A Phase 1, Multicenter, Open-Label, Dose Escalation and Expansion Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of Orally Administered FHD-286 in Subjects with Metastatic Uveal Melanoma

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Primary:• To determine the safety and tolerability of FHD-286 when administered as an oral monotherapy in subjects with metastatic uveal melanoma (UM)• To identify the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D) of FHD-…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON53846

Source
ToetsingOnline

Brief title
FHD-286-C-001

Condition

- Metastases

Synonym
Metastatic Uveal Melanoma, UM

Research involving
Human

Sponsors and support

Primary sponsor: Foghorn Therapeutics Inc.
Source(s) of monetary or material Support: Industry

Intervention

Keyword: FHD-286, Metastatic Uveal Melanoma, Open-Label, Phase 1

Outcome measures

Primary outcome

Incidence of treatment-emergent adverse events (TEAEs), AEs, dose-limiting

toxicities (DLTs), serious AEs (SAEs), and AEs leading to discontinuation;

safety laboratory assessments

Secondary outcome

• Objective Response Rate (ORR)

• Duration of Response (DOR)

• Time to Response (TTR)

• Time to Progression (TTP)

• Progression Free Survival (PFS)

• Overall Survival (OS)

• PK parameter: Area under the plasma concentration time curve (AUC)

• Plasma concentration vs. time profiles

Study description

Background summary

FHD-286 blocks the activity of two proteins, called BRG1 and BRM, that are involved in unpacking tightly wound deoxyribonucleic acid (DNA) in cells. By controlling the unpacking of DNA, these proteins impact which genes in our DNA are active, or *turned on.* In certain types of cancer, the activity of the BRG1 or BRM protein inappropriately allows growth and survival genes to be turned on in the diseased cells, resulting in tumor growth. FHD-286 was tested in animals before giving it to humans. In these animal studies, FHD-286 was found to stop the growth of UM tumors which indicates that it may have potential to help treat UM in humans.

Study objective

Primary:
• To determine the safety and tolerability of FHD-286 when administered as an oral monotherapy in subjects with metastatic uveal melanoma (UM)
• To identify the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D) of FHD-286 in subjects with metastatic UM

Secondary:
• To determine the pharmacokinetics (PK) of FHD-286 when administered as an oral monotherapy in subjects with metastatic UM
• To characterize the preliminary clinical activity associated with FHD-286 in subjects with metastatic UM by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

Exploratory:
• To evaluate the PK/pharmacodynamic (PD) relationship of FHD-286 and changes in peripheral tissue (blood and skin) and tumor biomarkers
• To assess the associations of FHD-286 exposure, clinical activity, and safety with PD and response markers in tumor and peripheral tissues (blood and skin)
• To investigate potential predictive and downstream markers of tumor response and/or resistance in tumor and peripheral tissues (blood and skin)

Study design

This is a Phase 1, multicenter, open-label, dose escalation and expansion study

Intervention

FHD-286 will be supplied as 2.5 mg and 5 mg strength capsules to be administered orally. The starting dose of FHD-286 to be administered to the first cohort is 5 mg once daily. The dose of FHD-286 administered to a subject will be dependent upon which dose cohort is open for enrollment when the subject qualifies for the study. All doses of FHD-286 will be administered orally under fasted conditions, with the exception of at least 6 subjects who will receive a single dose under fed conditions. Food intake instructions and

surrounding administration of FHD-286 may change based on emerging data.

Study burden and risks

The study contains a screening phase, treatment phase and a follow-up phase. We anticipate a 6 month treatment phase for patients with a 28 days safety follow up phase
Visits can last from 2-10+ hours for longer PK days.

The subject will have to undergo several examinations, tests and/or procedures before, during and after his/her treatment. Please refer to the procedure table In the ICF and Schedule of Assessment of the protocol for more information.

In addition, questions are asked about the medical history, demographics and eligibilty questions
Subjects will also be tested for HIV and hepatitis. Female patients will be tested for pregnancy .

The anticipated total duration of the study is approximately 6 months (26 weeks).

