A Modular, Multipart, Multi-arm, Open-label, Phase I/IIa Study to Evaluate the Safety and Tolerability of EP0042 Alone and in Combination with Anti-cancer Treatments in Patients with Advanced Malignancies

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This study has been transitioned to CTIS with ID 2024-514588-24-00 check the CTIS register for the current data. Core Primary Objectives:1. To investigate the safety and tolerability of EP0042 given alone or in combination with anti-cancer...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON52508

Source
ToetsingOnline

Brief title
EP0042-101

Condition

- Leukaemias

Synonym
Cancer, Malignancy

Research involving

Human

Sponsors and support

Primary sponsor: Ellipses Pharma Limited
Source(s) of monetary or material Support: Ellipses Pharma Limited

Intervention

Keyword: advanced cancer, AML (acute myeloid leukaemia), EP0042-101

Outcome measures

Primary outcome

Module 1 Primary Endpoints:

1. Incidence of DLT, adverse events (AEs), serious adverse events (SAEs) and changes in laboratory parameters, physical examination, vital signs and electrocardiograms (ECGs).

Module 2 Primary Endpoints:

1. Incidence of DLTs, AEs, SAEs and changes in laboratory parameters, physical examination, vital signs and electrocardiograms.

Secondary outcome

Module 1 Secondary Endpoints:

1. Plasma PK parameters (AUClast, AUCinf, Cmax and/or Cmin, Tmax, t1/2, CL/F, V/F and/or Vz/F) after single and multiple doses

2. Best overall response (BOR)

3. Duration of response (DOR)

4. Overall survival (OS)

Module 2 Secondary Endpoints:

1. Plasma PK parameters (AUClast, AUCinf, Cmax and/or Cmin, Tmax, t1/2, CL/F,

V/F and/or Vz/F) of EP0042 and combination agents after single and multiple

doses.

2. BOR

3. DOR

4. Event free survival (EFS)

5. Relapse free survival (RFS)

6. OS

Study description

Background summary

Acute myeloid leukaemia (AML) is a blood cancer characterised by excessive production of abnormal white blood cells called blasts, in the blood and bone marrow. AML is a rare disease with one of the lowest survival rates and can lead to death within weeks if left untreated. Chemotherapy can be used to treat newly diagnosed AML, however most patients who achieve complete remission relapse within 1-3 years.

The study medication, EP0042, has been developed to treat AML by combining the activities of 2 established cancer treatment pathways called FLT3 inhibitor and Aurora kinase inhibitor. The FLT3 gene is involved in production and survival of leukaemia and other cancer cells. Aurora kinase is an enzyme involved in the division and multiplication of cells in different tumours. Both types of medicines have been given to patients with AML in other studies as separate drugs, but this study will investigate the combination of the 2 cancer treatments in 1 drug.

This is a first time in human study to test the effect of EP0042 alone and in combination with anti-cancer treatments in patients with advanced cancer.

Study objective

This study has been transitioned to CTIS with ID 2024-514588-24-00 check the CTIS register

for the current data.

Core Primary Objectives:
1. To investigate the safety and tolerability of EP0042 given alone or in combination with anti-cancer treatments.

Module 1 Primary Objectives:
1. To investigate the safety and tolerability of EP0042 given as a monotherapy in patients with relapsed or refractory (R/R) AML (AML, MDS or CMML).

Module 2 Primary Objectives:
1. Part A: To evaluate the safety, tolerability, of EP0042 + a Bcl-2 inhibitor (venetoclax) in patients with R/R FLT3 wildtype (WT) AML.
2. Part B: To evaluate the safety, tolerability, of EP0042 in combination with a Bcl-2 inhibitor (venetoclax) + a hypomethylating agent (azacitidine) in patients with R/R FLT3 WT or newly diagnosed AML.

Core Secondary Objectives:
1. To characterizse the pharmacokinetics (PK) of EP0042, given alone or in combination with anti-cancer treatments, after a single dose and at steady state after multiple dosing.
2. To assess the biological and anti-tumor activity of EP0042, given alone or in combination with anticancer treatments.

