A Phase I/II Open-Label, Three-Part, Dose-Finding and Separate Cohort Expansion Trial to Assess the Safety, Tolerability and Preliminary Efficacy of Repeated Doses of CLEVER-1 Antibody FP-1305, in Subjects with Advanced Solid Tumours.

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Principal objectives: •To determine the safety, tolerability and recommended dose of FP-1305 in subjects withadvanced solid tumours of the selected tumourtypes without standard treatment options.• To determine the safety, tolerability and early...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54504

Source
ToetsingOnline

Brief title
MATINS

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym

advanced solid tumours

Research involving
Human

Sponsors and support

Primary sponsor: Faron Pharmaceuticals Ltd
Source(s) of monetary or material Support: Faron Pharmaceuticals

Intervention

Keyword: Advanced Solid Tumours., Antibody FP-1305, CLEVER-1

Outcome measures

Primary outcome

Part I

• Tolerable dose(s) was determined by the TITE-CRM based on the occurrence/non-occurrence of dose limiting toxicities (DLT) in the trial subjects.

Part II

• Safety and tolerability will be defined by physical examination, adverse events and by safety laboratory tests. Adverse events are collected, graded and reported according to the NCI-CTCAE version 5.0. Medical Dictionary for Regulatory Activities (MedDRA) terminology will be used to classify, record, manage, and analyse the data. Tolerability of new dose(s) will be determined based on the occurrence/non-occurrence of DLT during 28 days following the first dose of FP-1305 in subjects evaluable for DLT assessment in Part II.

• The ORR, CBR and irORR (separetely) to the treatment will be determined by tumour imaging according to Response Evaluation Criteria In Solid Tumors

(RECIST) 1.1 based on images obtained during Cycle 7. The clinical benefit rate (CBR) is the proportion of subjects that have a complete response (CR), partial response (PR), or stable disease (SD). The irORR will also be calculated. Results from each tumour type, dose level and dosing frequency will be reported separately.

Part III

• The ORR, CBR and IrORR (separetely) to the treatment will be determined by tumour imaging according to RECIST 1.1 based on images obtained during Cycle 7. Results from each tumour type will be reported separately.

Secondary outcome

Secondary outcome measures:

Part I

• The PK profile of a single dose (during Cycle 1) and repeated doses (during Cycles 1-5) of FP 1305 was determined by repeated measurements of the drug concentration in the circulation. Peak concentration (Cmax), trough concentration (Cmin), area under the plasma concentration versus time curve (AUC), clearance, volume of distribution, and terminal half-life (t1/2) for each dose level was determined.

• Immunogenicity was evaluated by assessing anti-drug antibodies in the circulation periodically during treatment and follow-up.

• The ORR to the treatment was determined by tumour imaging according to RECIST 1.1. The CBR is the proportion of subjects that have a complete response, partial response, or stable disease. The irORR was also calculated.

Part II

• The PK profile of a single dose (during Cycle 1) and repeated doses (during Cycles 2-5) of FP 1305 will be determined by repeated measurements of the drug concentration in the circulation. Peak concentration (Cmax), trough concentration (Cmin), AUC, clearance, volume of distribution, and terminal half-life (t1/2) for each dose level will be determined. Results from each tumour type will be reported separately.

• Immunogenicity will be evaluated by assessing anti-drug antibodies in the circulation periodically during treatment and follow-up. Results from each tumour type will be reported separately.

• Potential genetic, cellular and other predictive markers will be associated with FP 1305 clinical activity as determined by ORR, CBR and irORR. This includes but not limited to the correlation of response and immune cell profile, cytokine/chemokine profile and the proportion of CLEVER 1-positive monocytes; Cluster of Differentiation (CD)4, CD8, their ratio and regulatory T cells in the circulation and in tumour specimens prior to treatment and in circulation during the first cycle of treatment.

• The duration of response is measured from the time of initial response until documented tumour progression, death, or dropout.

• Safety and tolerability will be defined by physical examination, adverse events and by safety laboratory tests. Adverse events are graded and reported according to the NCI-CTCAE version 5.0. MedDRA terminology will be used to classify, record, manage, and analyse the data.

Part III

• The population PK of FP 1305 will be determined by measurements of the drug concentration in the circulation between Cycles 1 and 5. Results from each tumour type will be reported separately.

• Immunogenicity will be evaluated by assessing anti-drug antibodies in the circulation periodically during treatment and follow-up. Results from each tumour type will be reported separately.

• The duration of response is measured from the time of initial response until documented tumour progression, death, or dropout.

• Progression free survival as the time from subject allocation into the trial until documented disease progression according to RECIST 1.1 or death will be measured in the population that has been dosed at least once.

• Overall survival is defined as the time from subject allocation into the trial until death from any cause and will be measured in the population that has been dosed at least once. Data will be censored on the last documented data that the subject has been alive.

