AN OPEN-LABEL, SINGLE SEQUENCE, CROSSOVER DRUG-DRUG INTERACTION STUDY ASSESSING THE EFFECT OF PEXIDARTINIB ON THE PHARMACOKINETICS OF CYP3A4 AND CYP2C9 SUBSTRATES IN PATIENTS

Published: 12-09-2017
Last updated: 12-04-2024

Primary ObjectivesTo assess the effects of pexidartinib on the PK parameters of single-dose midazolam and tolbutamide in patients.Secondary ObjectivesTo evaluate:- To determine the overall response rate (ORR) in patients with TGCT,kit-mutant...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skeletal neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON55479

Source
ToetsingOnline

Brief title
PL3397-A-U126

Condition

- Skeletal neoplasms benign

Synonym
Cancer, neoplasms

Research involving

Human

Sponsors and support

Primary sponsor: Daiichi Pharmaceutical
Source(s) of monetary or material Support: Daiichi Pharmaceutical

Intervention

Keyword: midazolam, pexidartinib, pharmacokinetics, tolbutamide

Outcome measures

Primary outcome

PK parameters of midazolam and tolbutamide: Cmax, tmax, and AUClast. If data

permits,

other PK parameters including t1/2 and AUCinf will be calculated.

Secondary outcome

PK

- Plasma PK parameters (Cmax, Tmax, AUClast) will be calculated for

pexidartinib and its metabolite, ZAAD-1006a

- Plasma PK parameters (Cmax, Tmax, AUClast) will be calculated for

midazolam metabolite, 5-hydroxy midazolam and also metabolite to parent

ratio (MPR) for 5-hydroxy midazolam and midazolam will be calculated

Efficacy

- Best objective response per RECIST 1.1

- Duration of response

- Time to progression (for TGCT and other non-malignant tumors)

- Progression-free survival (for malignant tumors)

Safety

- TEAEs

- Vital signs

- Electrocardiograms (ECGs)

- Clinical laboratory tests including AST/ALT/Total bilirubin (TBil)

Exploratory Endpoints

- PGx biomarkers

- Optional: PDy biomarkers

- Optional: Tumor biomarker analysis

Study description

Background summary

Pexidartinib is a novel orally active small-molecule tyrosine kinase inhibitor that targets
Colony-stimulating factor 1 (CSF1) receptor (CSF1R), KIT (the receptor for stem cell
factor), and oncogenic fms-like tyrosine kinase 3 (FLT3), the receptor for FLT3 ligand.
When screened in vitro against a broad panel of 226 kinases, pexidartinib showed potent and selective inhibition against its intended targets: CSF1R, KIT, and activated FLT3. Pexidartinib also blocked osteoclast differentiation and cell growth of CSF1-dependent cell lines. Pexidartinib blocks CSF1R activity in a variety of in vivo models. Pexidartinib shows dose-dependent inhibition of splenomegaly in an engineered CSF1R-dependent mouse model. In the collagen-induced arthritis model, pexidartinib shows substantial efficacy by blocking the activity of macrophages and osteoclasts that infiltrate the diseased joints, reduces synovial inflammation and cartilage destruction, and reduces clinical scores for joint and digit swelling and redness even with treatment of advanced disease.

The effects of pexidartinib on multiple aspects of tumorigenesis have been characterized

in cellular and in vivo assays. The proliferation of cell lines that depend on CSF1, stem
cell factor (SCF), or endogenous FLT3- internal tandem duplications (ITD) is inhibited at
half maximal inhibitory concentration (IC50) values below 1 *mol/L. Furthermore, CSF1-induced autophosphorylation of CSF1R and SCF-induced autophosphorylation of KIT are potently inhibited by pexidartinib. Finally, the receptor activator of NF-kappa B
ligand (RANK-L)- and CSF-1-dependent differentiation of osteoclast precursors is also
potently inhibited by pexidartinib. These in vitro results translate to pexidartinib effects
in a variety of in vivo models for CSF1R-dependent proliferation, CSF1R-dependent
osteoclast differentiation, FLT3-ITD-dependent tumor growth, and KIT-dependent mast
cell proliferation.

Study objective

Primary Objectives
To assess the effects of pexidartinib on the PK parameters of single-dose midazolam and tolbutamide in patients.