Possible side effects that are already known are described in the Investigator's Brochure and the patient informed consent form.

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

1. Subject must be >= 18 years of age.
2. Subject must have a diagnosis of metastatic histologically or cytologically confirmed UM. If histologic or cytologic confirmation of the tumor is not available, clinical confirmation of a diagnosis of metastatic UM, as per standard practice for UM, by the treating investigator can be obtained, and fall into any of the following categories:
• Newly diagnosed subject who has not yet received liver-directed or systemic treatment
• Subject ineligible for any available therapy likely to convey clinical benefit
• Subject who has disease progression after treatment with available therapies and/or who is intolerant to those treatments.
Note: Inclusion criterion 15 provides timing requirements for prior therapy.
3. Subject must have measurable disease by RECIST v1.1, defined as at least 1 lesion that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as >= 10 mm with calipers and/or CT scan. Measurable lesions cannot have undergone any local treatment (including liver-directed radio- or immune- therapies) or radiation, unless there has been interim progression of that lesion, nor can any local treatment or radiation involving measurable lesions be anticipated.
Note: A malignant lymph node must be >= 15 mm on the short axis when assessed by CT scan to be considered pathologically enlarged and measurable.
4. Subject must be able to understand and be willing to sign an informed consent.
5. Subject must be willing and able to comply with scheduled study visits and treatment plans.
6. Subject must be willing to undergo all study procedures (fresh biopsies at baseline, at least 1 additional biopsy on-treatment, and 1 EOT biopsy [unless contraindicated due to medical risk]; archival biopsies of sufficient sample size collected within 6 months of first dose and subsequent to other prior therapies will be accepted as a substitute for a fresh baseline biopsy; other exceptions to this are at the discretion of the Sponsor), laboratory testing, and imaging every 8 weeks for 48 weeks and 12 weeks thereafter until

relapse/progression, start of alternate anticancer therapy, or withdrawal from the study, independent of dose delays, interruptions, or reductions.
7. Subject must have adequate venous access for blood collection.
8. Subject must have an ECOG PS of <= 2.
• Arm 2 (Dose Expansion Phase): Subjects enrolling in Arm 2 must have an ECOG PS of <= 3.
9. Subject must have a life expectancy of >= 3 months.
• Arm 2 (Dose Expansion Phase): Subjects enrolling in Arm 2 must have a life expectancy of >= 2 months.
10. Subject must have adequate hepatic function as evidenced by:
• Serum total bilirubin <= 1.5 × upper limit of normal (ULN) (<= 3.0 × ULN for subjects with Gilbert*s syndrome)
• Aspartate aminotransferase (AST), alanine aminotransferase (ALT) <= 3.0 × ULN (<= 5.0 × ULN if liver metastases are present)
• Prothrombin time (PT) <= 1.5 × ULN or international normalized ratio (INR) <= 1.4
• Activated partial thromboplastin time (aPTT) <= 1.5 x ULN
Note: Anticoagulation therapy is permitted as long as coagulation parameters are within therapeutic range.
• No known portal vein thrombosis
Note: Subjects with organ function outside the parameters outlined in the above inclusion criterion may be permitted to enroll only in Arm 2 of the Dose Expansion Phase at the discretion of the Investigator and the Sponsor.
11. Subject must have adequate renal function as evidenced by:
• Glomerular filtration rate (GFR) >= 50 mL/min (based on a contemporary, widely accepted, and clinically applicable equation that estimates glomerular filtration rate or a measure of glomerular filtration rate)
Note: Subjects with organ function outside the parameters outlined in the above inclusion criterion may be permitted to enroll only in Arm 2 of the Dose Expansion Phase at the discretion of the Investigator and the Sponsor.
12. Subject must have adequate bone marrow function as evidenced by:
• Hemoglobin >= 9 g/dL (Transfusions to achieve this level are allowed.)
• White blood cells (WBCs) >= 2.0 × 109/L
• Absolute neutrophil count (ANC) > 1.0 × 109/L
• Platelets >= 50 × 109/L (Transfusions to achieve this level are allowed.)
Note: Subjects with organ function outside the parameters outlined in the above inclusion criterion may be permitted to enroll only in Arm 2 of the Dose Expansion Phase at the discretion of the Investigator and the Sponsor.
13. Subject must have adequate cardiovascular, respiratory, and immune system function as evidenced by the below criteria and in the opinion of the Investigator:
• LVEF of >= 40% by ECHO (or other means)
14. Subject must agree to abide by dietary and other considerations required during the study.
15. Timing requirements with respect to prior therapy and surgery are as follows:
• At least 2 weeks or at least 5 half-lives, whichever is shorter, must have

