A Phase 2 Study to Evaluate the Efficacy and Safety of Belzutifan (MK-6482, formerly PT2977) Monotherapy in Participants with Advanced Pheochromocytoma/Paraganglioma (PPGL), Pancreatic Neuroendocrine Tumor (pNET), or von Hippel-Lindau (VHL) Disease-Associated Tumors, Advanced Gastrointestinal Stromal Tumor (wt GIST), or Advanced Solid Tumors With HIF-2α related Genetic Alterations

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This study has been transitioned to CTIS with ID 2023-504853-11-00 check the CTIS register for the current data. To evaluate the ORR of belzutifan per RECIST 1.1 by blinded independent central review (BICR).

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neoplastic and ectopic endocrinopathies
Study type	Interventional

Summary

ID

NL-OMON53900

Source
ToetsingOnline

Brief title
MK6482-015

Condition

- Neoplastic and ectopic endocrinopathies
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
angiomatosis cerebelli et retinae-associated tumors, Von Hippel Lindau-disease associated tumors

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: MSD / Merck Sharp & Dohme

Intervention

Keyword: Advanced Pheochromocytoma/Paraganglioma, Belzutifan, HIF-2a, Pancreatic Neuroendocrine Tumor, von Hippel-Lindau (VHL) Disease-Associated Tumors

Outcome measures

Primary outcome

- Primary Objectives: To evaluate the ORR of belzutifan per RECIST 1.1 by

blinded independent central review (BICR).

Primary Endpoints: Objective Response (OR): a confirmed complete response (CR)

or partial response (PR)

- Primary Objectives: Cohort B1: To evaluate the ORR of belzutifan per RECIST

1.1 by BICR in VHL disease associated PPGL.

Primary Endpoints: OR.

- Primary Objectives: Cohort B1: To evaluate the ORR of belzutifan per RECIST 1.1 by BICR in VHL disease associated pNET.

Primary Endpoints: OR.

- Primary Objectives: Cohort B1: To evaluate the ORR of belzutifan per RECIST 1.1 by BICR in VHL disease associated RCC among China/Japan participants

Primary Endpoints: OR.

Secondary outcome

• Secondary Objective: To evaluate the duration of response (DOR) of belzutifan in participants with a confirmed CR or PR per RECIST 1.1 by BICR.

Secondary endpoints: DOR: the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first

• Secondary Objective: To evaluate the time to response (TTR) of belzutifan in participants with a confirmed CR or PR per RECIST 1.1 by BICR.

Secondary endpoints: TTR, defined as the time from first dose of belzutifan to first documented evidence of CR or PR

• Secondary Objective: To evaluate disease control rate (DCR) of belzutifan per RECIST 1.1 by BICR.

Secondary endpoints: Disease control: a confirmed CR, PR, or SD

• Secondary Objective: To evaluate progression-free survival (PFS) per RECIST 1.1 by BICR in participants receiving belzutifan.

Secondary endpoints: PFS: the time from first dose of belzutifan to the first documented PD or death from any cause, whichever occurs first

• Secondary Objective: To evaluate the overall survival (OS) of participants receiving belzutifan.
Secondary endpoints: OS: the time from first dose of belzutifan until death from any cause

• Secondary Objective: To evaluate the safety of belzutifan.
Secondary endpoints: Adverse Events (AEs) and discontinuations due to AEs

• Secondary Objective: Cohort B1: To evaluate the tumor specific DOR, TTR, DCR, PFS of belzutifan per RECIST 1.1 by BICR and time to surgery (TTS) in VHL disease associated a.) PPGL, b.) pNET.
Secondary endpoints: DOR, TTR, DCR, PFS and TTS. TTS is defined as the time from the first dose of belzutifan to the first documented surgical intervention or tumor reduction procedure

• Secondary Objective: Cohort B1: To evaluate the DOR, TTR, DCR, and PFS of belzutifan per RECIST 1.1 by BICR and TTS in VHL disease associated RCC among China/Japan participants.
Secondary endpoints: DOR, TTR, DCR, PFS and TTS

for other tertiary outcomes please refer to the protocol.