• Safety and tolerability will be defined by physical examination, adverse events and by safety laboratory tests. Adverse events are graded and reported according to the NCI-CTCAE version 5.0. MedDRA terminology will be used to classify, record, manage, and analyse the data.

Study description

Background summary

This is a first in human study to identify whether FP-1305 is suitable to use in oncology patients. The previous pre-clinical studies have demonstrated that

FP-1305 binds to a receptor known as CLEVER-1. CLEVER-1 has been shown to support tumour growth. No significant adverse events were witnessed in primates and the dose used will be 300 fold lower than the dose provided to primates which showed no toxicity.
Based on our existing data CLEVER-1 is expressed in these tumour types. Inhibition of CLEVER-1 with FP-1305 may have an anti-tumour effect in these patients.
Subject safety will be closely monitored after the first infusion and regularly throughout the trial. In Part 1, only a single patient at a time was dosed on a new dose level. Dose is escalated step wise once lower dose has been demonstrated safe in study subjects. Dose level is raised until the maximum tolerated dose is reached.
The proposed trial design enables a flexible approach to identify a safe and tolerable dose which has a biological effect and to expand the cohorts of different tumour types after the dose has been selected. Analysis of the primary efficacy in the expansion cohorts early enough with sufficient statistical power allows for a rapid adaptation of the protocol in order to focus on the tumour types in which the treatment demonstrates the most promising activity.
In addition to the Q3W dosing, Protocol Addendum introduces once in two weeks (Q2W) and once in week (Q1W) dosing schemes to be investigated in the Part II of the study. The scientific rationale for investigating more frequent dosing (Q2W and Q1W) is based on Part I PK and receptor occupancy of the CLEVER-1 (refer to Investigator*s Brochure).
During Part II, additional dose levels are tested to investigate tolerability and safety in a broader dose range, and to receive additional data about the PK, RO and preliminary efficacy. The selected doses are 30 mg/kg and 100 mg/kg; other intermediate doses (below 100 mg/kg) may be included if deemed necessary based on accumulated data. The scientific rationale for investigating higher doses (30 mg/kg and 100 mg/kg) is based on the cumulative study data, e.g. PK (relatively fast T1/2) and RO (transient) of the CLEVER-1 at dose levels of 0.1 - 10 mg/kg (refer to Investigator*s Brochure), and accumulated safety data indicating good tolerability of the IMP and no DLT events registered.
Inclusion of multiple distinct cancer types to the first cohort of ten subjects at a new dose level is possible, justified by allowing the investigation of the safety of the dose level in a wider population than just one particular cancer type in Part II. However, if deemed necessary, multiple cohorts with distinct cancer types may be selected to be explored at a dose level (and at more frequent dosing). This approach is justified by allowing the investigation of the safety and preliminary efficacy properly in Part II, as distinct cancer types may respond differently to the treatment.

Study objective

Principal objectives:
•To determine the safety, tolerability and recommended dose of FP- 1305 in subjects withadvanced solid tumours of the selected tumour

types without standard treatment options.
• To determine the safety, tolerability and early efficacy of FP-1305 therapy alone by using measures known as the objective response rate (ORR) (which measures the portion of patients with tumour shrinkage over a period of time), Clinical Benefit Ration (CBR) and immune-related ORR (irORR) (same as above but with particular immune response focus) in distinct groups of subjects with advanced solid tumours of the selected tumour types.
• To assess the objective response rate (ORR, CBR and irORR) in distinct expansion groups of subjects with advanced solid tumours in subjects who show presence of CLEVER-1 molecule from selected tumour types at a selected dose.
Secondary objectives:
To study Pharmacokinetics (drug activity) after different doses
• To assess the immune response to FP-1305
• To understand pharmacokinetics and the anti-drug antibodies (immune system produces a response to the drug to disable it) in different tumour types
• To determine the presence of CLEVER-1 molecule in patients
• To assess ORR & duration of response in different tumour types
• To study Progression free Survival and Overall Survival

Study design

This is a first in human study to determine the safety, tolerability and preliminary efficacy of FP-1305 administered in three week intervals in addition to 2 week and single week intervals. Each interval is known as termed a cycle.

The study is made up of 3 parts:
Part I: aimed to escalate the dose at defined levels and was aimed to determine the maximum tolerated dose in trial subjects with selected solid tumours. At each dose level, the first patient was observed for the full cycle before a second patient was introduced. This was repeated until the highest dose was reached. Following some statistical analysis, further doses might be opened up to determine the dose to be used in Part II. This is now complete.

Part II: following a review of Part I, tumour types will be selected for expansion of patient numbers. The study will continue in these populations for approximately a year. The dose is selected based on Part I.
Part II has been expanded to include more dosage levels and also more frequent dosing.