Secondary Objectives
To evaluate:
- To determine the overall response rate (ORR) in patients with TGCT, kit-mutant melanoma, kit-mutant GIST, or other tumors
- To assess the safety and tolerability of pexidartinib alone and in combination with single-dose midazolam and tolbutamide
- To determine the safety of pexidartinib given as monotherapy over longer periods
- To evaluate the PK of pexidartinib and ZAAD-1006a

Exploratory Objectives
To evaluate:
- Other measures of efficacy including:
- Duration of response
- Time to progression (for TGCT)
- Progression-free survival (for malignant tumors)
- Pharmacogenomic (PGx) analysis
- Optional (at the discretion of the Investigator/patient): Pharmacodynamics (PDy) of pexidartinib in treated patients
- Optional (at the discretion of the Investigator/patient): Tumor biomarker analysis

Study design

This open-label, single sequence, crossover study will comprise 2 parts:

Part 1: An initial single sequence crossover part to evaluate the effect of pexidartinib on the PK of midazolam and tolbutamide, the DDI Phase.

Part 2: An evaluation of efficacy and safety of pexidartinib treatment in various tumors.

Screening will take place between Day -21 and Day -1. The total duration of participation (excluding Screening) for each patient in Part 1 will be approximately 15 d. Pexidartinib treatment (800 mg/d, 400mg BID) will commence on Day 3. Thereafter, pexidartinib treatment will continue BID into Part 2 of the study at the doses defined below to evaluate efficacy and safety until there is no longer clinical benefit or until other reasons for discontinuation are met.

Part 1:
- On Day 1 patients will receive the single oral dose of midazolam (2 mg) and tolbutamide (500 mg), and PK samples will be collected over approximately 48 h.
- On Day 3 pexidartinib (800 mg/d) in twice daily (400mg BID) dosing will be initiated and continue throughout the remainder of Part 1 and into Part 2. On the first day of pexidartinib treatment (Day 3), a single dose of midazolam (2 mg) and tolbutamide (500 mg) will be co-administered with the morning pexidartinib dose (400 mg), and PK samples will be collected over 10 h (pexidartinib), 48 h (midazolam and tolbutamide).
- On Day 13, a single dose of midazolam (2 mg) and tolbutamide (500 mg) will be co-administered with the morning dose of pexidartinib (400 mg), and PK samples will be collected over 10 h (pexidartinib) or 48 h (midazolam and tolbutamide).

In Part 2, patients will continue to receive pexidartinib BID at a dose of 800 mg/d. Patients will be assessed for safety and efficacy. An optional tumor biopsy or archival tumor specimen under specific informed consent and/or blood samples for circulating tumor DNA may be collected at Screening and during pexidartinib treatment for exploratory analysis of tumor biomarkers at the discretion of the Investigator/patient.

Intervention

- tolbutamide reference treatment: single oral dose of tolbutamide (500 mg) on Day 1.
- Midazolam reference treatment: single oral dose of midazolam (2 mg) on Day 1.
- tolbutamide test treatment: single oral dose of tolbutamide (500 mg) on Day 3 concomitantly with pexidartinib and on Day 13 following approximately 10 d of pexidartinib BID dosing.

- Midazolam test treatment: single oral dose of midazolam (2 mg) on Day 3 concomitantly with pexidartinib and on Day 13 following approximately 10 d of pexidartinib BID dosing.
- Pexidartinib treatment: Pexidartinib will be administered orally as a total daily dose of 800 mg administered as split dose of 400 mg (am) and 400 mg (pm) continuously in 28-d cycles starting from Day 3.

Study burden and risks

Pexidartinib demonstrated pharmacologic and anti-tumor activity in a variety of in vitro
and tumor models. It is currently being investigated in a variety of Phase 1-3 studies for
the treatment of tumors and TGCT. Evidence of clinical activity has been observed in
TGCT.

Safety data for pexidartinib are from nonclinical and clinical studies. Liver toxicity and
myelosuppression are important identified risks and embryofetal toxicity is considered as
an important potential risk with pexidartinib. Liver toxicity observed in clinical studies
includes cases of liver cholestasis with single agent treatment in the Phase 3 PLX108-10
study. Risk minimization measures, such as frequent monitoring during the first 8 wk of
pexidartinib treatment, are included in this protocol. Protocol-defined dose reductions
and discontinuations of pexidartinib, increased frequency of laboratory monitoring, and
reporting of findings should be followed. In addition, rechallenge with pexidartinib
should not be attempted without prior discussion with the Sponsor*s Medical Monitor.
Risk benefit of pexidartinib should be assessed for each potential patient.

