A phase I, open-label, multicenter study to evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and various degrees of hepatic function

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Primary:To assess the effect of various degrees of impairment in hepatic function as measured by NCICTEPcriteria, on the pharmacokinetics of panobinostat.Secondary:To assess the effect of various degrees of hepatic functions on the safety of...

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

Summary

ID

NL-OMON34474

Source
ToetsingOnline

Brief title
PK of panobinostat in psolid tumors and hepatic impairment

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
pharmacokinetic of panobinostat in various degrees of hepatic function

Research involving
Human

Sponsors and support

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

Intervention

Keyword: hepatic impairement, panobinostat, pharmacokinetics, solid tumors

Outcome measures

Primary outcome

The primary plasma PK parameters are AUC0-t, AUC0-*, and Cmax of panobinostat.

Tmax will also be evaluated. In addition, percent panobinostat bound to plasma

protein will be evaluated.

Secondary outcome

Safety: type, grade and frequency of adverse events (AEs), serious adverse

events (SAEs), changes in hematology and chemistry values (especially those

associated with hepatic and bone marrow function), assessment of physical

examinations, vital signs and ECGs

Study description

Background summary

Panobinostat (LBH589) is a deacetylase inhibitor (DACi) which belongs to a structurally novel cinnamic hydroxamic acid class of compounds. It is a potent class I/II pan-DAC inhibitor (pan-DACi) that has shown anti-tumor activity in pre-clinical models and patients with solid tumors and hematological malignancies.
As results from a recently completed radio-labeled human ADME study in patients indicated that both kidney and liver are involved in the elimination and metabolism of panobinostat, understanding the impact of altered organ function status on panobinostat PK
has become important and thus provides a rationale for this study.
Panobinostat is likely to be utilized in cancer patients with co-existing

morbidities such as impaired hepatic function. Patients with liver impairment may be at risk with decreased ability to eliminate panobinostat. Decreased elimination of the drug as a result of impaired organ
function may lead to an increased systemic exposure and possible toxicity. Although, a number of patients with mild or moderate hepatic dysfunction have been included in prior clinical studies of single agent panobinostat, currently, there has been no formal evaluation of the disposition of panobinostat in patients with cancer and impaired hepatic function.

Study objective

Primary:
To assess the effect of various degrees of impairment in hepatic function as measured by NCICTEPcriteria, on the pharmacokinetics of panobinostat.

Secondary:
To assess the effect of various degrees of hepatic functions on the safety of panobinostat and to evaluate whether there is a relationship between PK and safety parameters in patient with various degrees of hepatic functions.

Study design

This is a phase I, open-label, multi-center study to evaluate the PK and safety of oral panobinostat in patients with advanced solid tumors with varyious degrees of hepatic function. Initially, patients with normal hepatic function and mild or moderate hepatic dysfunction will be enrolled in the study. A decision to enroll patients with severe liver impairment will be made following review of the preliminary safety data of all patients dosed and completed the core phase and cycle 1 of treatment (extension) phase, of which at least three (3) patients must be from the moderate group. In an unlikely scenario, the first 3 patients enrolled in the study may all belong to the moderate hepatic dysfunction group and may not, exhibit major toxicities. Such a case, historical data from prior studies of oral panobinostat, where patients with normal hepatic function and mild hepatic dysfunction have been enrolled, will be taken into account prior to making a decision to open enrollment for the severe hepatic dysfunction patients.

The study will have 2 phases.
The core phase, in which on day 1 the patient will be administered one dose of panobinostat followed by pharmacokinetic assessments and ECG monitoring. on days 1 to 5 (post-dose).
Treatment will be continued on day 8, which is day 1 of the extension phase. The extension phase will excists of 28-days cycles. Panobinostat will be administered 3 times weekly until progression or unacceptable toxicity.

Intervention

Studiedrug: panobinostat 30mg, oral

Corephase (pharmacokinetics) (dag 1-7): a single dose panobinostat 30 mg on day 1

Extensionphase: 30 mg panobinostat 3 x weekly.

Study burden and risks

Side effects from panobinostat seen in animals that might happen in human. Most frequently reported adverse events seen in patients treated with oral panobinostat are:
* Decrease in the platelets
* Mild to moderate nausea, vomiting, and diarrhea
* Decreased appetite
* Fatigue, feeling weak or tired.
Taking blood may cause pain, bleeding, and/or bruising.

Contacts

Public
Novartis

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Scientific
Novartis

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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. ECOG performance status * 2
2. Documented diagnosis of advanced solid tumor for which no standard systemic therapy exists
3. Baseline laboratory results
a. Absolute neutrophil count (ANC) * 1.5 x 109 /L
b. Platelet count * 100 x 109 /L
c. Serum creatinine * 1.5 x ULN
d. Serum potassium, magnesium, sodium, total calcium within normal limits
4. Mandatory use of double barrier method of contraception during the course of the study and for 3 months after completing study
5. Normal or abnormal hepatic organ function as defined in table 4-1 in the protocol

Exclusion criteria

1. Prior treatment with DAC inhibitors including panobinostat
2. Patient needing valproic acid during the study or within 5 days prior to first panobinostat dose
3. Concomitant anti-cancer therapy
4. Diuretics: potassium sparing diuretics are allowed
5. Active CNS disease or brain metastasis, except those previously treated and stable for at least 3 months
6. Evidence of another malignancy not in remission or history of such a malignancy within the last 3 years (except for treated basal or squamous cell carcinoma or in situ cancer of the cervix)
7. The following therapies:
a. prior chemotherapy * 3 weeks prior to start
b. biologic immunotherapy including monoclonal antibodies or experimental therapy * 4 weeks prior to start
c. radiation therapy * 4 weeks or limited field radiotherapy * 2 weeks prior to start
d. therapy-related toxicities to * CTCAE grade 1 at baseline, with the exception of alopecia
8. major surgery * 2 weeks prior to starting study drug
9. Unresolved diarrhea * CTCAE grade 2
10. Impaired cardiac function, including any one of the following:
a. LVEF < the lower limit of institutional norm
b. a permanent cardiac pacemaker
c. congenital long QT syndrome

d. ventricular tachy-arrhythmias
e. resting bradycardia (< 50 beats / minute)
f. QTcF > 450 msec on screening ECG
g. Complete left bundle branch block (LBBB), bifascicular block (RBBB with either left anterior hemiblock or left posterior hemiblock)
h. Any clinically significant ST segment and/or T-wave abnormalities
i. Presence of unstable atrial fibrillation (ventricular response rate > 100 bpm).
j. Myocardial infarction or unstable angina pectoris * 6 months prior to starting studydrug
k. Congestive heart failure (New York Heart Association class III-IV)
l. Other clinically significant heart disease and vascular disease (e.g. uncontrolled hypertension)
11. Medications with relative risk of prolonging the QT interval or inducing torsade de pointes
12. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of panobinostat
13. Other concurrent severe and/or uncontrolled medical conditions (e.g. uncontrolled diabetes, active or uncontrolled infection, chronic obstructive or chronic restrictive pulmonary disease including dyspnea at rest from any cause, uncontrolled thyroid dysfunction) that could cause unacceptable safety risks
14. A known history of HIV seropositivity (test for screening is not required)
15. Patient has ascites requiring intervention
16. Patient has hepatic encephalopathy
17. use of warfarin
18. Use of CYP3A4/5 inhibitors

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):	07-03-2011
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	panobinostat

Ethics review

Approved WMO Date:	03-12-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-02-2011
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2009-012262-31-NL

Register	ID
ClinicalTrials.gov	NCT01007968
CCMO	NL34482.058.10