elapsed since administration of the last dose of any prior systemic anticancer therapy, including investigational agents. At least 4 weeks must have elapsed if the last regimen included an anti-PD-1/PD-L1 antibody or an anti-CTLA4 antibody. At least 6 weeks must have elapsed
if the last regimen included BCNU or mitomycin C. (Subjects must be intolerant to and/or have experienced disease progression on their prior therapy in the opinion of the treating physician.)
• Subjects must be recovered from any clinically relevant effects of any prior surgery.
• At least 2 weeks must have elapsed since the last radiotherapy. Palliative radiation therapy is permitted so long as it does not involve the target lesion(s) (see exclusion criterion 18).
• At least 2 weeks or at least 5 half-lives, whichever is shorter, must have elapsed since the last liver-directed therapy.
16. Toxicity related to prior therapy must have returned to <= Grade 1 by CTCAE by approximatelly 14 days prior to study start. Exceptions include Grade 2 alopecia, and appropriately controlled Grade 2 hypophysitis, thyroid dysfunction, and adrenal insufficiency.
17. Female subjects must be:
• Postmenopausal, defined as at least 12 months post-cessation of menses (without an alternative medical cause); or
• Permanently sterile following documented hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or tubal ligation or if sexually active with male partners, these partners must be azoospermic (vasectomized or due to a medical cause) as affirmed by the subject; or
• Nonpregnant, nonlactating, and if sexually active with fertile male partner having agreed to use a highly effective method of contraception (ie, hormonal contraceptives associated with inhibition of ovulation or intrauterine device [IUD], or intrauterine hormone-releasing system [IUS], or sexual abstinence) from Screening Visit until 90 days after the final dose of study drug.
Note: The potential risk to female fertility posed by FHD-286 is unknown; it is recommended that subjects discuss options for fertility preservation with their doctor prior to study start.
18. Male subjects must have azoospermia (vasectomized or due to a medical cause) or if fertile and sexually active must agree to use a highly effective method of contraception with their partners of childbearing potential (ie, hormonal contraceptives associated with the inhibition of ovulation or IUD, or IUS, or sexual abstinence) from Screening until 90 days after final dose of study drug. Male subjects must agree to refrain from donating sperm during this time period.
Note: The potential risk to male fertility posed by FHD-286 is unknown; it is recommended that subjects discuss options for fertility preservation with their doctor prior to study start.