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.Age * 18 y or * the legal age for being considered as an adult in the country where the patient is screened at the time of signing informed consent.
2.DA histopathologically diagnosed tumor as follows: a.DTenosynovial giant cell tumor (TGCT), which is associated with severe morbidity or functional limitations and for whom surgery is not an option. Prior pexidartinib is permitted for TGCT patients unless ineffective or not tolerated and there has been a washout period of at least 4 weeks.
b.DKIT-mutant tumor, including melanoma or gastrointestinal stromal tumor (GIST), for which there is no standard systemic therapy.

c.DOther solid tumors (all comers) for which there is no standard systemic therapy and there is a rationale for use of pexidartinib at the Investigator's discretion.
3.DWomen of childbearing potential must have a negative serum pregnancy test within 14 d prior to enrollment. (Where demanded by local regulations, this test may be required within 72 h prior to enrollment).
4.DMen and women of childbearing potential are permitted in the study as long as they consent to avoid getting their partner pregnant or becoming pregnant, respectively, by using a highly effective contraception method, as described below, throughout the study and up to 90 d after completion. Highly effective

methods of contraception include intra-uterine device (nonhormonal or hormonal); bilateral tubal occlusion; vasectomy; sexual abstinence (only if this is in line with the patient's current lifestyle); or barrier methods (eg, condom, diaphragm) used in combination with hormonal methods associated with inhibition of ovulation. Women of nonchildbearing potential may be included if they are either surgically sterile or have been postmenopausal for * 1 y. Women who have documentation of at least 12 mo of spontaneous amenorrhea and have a follicle stimulating hormone level > 40 mIU/mL will be considered postmenopausal. The cut-off for performing a follicle- stimulating hormone test is * 50 years old.
5.DAdequate hematologic, hepatic, and renal function, defined by:
*DAbsolute neutrophil count * 1.5 × 109/L.
*DHemoglobin > 10 g/dL.
*DPlatelet count * 100 × 109/L.
*DAspartate aminotransferase (AST) and alanine aminotransferase (ALT) * upper limit of normal (ULN).
*DTotal bilirubin (TBil) and direct bilirubin (DBil) * ULN with an exception of patients with confirmed Gilbert's syndrome. For patients with confirmed Gilbert's syndrome, the total bilirubin should be * 1.5 × ULN.
*DSerum creatinine * 1.5 × ULN.
6.DWillingness and ability to use a paper pill diary.
7.DWillingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements.

Exclusion criteria

1.Known active or chronic human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection, or positive hepatitis B (HepB) surface antigen. Prior hepatitis infection that has been treated with highly effective therapy with no evidence of residual infection and with normal liver function (ALT, AST, total and direct bilirubin * ULN) is allowed.
2.DKnown active tuberculosis.
3.DHepatobiliary diseases including biliary tract diseases, autoimmune hepatitis, inflammation, fibrosis, cirrhosis of liver caused by viral, alcohol, or genetic reasons. Gilbert's disease is allowed if TBil is * 1.5 × ULN.
4.Women who are breastfeeding.
5.Patients with poor metabolizer status of cytochrome P450 (CYP) 2C9.
6.Patients on potent CYP2C9, CYP3A4, and uridine 5' diphospho-glucuronosyltransferase (UDGT) family 1 member A4 (UGT1A4) inducer and inhibitors and potent P glycoprotein (P-gp) inhibitors and inducers, unless these medications are discontinued at least 14 d before study drug administration. Foods or beverages containing CYP3A4/5 inhibitors (eg, grapefruit, pomegranate, pomelo, and star fruit) should be avoided throughout the study.

7.Anti-tumor or investigational agent therapy within 4 weeks prior to Day 1.
8.A screening Fridericia-corrected QT (QTcF) interval * 450 ms (men) or * 470 ms (women).
9.History of hypersensitivity to any investigational products, including their excipients.
10.Inability to swallow oral medication.
11.Inability to complete study procedures.
12.Patients on tolbutamide or midazolam and unable to change to alternate therapy. Prior therapy with tolbutamide or midazolam is allowed with a washout period of at least 4 wk.
13.Patients with contraindications for tolbutamide or midazolam

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-08-2018
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MIDAZOLAM HYDROCHLORIDE SYRUP
Generic name:	MIDAZOLAM HYDROCHLORIDE SYRUP
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Pexidartinib

Generic name:	Pexidartinib
Product type:	Medicine
Brand name:	Tolbutamide
Generic name:	Tolbutamide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-09-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	24-04-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	30-04-2019
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	14-01-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	03-06-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	27-08-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	28-10-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	11-12-2020
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-02-2021
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	EUCTR2017-001687-38-NL
CCMO	NL62531.058.17