at Multiple Timepoints from Day 1 of Cycle 1 till Day 16 of Cycle 1
12. AUC0-t of Midazolam in Arm A at Multiple Timepoints from Day 1 of Cycle 1 till Day 16 of Cycle 1
13. Area under the Concentration-time Curve Extrapolated to Infinity (AUC0-∞) of Midazolam in Arm A at Multiple Timepoints from Day 1 of Cycle 1 till Day 16 of Cycle 1

Key secondary outcome(s)
There are no secondary outcome measures

Completion date
05/07/2024

Eligibility

Key inclusion criteria
1. Participants must be at least 18 years of age at time of signing Informed Consent Form
2. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs
3. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm
4. Incurable metastatic phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)-wild type or PIK3CA-mutated solid tumours previously treated with multiple (≥2) lines of therapy
5. For Arm A of the study: non-obese, non-diabetic participants with BMI <30 kilogram per square metre (kg/m²), fasting blood sugar (FBG) <126 milligram per decilitre (mg/dL) (7.0 mmol /L) and glycated haemoglobin (HbA1C) <5.7% at screening
6. For Arm B1 and Arm B2 of the study: Obese participants and/or prediabetic participants with BMI ≥30 kg/m², FBG 126-140 mg/dL (7.0-7.8 mmol/L) and HbA1C between 5.7% and <7% at screening
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤2
8. Life expectancy of ≥12 weeks
9. Adequate hematologic and organ function within 14 days prior to initiation of study treatment

10. Ability, in the investigator’s judgment, and willingness to comply with all study-related procedures

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
3

Key exclusion criteria
1. Any history of leptomeningeal disease or carcinomatous meningitis
2. Type 2 diabetes requiring ongoing systemic treatment at the time of study entry; or any history of Type 1 diabetes
3. Prior treatment with any phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), or mammalian target of rapamycin (mTOR) inhibitor, or any agent whose mechanism of action is to inhibit the PI3K-AKT-mTOR pathway
4. Inability or unwillingness to swallow pills
5. Malabsorption syndrome or other condition that would interfere with enteral absorption
6. Known and untreated, or active central nervous system (CNS) metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control). Participants with a history of treated CNS metastases are eligible with few criteria
7. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures once per 2 weeks or more frequently
8. Serious infection requiring IV (intravenous) antibiotics within 14 days prior to Day 1 of Cycle 1
9. Any concurrent ocular or intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, would require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition
10. Active inflammatory (e.g., uveitis or vitritis) or infectious (e.g., conjunctivitis, keratitis, scleritis, or endophthalmitis) conditions in either eye or history of idiopathic or autoimmune-associated uveitis in either eye
11. Participants requiring any daily supplemental oxygen
12. Symptomatic active lung disease, including pneumonitis
13. History of or active gastrointestinal inflammatory disease (e.g., Crohn’s disease or ulcerative colitis) or any active bowel inflammation (including diverticulitis)
14. Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy
15. Clinically significant and active liver disease, including severe liver impairment (Child-Pugh Class B/C), viral or other hepatitis, current alcohol abuse, or cirrhosis
16. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-

related illness
17. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, metabolic, or infectious disease) or any other diseases, active or uncontrolled pulmonary dysfunction, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, that may affect the interpretation of the results, or that renders the participant at high risk from treatment complications
18. Major surgical procedure, or significant traumatic injury, within 4 weeks prior to initiation of study treatment or anticipation of the need for major surgery during study treatment
19. Minor surgical procedures <7 days prior to initiation of study treatment
20. Chemotherapy within 2 weeks or 5 half-lives, whichever is longer, prior to initiation of study treatment. Radiotherapy, or any other anti-cancer therapy within 2 weeks prior to initiation of study treatment
21. Investigational drug(s) within 4 weeks before initiation of study treatment
22. Unresolved toxicity from prior therapy, except for hot flashes, alopecia, and Grade <2 peripheral neuropathy
23. History of other malignancy within 5 years prior to screening with few exceptions
24. History of or active clinically significant cardiovascular dysfunction
25. Clinically significant electrolyte abnormalities (e.g., hypokalaemia, hypomagnesemia, hypocalcaemia)
26. Chronic corticosteroid therapy of ≥10 mg of prednisolone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease
27. Treatment with strong CYP3A4 inducers or strong CYP3A4 inhibitors within 1 week or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment and until the end of study treatment
28. Treatment with mild or moderate CYP3A4 inhibitors or inducers (including St. John’s wort) within 1 week or 5 drug-elimination half-lives, whichever is longer, prior to dosing until Day 16 of Cycle 1 for participants in Arm A of the study
29. Allergy or hypersensitivity to components of the inavolisib formulation
30. Pregnant, lactating, or breastfeeding, or intending to become pregnant during the study or within 60 days after the final dose of study treatment
31. Women of childbearing potential (including those who have had a tubal ligation) must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment

Date of first enrolment
05/09/2022

Date of final enrolment
12/01/2024

Locations

Countries of recruitment
Moldova

Romania

Study participating centre

Arensia Research Clinic at Carol Davila Hospital
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Study participating centre
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Study participating centre
Arnesia Exploratory Medicine - Moldova - Institute of Oncology
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Sponsor information

Organisation
F. Hoffmann-La Roche Ltd

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?
Study website	Study website	11/11/2025	11/11/2025	No	Yes