Exclusion criteria

1. Subject is unable to provide informed consent and/or to follow protocol requirements.
2. Subject has thrombocytopenia (platelets < 50 × 109/L) or another major bleeding disorder/diathesis.
Note: Subjects with platelets < 50 × 109/L may be permitted to enroll only in Arm 2 of the Dose Expansion Phase at the discretion of the Investigator and the Sponsor.
3. Subject has active brain metastases and/or leptomeningeal disease. Subjects with known central nervous system (CNS) metastases are only permitted under the following conditions; exceptions may be made on a case-by-case basis with approval of the Sponsor: Brain metastases must have been stable for approximately 2 months since completion of most recent CNS-directed intervention. Subject may be on corticosteroids so long as the dose is stable for approximately 14 days or decreasing at the time of study entry.
Anti-epileptic therapy is allowed so long as medications are not otherwise excluded (see exclusion criteria 13 and 14) and seizures have been controlled for approximately 4 weeks since last anti-epileptic medication adjustment.
• Dose Escalation Phase: Subjects with known CNS metastases that meet the above conditions are permitted to enroll in dose escalation.
• Arm 1 (Dose Expansion Phase): Subjects with known or suspected CNS metastases are excluded from Arm 1.
• Arm 2 (Dose Expansion Phase): Subjects with CNS metastases that meet the above conditions are permitted to enroll in Arm 2.
4. Subject has other malignancy which may interfere with the diagnosis and/or treatment of metastatic UM.
5. Subject has active hepatitis B virus (HBV) or hepatitis C virus (HCV) infections; subjects with a sustained viral response to HCV treatment or immunity to prior HBV infection will be permitted. Subject has known positive HIV antibody results or acquired immunodeficiency syndrome (AIDS)-related illness; subjects with CD4+ T-cell counts >= 350 cells/µL will be permitted, as will subjects who have not had an AIDS-related illness within the past 12 months.
6. Subject has an active infection. Subject is permitted to enroll once any required antibiotic and/or antifungal therapy has been completed and/or infection is determined to be controlled.
7. Subject has an uncontrolled intercurrent illness.
8. Subject has corrected QT interval (QTc) using Fridericia*s formula (QTcF) > 470 msecs or other factors that increase the risk of QTc prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome) including heart failure that meets New York Heart Association (NYHA) class III and IV definitions (see Appendix 15.2). Subjects with bundle branch block and a prolonged QTc should be reviewed by the Sponsor for potential inclusion.
9. Subject has any other medical or psychological condition, deemed by the

Investigator to be likely to interfere with a subject*s ability to sign informed consent, cooperate, or participate in the study.
10. Subject has known hypersensitivities to components of the FHD-286 formulation.
11. Subject is unable to tolerate the administration of oral medication or has gastrointestinal (GI) dysfunction that would preclude adequate absorption, distribution, metabolism, or excretion of study drug.
12. Subject is participating in any other clinical trials. Exceptions include participation in any observational or nontherapeutic clinical trials.
13. Subject is on medications that are strong CYP3A inhibitors, are strong CYP3A inducers, or are sensitive CYP3A substrates with narrow therapeutic indices (TIs) (see Appendix 15.5).
14. Subject is on medications with narrow TIs that are sensitive P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) substrates and are administered orally, such as digoxin (see Appendix 15.6).
15. Administration of proton pump inhibitors (PPI) should be stopped or switched to another acid-reducing agent (ARA; eg, antacids or histamine H2-receptor antagonists [H2 blockers]) 7 days before administration of study drug. In the event that it is medically necessary to dose PPIs concomitantly with FHD-286, this may be permitted with Sponsor approval.
16. Subject is requiring clinically significant or increasing doses of systemic steroid therapy or any other systemic immunosuppressive medication. The use of a stable dose of systemic steroids and/or immunosuppressive medication is permitted with Sponsor approval. Local or targeted steroid and immunosuppressive therapies (eg, inhaled or topical steroids) are acceptable. Appropriate steroid replacement to manage endocrine toxicities resulting from prior systemic anticancer therapy is permitted. See exclusion criterion 3 for exceptions regarding steroid therapy for subjects with CNS metastases. See exclusion criterion13for exclusions regarding medications that are strong CYP3A inhibitors, strong CYP3A inducers, or sensitive CYP3A substrates with narrow TIs.
17. Subject has undergone any prior treatment with a BRG1/BRM inhibitor.
18. Palliative radiation or other intervention directed at or involving the target lesion(s) is not allowed. Exceptions to this may be made at the discretion of the Sponsor. See inclusion criterion 15.
19. Subject is pregnant or breastfeeding or is planning to become pregnant within 1 year of study. Subject is a woman or man of childbearing capabilities who is unwilling to use effective contraception.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-03-2023
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	FHD-286
Generic name:	FHD-286

Ethics review

Approved WMO Date:	15-06-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	08-02-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	01-05-2023
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	23-05-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	29-09-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	26-10-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2021-001529-35-NL
ClinicalTrials.gov	NCT04879017
CCMO	NL80362.058.22