Study description

Background summary

Hypoxic (pseudohypoxic) signaling with HIF-2α as one of the major drivers of tumorigenesis has been well documented in pheochromocytomas and paragangliomas. HIF-2α has been described as the *Achilles* heel* of tumors with a predominant pseudohypoxic microenvironment such as PPGL, somatostatinomas, RCC, GIST, pNET (VHL disease), hemangioblastoma, pituitary tumors, and other disorders such as polycythemia and retinal abnormalities. Increased accumulation of oncometabolites (from Krebs cycle) like succinate and fumarate (due to mutations in SDHx and FH genes [commonly seen in hereditary PPGL]) results in competitive inhibition of PHDs and thus HIF stabilization leading to a pseudohypoxic environment; these oncometabolites can also lead to epigenetic silencing (through DNA hypermethylation) of genes related to chromaffin cell differentiation promoting tumor growth. On the other hand, mutations in the hypoxia signaling pathway (VHL, HIF-2α, PHD1, PHD2) can directly stabilize HIF-2α, leading to upregulation of the VEGF and related pathways leading to tumor growth formation and progression. Novel HIF-2α gain-of-function somatic mutations have been described with the occurrence of paraganglioma, somatostatinoma, and polycythemia. Further, about 17% of apparently sporadic malignant pheochromocytomas have VHL gene abnormalities, while germline VHL mutations have been noted in approximately 9.6% to 17.6% of PPGL in larger cohorts, but a lower frequency has been reported (4%) from the cancer genome atlas PPGL cohort (see Section 2.2.1.1 for details). Only 1% of pNETs in contrast have reported germline VHL mutations, but up to 25% of sporadic pNETs have VHL genomic alterations (promoter methylation and deletion) and activation of the HIF pathway. Distinct molecular subtypes of pNET have been identified of which the metastases-like pNET molecular subtype has been shown to be associated with hypoxia, metabolic reprogramming, and dysregulated HIF pathway.

Belzutifan is currently approved in the US for the treatment of adult VHL disease patients who require therapy for associated RCC, CNS HB or pNET, not requiring immediate surgery. Thus, targeting HIF-2α by small molecule inhibitors such as belzutifan is an attractive therapeutic option in neuroendocrine tumors such as PPGL, pNET and VHL disease associated tumors. Participants enrolled in this study will be treated with oral belzutifan, 120 mg once daily. Objective responses in participants with PPGL or pNET(and an improvement in the excessive or peptide hormone secretion associated with these tumors) and VHL disease associated tumors, is expected to improve morbidity, symptoms, and reduce mortality. MK*6482-015 study will satisfy the post marketing commitments following belzutifan approval in the US and additionally

study belzutifan in China/Japan participants.

Study objective

This study has been transitioned to CTIS with ID 2023-504853-11-00 check the CTIS register for the current data.

To evaluate the ORR of belzutifan per RECIST 1.1 by blinded independent central review (BICR).

Study design

This is a nonrandomized, multisite, open-label study of belzutifan monotherapy in participants with advanced PPGL or pNET or VHL disease localized tumors.

Approximately 70 participants in Cohort A1 and A2 each, 92 participants in Cohort B1 (VHL disease) (30 PPGL, 30 pNET and 32 RCC [China/Japan]) , 35 participants in Cohort C and 55 participants in cohort D will be enrolled and allocated to receive treatment with belzutifan 120*mg qd. Belzutifan treatment will continue until a discontinuation criterion (Section 7.1 protocol) is met.

Intervention

Belzutifan (MK-6482) 120mg QD until unacceptable toxicity or unequivocal progression.