Part III: Following further reviews, the tumours with best response according to (Objective Response Rate) ORR will be further expanded to more patients.
For each part of the study, there will be a screening period, a treatment period with FP-1305 that will last as long as the doctor thinks FP-1305 is helping the patient (for a maximum of one year), and a follow-up period, that will last a maximum of 4 weeks after the patient stop treatment with FP-1305.
If the patient decides to take part in this study, the patient will first be

asked to sign and date this PICD.

The patient will then enter the Screening Period: This is usually done in one day but may take up to 4 weeks.
During screening, the study doctor will assess whether the patient meet the study requirements. The study doctor will ask the patient questions about general health, the cancer, other past and ongoing illnesses, and the medications the patient are taking, and other research studies the patient have taken part in.
The patient will be asked for a few blood tests to test for any infections, blood cells and blood chemistry. A pregnancy test will be requested if the patient have the ability to become pregnant. If the patient has symptoms that suggest the cancer has spread to the brain, the patient will be asked to go for a brain scan.
If the study doctor determines that the patient meet the study requirements, the patient will be eligible to participate in the study.

During the Treatment Period:
Part I and II are similar in terms of visit schedule however Part III has fewer visits and will be highlighted below. The study will be divided in treatment cycles that last approximately 3 weeks each. On the first day 1 (D1) of each cycle the patient will receive FP-1305.The treatment may be continued after one year based on the consideration on the investigator.
Part II has been expanded to more frequent dosing and thus Q2W and Q1W have more visits.

FP-1305 will be given to the patient on the first day of every cycle, approximately every 3 weeks for as long as the study doctor thinks FP-1305 is helping the patient (for a maximum of one year).
Throughout the study the patient will be regularly asked about the general health, any other medications the patient are taking and any side effects or complications that may occur while the patient receive FP-1305.

During Follow-up:
After the patient have finished receiving FP-1305 treatments, the patient will be invited for a follow-up visit approximately 3 weeks later.
The follow up visit will approximately take 3 hours.
the study doctor will check the general healthy by doing a physical examination and doing some blood test.

The care of the subject should follow clinical routines. However, treatment can continue beyond one year, if beneficial for the study subject, as judged by the investigator (and provided that the clinical development and manufacturing of FP-1305 continues and it is not available via other routes). In such case, the data collection is limited to the collection of treatment related adverse events (disease progression will be collected through AE reporting) and overall

survival.

Intervention

Non clinical interventions/procedures:
Main Study Informed Consent,
Genetic data informed consent,
Review of Inclusion/Exclusion Criteria,
Demographic data and medical history,
Concomitant medications

Clinical interventions/procedures:
Height, Weight and Physical
Vital Signs
ECG
ECOG
Urine dispstick test (parts I and II)
Pregnancy test
Blood sampling (various including PK) for Part I, II and III
Tumour Biopsy
Tumour imaging
Brain Imaging

Study burden and risks

The study is a first in human study, hence the safety profile is to be developed. Throughout the study the health of the subject will be regularly monitored and appropriate medical intervention will be available if required. Because of this, the only information on side effects comes from studies in animals.
In animals given higher doses than what you will receive, scientists have seen possible damage to the liver. This will be monitored closely by the various blood tests and will be minimised as only one patient will be on each dose level for 3 week period to allow sufficient monitoring.
FP-1305 stimulates the immune system, it is possible that the patient might experience a general body reaction from the infusion. This includes difficulty breathing, low blood pressure high blood pressure, headache, skin rashes and increased temperature. This again will be monitored closely by the study team and treated accordingly.

Electrocardiogram (ECG)
This test is also non-invasive and not painful. The electrocardiogram (ECG) is a tracing of patients heart beating, made by recording tiny changes of electricity produced by their heart at the surface of the skin. To record these changes electrode stickers will be put on patients chest with wires attached to them. It will take about 5-10 minutes

Blood sample analysis
Blood samples will be collected for examination at each visit. Collecting the blood samples might cause discomfort during the study. An anaesthetic cream can be apply to make the area numb and reduce the discomfort.

Taking a tissue biopsy can be painful and carry a risk of swelling, bleeding and infection in the organ from where the biopsy is taken. There are other risks that depend on where the tumour is in the body, for example, the lungs, the liver, the gut, or the skin. This is part of routine care, while in the study this could be more frequent than usual, the medical team will be suitably trained for this task.

CT Scan: The is a risk of generalized body reaction form the contrast agent used to get special images from the CT scan. This includes potential damage to the kidneys. The patient will be monitored closely during the procedure.

The MRI scan makes noise, and leave little space for movement, so the patient may feel anxious during the test. The patient will be monitored throughout the procedure.