Module 1 Secondary Objectives:
1. To characterizse the (PK) of EP0042, given as a monotherapy, after a single dose and at steady state after multiple dosing.
2. To assess the efficacy of EP0042, given as a monotherapy in patients with relapsed or refractory AML (and MDS or CMML).

Module 2 Secondary Objectives:
1. To characterize the PK of EP0042 + combination agent(s), after a single dose and at steady state after multiple dosing.
2. To assess the efficacy of EP0042 + combination agent(s) in patients with AML.

Study design

Module 1, in patients with AML, will be performed initially and include intensive safety monitoring to ensure the safety of study patients. Module 2 will explore the combination of EP0042 with other approved anti-cancer treatments. Further modules may be added later as substantial protocol amendments.

The EP0042 starting dose and schedule of EP0042 in Module 1 was selected using the pre-clinical data and the Food and Drug Administration (FDA) and ICHS9

guidance for industry for selection of a starting dose in cancer patients. The starting dose in subsequent modules will be determined by the Safety Monitoring Committee (SMC) based on emerging clinical data. In each module, the frequency of dosing and washout (off-treatment period) may change based upon emerging data, as reviewed and agreed by the SMC, without the requirement to submit a substantial amendment to the protocol. The frequency of PK sampling may also be modified based on SMC review and may include up to three additional PK samples of 4 ml within any given cycle, in order to better characterize the PK profile, based upon emerging PK data. Only patients who provide written informed consent and meet all inclusion and no exclusion criteria will be enrolled into the respective study module.

Once the maximum tolerated dose (MTD) has been identified in Module 1, recruitment of approximately 9-18 additional patients may be initiated in order to obtain further safety and efficacy data for identification of the optimal dose and schedule to take forward into Module 2.

In all treatment combinations (e.g. Module 2, EP0042 + venetoclax + azacitidine) the dose of each approved standard of care combination agent will not exceed its approved dose.

Intervention

This is a modular, Phase I/IIa study to investigate the optimal dose of EP0042 when used as monotherapy dose or in combination with other anti-cancer treatments.

The design consists of a core study protocol and individual modules, as follows:

1. Module 1: EP0042 Monotherapy dosing in patients with relapsed/refractory (R/R) acute myeloid leukemia (AML), chronic myelomonocytic leukemia (CMML) or myelodysplastic syndrome (MDS): dose escalation and dose optimization.

2. Module 2: EP0042 Combinations in R/R AML patients.

This protocol includes Modules 1 and 2. Additional modules may be added in the future. Initiation of further modules will occur only following approval of a substantial protocol amendment.

Study burden and risks

Risks, burdens and benefit:
Module 1 of the study is a first in human Phase I dose escalation study with EP004, a dual FLT-3 and Aurora Kinase A/B inhibitor, in patients with AML.Both FLT-3 and Aurora Kinase A/B inhibitors have individually shown levels of clinical efficacy, with the dual combination, as EP0042,

demonstrating evidence of anti-tumour activity in both in vitro and in vivo preclinical experiments. The safety profile of both Aurora kinase inhibitors and various FLT-3 inhibitors have been well profiled in clinical trials. The study design aims to minimize potential risks and is being conducted with several parameters identified to maximize the benefit of and minimize the risks to patients enrolled in the study. Measures taken to minimize the risks to patients participating in the study include: a Cycle 0 for patients in cohort 1 (to determine the half-life of EP0042 after a single dose of EP0042, before entering repeat dosing in Cycle 1, to assess and reduce the risk of accumulation with appropriate dose/schedule adjustment), staggered dosing (7 days apart) of the first 2 patients in each cohort, regular monitoring of peripheral blood counts, vital signs, ECGs, physical examinations, laboratory safety tests and dose escalation adjustment pending safety signals.