Study burden and risks

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

The proposed study will enroll participants with advanced (unresectable/metastatic) PPGL or pNET. As described in the belzutifan IB, belzutifan, a potent and selective inhibitor of HIF 2α, has demonstrated antitumor activity in sporadic ccRCC and VHL disease associated RCC and other VHL disease associated tumors (Section 2.2.6, please refer to the protocol), and hence warrants further investigation in other tumors where HIF-2α plays a major role in tumorigenesis and progression. Adverse drug reactions identified for belzutifan include have been anemia, fatigue, nausea, dyspnea, dizziness, and hypoxia. Hypoxia has frequently occurred in conjunction with acute comorbid conditions such as pneumonia, pleural effusion, etc., and have responded to appropriate management. Given the high risk of progression of disease in patients with advanced PPGL or pNET after progressing on available therapies, there is an unmet medical need for more effective and tolerable treatment, and

as belzutifan has been shown to be well tolerated across various tumor types, a positive benefit/risk profile is expected given the mechanistic rationale and justification for use of HIF-2α inhibitors in these neuroendocrine tumors.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

The below mentioned inclusion criteria are the most important ones. A complete list of specific inlcusion criteria can be found in the protocol.
Cohort A1: (PPGL)
1. Has documented histopathological diagnosis (local report) of pheochromocytoma or paraganglioma.

2. Has locally advanced or metastatic disease that is not amenable to surgery or curative intent treatment.
3. Adequately controlled blood pressure defined as BP <=150/90 mm Hg (<=135/85 mm Hg for adolescents) and with no change in antihypertensive medications (for participants with concomitant hypertension) for at least 2 weeks prior to start of study treatment.
Cohort A2: (pNET)
4. Has documented histopathological or cytopathological diagnosis (local report) of well-differentiated, low or intermediate grade (G1 or G2 pNET per 2017 WHO classification and grading) pNET.
5. Has locally advanced disease or metastatic disease that is:
a. Not amenable for surgery, radiation, locoregional therapies or combination modality of such treatments with curative intent.
b. Experienced disease progression on or after at least 1 line of prior systemic therapy that includes an approved targeted agent such as everolimus (mTOR inhibitor) or sunitinib (anti-VEGF targeted agent). Participants who have received >3 prior systemic therapies will be capped to <=20% of the cohort.
6. Has disease progression within the past 12 months from Screening.
7. Has measurable disease per RECIST 1.1 by CT or MRI as assessed by local site investigator/radiology assessment and verified by BICR.
a. Irradiated lesions or lesions treated with locoregional therapies should not be used as target lesions unless they clearly demonstrate growth since completion of radiation.
b. Metastatic lesions situated in the brain are not considered measurable and should be considered nontarget lesions. (This criterion does not apply to Cohort B1 participants)
c. Only lesions of the primary indication for the cohort may be evaluated for measurability; other neoplastic lesions will be documented by the investigator and this information provided to the independent reviewers to ensure that such lesions are not included in the RECIST assessment. See also Exclusion Criterion
2. For Cohort B1 tumor specific requirements refer inclusion criteria #16 and #17
8. Is male or female, 12 years of age inclusive (>=40 kg for adolescents [12-17 years of age]), at the time of providing the informed consent. Only adult participants (>=18 years of age) are eligible to participate for Cohort B1.
9. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after the last dose of study intervention:

• Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
OR
• Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

- Agree to use a male condom plus partner use of an additional contraceptive

method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
• Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
10. A female participant is eligible to participate if she is not pregnant or breastfeeding, and some conditions apply, please refer to the protocol for details.
11. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the main study without participating in FBR.
12. Submit an archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion (not previously irradiated). FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue if the lesion is accessible and a biopsy is not clinically contraindicated. Details pertaining to tumor tissue submission can be found in the Laboratory Manual.
13. Has an ECOG performance status of either 0 or 1, as assessed within 7 days of treatment initiation.
14. Has adequate organ function (see table 1 protocol)
Cohort B1 specific inclusion criteria
15. Have a diagnosis of VHL disease as determined by a germline test (documented germline VHL gene alteration) locally and/or clinical diagnosis, which can be made in the instances as described in the protocol.
16. Have at least 1 measurable PPGL or pNET per RECIST 1.1 by CT or MRI as assessed by local site investigator/radiology assessment and verified by BICR. BICR must verify the presence of radiologically measurable disease per RECIST 1.1 for either PPGL or pNET for the participant to be eligible for the study.
please refer to the protocol for the other criteria.