Study visits: frequency and duration: The frequency and duration of study visits might have an impact on the participant daily life

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Written Informed Consent
2) Aged >= 18 years male or female
3) Tumour sample should be collected during screening period. If a recent tumour biopsy obtained within six months before the date of consent is available (or older, as agreed on a case by case basis with the sponsor), that may be used. At the discretion of the sponsor, the tumour sample may be optional for certain subjects in Part III
4) Life expectancy > 12 weeks
5) Histologically confirmed advanced (inoperable or metastatic) malignancies in which (according to the view of the investigator) no curative, effective or suitable treatment options exist:
o Hepatocellular carcinoma
o Gallbladder cancer or intra- or extrahepatic cholangiocarcinoma
o Colorectal adenocarcinoma
o Serous poorly differentiated (Grade 3) ovarian adenocarcinoma or undifferentiated ovarian cancer
o Pancreatic ductal adenocarcinoma
o Immunotherapy (IO) resistant cutaneous melanoma (progression during programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody therapy)
o Uveal melanoma in Parts II and III
o Gastric adenocarcinoma (including adenocarcinoma of the distal esophagus / GE junction) in Parts II and III
o ER+ breast cancer in Parts II and III
o Anaplastic thyroid cancer in Parts II and III
6) ECOG performance status 0 or 1
7) Measurable disease in Parts II and III
8) Adequate bone marrow, liver and kidney function defined as
Blood white blood cell >= lower limit of normal
Blood neutrophil count >= 1x109/L Blood platelet count >= 100x109/L, for HCC >= 50x109/L
Blood haemoglobin >= 9.0 g/dL

Creatinine clearance > 40 mL/min calculated by Cockcroft-Gault formula AST <= 3 X ULN (<= 5 x ULN when HCC or hepatic metastases are present)
ALT <= 3 X ULN (<= 5 x ULN when HCC or hepatic metastases present)
Bilirubin <= 1.5 X ULN
Albumin >= 3.0 g/dL
The most recent measurements taken during the screening period must be within the required limits for the patient to be considered eligible (i.e. criteria met once during the screening period are not sufficient if there are more recent measurements available that are not within the required limits. It is however acceptable to repeat measurements if the initial measurements or subsequent measurements taken during the screening period are not within the required limits; the patient is eligible providing that the newest measurements are within the required limits). However, once a subject is out of the screening period, and has had eligibility confirmed and been enrolled, the pre-dose laboratory assessments are not subjected to inclusion criteria limits, but only for investigators assessment of subject safety.
9) Women of child-bearing potential must have a negative pregnancy test in serum prior to trial entry
10) Women of child-bearing potential and men who have partners of child-bearing potential must be willing to practise highly effective contraception for the duration of the trial and for three months after the completion of treatment

Exclusion criteria

1) Less than 21 days since the last dose of intravenous anticancer chemotherapy or less than five half-lives from a small molecule targeted therapy or oral anticancer chemotherapy before the first IMP administration
2) Any immunotherapy within preceding 6 weeks from the first IMP administration
3) Investigational therapy or major surgery within 4 weeks before the first IMP administration
4) Active clinically serious infection > Grade 2 NCI-CTCAE version 5.0 within preceding 2 weeks before first IMP administration
5) Brain metastases
6) Subject has not recovered from the previous therapies to Grade <= 1 severity as classified by the NCI-CTCAE version 5.0 (except Grade <= 2 alopecia, neuropathy or thyroid disorders)
7) Pregnant or lactating women
8) History of second malignancy except for non-melanotic skin cancer, cervical carcinoma in situ or superficial bladder cancer, or any other malignancy treated previously with curative intent and more than three years without relapse
9) Evidence of severe or uncontrolled systemic diseases, congestive cardiac failure New York Heart Association class >= 2, Myocardial Infarction within 6

months or laboratory finding that in the view of the investigator makes it undesirable for the subject to participate in the trial
10) Any medical condition that the Investigator considers significant to compromise the safety of the subject or that impairs the interpretation of IMP toxicity assessment
11) Confirmed human immunodeficiency virus infection
12) Symptomatic cytomegalovirus infection
13) Subjects with active auto-immune disorder (except type I diabetes, celiac disease, hypothyroidism requiring only hormone replacement, vitiligo, psoriasis, or alopecia)
14) The subject requires systemic corticosteroid or other immunosuppressive treatment
15) Subjects with organ transplants
16) Subjects in dialysis
17) Use of Live (attenuated) vaccines for 30 days prior to the start of study treatment, during treatment, and until last visit
18) Subject is unwilling or unable to comply with treatment and trial instructions
19) Subjects with known hypersensitivity to the IMP or any of the pharmaceutical ingredients

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-11-2019
Enrollment:	84
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	-
Generic name:	bexmarilimab

Ethics review

Approved WMO Date:	21-03-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-10-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-10-2020

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-09-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-04-2023
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
EudraCT	EUCTR2018-002732-24-NL
ClinicalTrials.gov	NCT03733990
CCMO	NL67687.078.19