There may be risks, discomforts and inconveniences associated with study procedures. Participants will be required to visit the research site and undergo tests and procedures more frequently than they would if they were not in the study. This may be seen as a potential burden to the participant. However, participants will be assured that these visits and procedures are very important and are required to ensure their safety by close monitoring of their health. Related study procedures will be performed by a qualified study nurse, a doctor or phlebotomy trained health care professional within the hospital.

Some of the procedures that will be performed in the study are described below:
- Bone marrow aspirate samples are collected using a needle and syringe which removes liquid bone marrow.
- Bone marrow trephine samples involve the collection of a 1 or 2 cm sample of bone marrow (these are optional and will only be requested if a bone marrow aspirate is not able to be obtained.')
- Blood draws for routine clinical haematology, biochemistry and biomarkers.

Informed Consent
All patients will be fully informed of all study assessments and what is required of them to take part in the study, each patient will be asked to complete a consent form in order to participate in the study.

Laboratory tests
Lab tests performed could be uncomfortable or painful but are necessary to monitor the patient's health status.
The Investigator must ensure that all participants* confidentiality will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents that are submitted to the sponsor, participants should be identified by an identification code and not by their names. The sponsor will control all data collected during the study, and will abide by the General Data Protection Regulation (GDPR).

Receiving treatment could result in a positive AML / MDS / CMML disease

response but there is no guarantee that the patients will receive a direct medical benefit by participating in this research study. However, it is hoped that the information gathered as part of this research study may help those with advanced cancers in the future.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Core Inclusion Criteria:
1. Male or female patients aged >= 18 years of age, at the time of informed consent, with histological or cytological confirmation of leukemia.
2. Ability to understand and provide written informed consent before any study-specific procedures, sampling, or analyses, including access to archival tumor tissue.

3. Ability to swallow and retain oral medication.

Exclusion criteria

Core Exclusion Criteria:
1. Suspected brain and/or leptomeningeal metastases that are symptomatic or untreated or that require current therapy.
2. Ongoing toxic manifestations of previous treatments that have not reduced to at least Common Terminology Criteria for Adverse Events (CTCAE) Grade 1. Exceptions to this are alopecia or certain Grade 2 treatment related toxicities, which in the opinion of the Investigator should not exclude the patient.
3. Creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 50 mL/min.
4. Receiving an investigational anti-cancer treatment concurrently or within 14 days or five half-lives of either the parent drug or any active metabolite prior to the start of treatment with EP0042. Patients with AML may receive hydroxyurea throughout the screening period and during the first 2 cycles of study treatment in the first module (FIH study).
5. Current refractory nausea and vomiting, malabsorption syndrome, disease significantly affecting gastrointestinal (GI) function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery such as gastric bypass.
6. Known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection per institutional protocol. Testing for HBV or HCV status is not necessary unless clinically indicated or the patient has a history of HBV or HCV infection.
7. Patients with active human immunodeficiency virus infection (HIV) infection (testing is not required). Patients living with HIV will be eligible if they have CD4+ T-cell count >= 350 cells/µL, no history of AIDS-defining opportunistic infections in the past 12 months, and can be managed on a regimen consistent with this protocol's permitted concomitant medications.
8. Malignant disease other than that being treated in this study, with the following exceptions:
a. Malignancies that were treated curatively and have not recurred within 2 years prior to study treatment.
b. Completely resected basal cell and squamous cell skin cancers.
c. Any malignancy considered to be indolent and that has never required therapy.
d. Completely resected carcinoma in situ of any type.
9. Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures, or interpretation of study results.
10. Any major surgical procedure (in the investigator's judgement) within 2 weeks of the first dose of study drug.

11. Pregnant, likely to become pregnant, or lactating women (where pregnancy is defined as the state of a female after conception and until the termination of gestation).

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-09-2021
Enrollment:	13
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	-

Ethics review

Approved WMO Date:	19-03-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	12-05-2021
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-08-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-08-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-08-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	21-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-02-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-03-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-04-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-514588-24-00
EudraCT	EUCTR2020-000168-53-NL
ClinicalTrials.gov	NCT04581512

Register	ID
CCMO	NL74204.078.20