Exclusion criteria

The below mentioned exclusion criteria are the most important ones. A complete list of specific inlcusion criteria can be found in the protocol.
1. Is unable to swallow orally administered medication or has a disorder that might affect the absorption of belzutifan.
2. Has a history of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 2 years with some exceptions, refer to the protocol
3. Has known CNS metastases and/or carcinomatous meningitis.
4. Has any of the following:
o A pulse oximeter reading <92% at rest, or

o Requires intermittent supplemental oxygen, or
o Requires chronic supplemental oxygen.
5. Has clinically significant cardiac disease, including unstable angina, acute myocardial infarction, or arterial bypass (CABG) or PTCA <=6 months from Day 1 of study drug administration, or New York Heart Association Class III or IV congestive heart failure. Concurrent uncontrolled hypertension defined as BP>150/90 mm Hg despite optimal antihypertensive medications within 2 weeks prior to the first dose of study treatment.
6. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study.
7. Has had major surgery <=4 weeks prior to first dose of study intervention.
Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.
8. Has received prior treatment (except somatostatin analogs for pNET participants) with chemotherapy, targeted therapy biologics, or other investigational therapy within the past 4 weeks of first dose of study intervention.
Note: Refer to exclusion criterion#2g for Cohort B1 participants.
9. Has received prior locoregional therapies or radiation within the past 4 weeks of first dose of study intervention.
10. Has received prior treatment with PRRT/radionuclide therapy (such as 177Lu-Dotatate) or other radiopharmaceutical therapy within the past 12 weeks from Screening for participants with pNET.
Note: Refer to exclusion criterion#2g for Cohort B1 participants.
11. Has received MIBG therapy or other radiopharmaceutical therapy within the past 12 weeks from Screening for participants with PPGL.
Note: Refer to exclusion criterion#2g for Cohort B1 participants.
12. Has received prior treatment with any HIF-2α inhibitor (including belzutifan).
13. Has a known hypersensitivity to the study treatment and/or any of its excipients.
14. Has toxicities from prior locoregional or systemic or any other therapies that is not recovered to CTCAE <=Grade 1 (with the exception of alopecia).
15. Has received colony-stimulating factors (eg, G-CSF, GM-CSF, or recombinant EPO) <=28 days prior to the first dose of study intervention.
16. Is currently receiving strong) inhibitors of CYP3A4 that cannot be discontinued for the duration of the study. Note: Topical preparations are acceptable.
17. Is currently receiving either strong or moderate inducers of CYP3A4 that cannot be discontinued for the duration of the study.
18. Is currently enrolled in and receiving study therapy, was enrolled in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks (28 days) of the first dose of study intervention.
19. Has an active infection requiring systemic therapy.
20. Has a known history of HIV infection.
21. Has a known active hepatitis B (defined as HBsAg reactive) or known active

HCV (defined as detection of HCV RNA [qualitative]) infection.
22. Participant has resting ECG indicating uncontrolled cardiac conditions, as judged by the investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >480 ms, electrolyte disturbances, etc.), or participant has congenital long QT syndrome.
23. For Cohort A2, has a tumor histology consistent with poorly differentiated pNET, neuroendocrine carcinoma, or NET of nonpancreatic origin.
24. For Cohort A2, participants who have uncontrolled symptoms from functional pNETs at study entry.
25. In the judgment of the investigator, is unlikely to comply with the study procedures, restrictions, and requirements of the study. Refer to
26. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant*s participation for the full duration of the study, or is not the best interest of the participant to participate, in the opinion of the treating investigator.
27. Has had an allogenic tissue/solid organ transplant.
28. For Cohort B1 participants, metastatic disease identified at Screening.
refer to the protocol for the other exclusion criteria

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-04-2023
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	WELIREG
Generic name:	Belzutifan

Ethics review

Approved WMO Date:	23-08-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-10-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-03-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-05-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	CTIS2023-504853-11-00
EudraCT	EUCTR2020-005028-13-NL
ClinicalTrials.gov	NCT04924075
CCMO	NL81790.028.22