An open-label, parallel group study to explore the pharmacokinetics of eribulin (E7389) in patients with advanced solid tumors and normal or reduced hepatic function according to the Child Pugh system.

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To study the influence of hepatic impairment on plasma pharmacokinetic parameters of eribulin mesylate (E7389) following an IV administration.

Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON33939

Source
ToetsingOnline

Brief title
NVT

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Cancer, Drug metabolism

Research involving
Human

Sponsors and support

Primary sponsor: Eisai
Source(s) of monetary or material Support: Eisai Limited

Intervention

Keyword: HEPATIC IMPAIRMENT, PHASE I, SOLID TUMOURS

Outcome measures

Primary outcome

Exploratory analyses of the influence of hepatic impairment on plasma

pharmacokinetics of eribulin mesylate (E7389) administered as intravenously.

Comparisons will be made between the single doses of eribulin mesylate (E7389)

administered to the three groups of patients

Secondary outcome

Further exploration of safety and tolerability of eribulin mesylate (E7389)

among patients with reduced hepatic function

Study description

Background summary

Eribulin mesylate (E7389) is a large polyether macrolide derived from a substance found in a rare marine sponge which exerts potent anticancer effects in both cell-based and animal models of cancer and is largely excreted via the liver. Phase I studies have determined the maximum tolerated dose and dosing schedule whilst phase II and III studies, in various tumour types including breast cancer, are ongoing or near completion.
A pharmacokinetic study in a subgroups of patients can determine whether an alternative dosing regimen may be indicated for efficacy and/or safety reasons. Clinical studies in patients with hepatic impairment, who constitute an important subgroup, can provide information that may help guide initial dosing in patients.

Study objective

To study the influence of hepatic impairment on plasma pharmacokinetic parameters of eribulin mesylate (E7389) following an IV administration.

Study design

Phase I, open-label, three parallel group study at two Dutch centres. Patients will be assigned to one of three groups according to Child-Pugh system for classifying hepatic impairment and will each receive a different dose of eribulin mesylate (E7389).
Pharmacokinetics assessments will be performed during cycle 1 only. Patients benefiting from eribulin mesylate (E7389) treatment may continue treatment for as long as clinical benefit is sustained.

Intervention

All three groups will receive on day 1 and day 8 of the 21 day cycle Eribulin intravenously as bolusinjection of infusion diluted in 100 ml NaCl 0,9% in 2-5 minutes.

Study burden and risks

Screenings phase is planned until 2 weeks before treatment (after written consent is obtained). Evaluation of: ECOG, in -and exclusion criteria, baseline tumor assessment according to RECIST criteria, medical and chirurgical history including medication use, physical examination, vital signs, length and weight, ECG, blood -and urine tests (including pregnancy test, if applicable).
Treatment phase will be 21 days. Eribulin will be given on day 1 and day 8. PK (Pharmacokinetic) assessments will be done during cycle 1 only at: : -0,5h pre-infusion, 15 min., 30 min., 60 min., 2u, 4h, 6h, 10h, 24h, 48h, 72h, 96h, 120u and 144h (= total 14 samples in 1 week).
Weekly assessments (at day 15 during the first two cycles only) exist of physical examination, adverse events and medication use. At the end of cycle 2 an ECG is done. Day 15 through day 21 tumor assessment will be performed according to RECIST criteria intervals that are the centre*s usual practice or sooner if there is evidence of progressive disease.
Study determination (0-30 days after the final dose or at discontinuation) ECOG, tumor assessment, physical examination, ECG, Weight, Vital Signs, blood -and urine tests, adverse events and medication use.

The investigational drug is a chemotherapeutic agent and therefore has known side effects which include a decrease in the numbers of white blood cells (neutropenia) which may increase the risk of infection, including pneumonia and cellulitis (an acute spreading bacterial infection) which could be life threatening.
Patients are therefore carefully and frequently monitored and are advised to contact their physician at the first signs of infection. Other occasional and

milder side effects include: anaemia, increased risk of bleeding (thrombocytopenia), numbness in hands and feet (neuropathy), headaches, dizziness, nausea, vomiting, diarrhoea, constipations, difficulty breathing (dyspnoea) and cough, fatigue, hair loss, dehydration, loss of appetite and fluid retention, a bad taste in the mouth and the development of sensitive areas like an ulcer in the mouth (mucositis) and throat (stomatitis).
Side effects of the study procedures are minimal and include local pain, swelling, bruising, bleeding and in rare cases infection at the site where blood is drawn or where the drug has been infused

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

General Inclusion Criteria for all Groups

1. Patients must have a histologically or cytologically confirmed advanced solid tumor that has progressed following standard therapy or for which no standard therapy exists (including surgery or radiation therapy)
2. Age >= 18 years
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
4. Life expectancy of >= 3 months
5. Adequate renal function as evidenced by serum creatinine <= 2.0 mg/dL (176 µmol/L) or calculated creatinine clearance >= 40 mL/minute (min) per the Cockcroft and Gault formula
6. Adequate bone marrow function as evidenced by absolute neutrophil count (ANC) >= 1.5 x 109/L, hemoglobin >= 10.0 g/dL (>= 6.2 mmol/L) (a hemoglobin < 10.0 g/dL (< 6.2 mmol/L) is acceptable if it is corrected by growth factor or transfusion), and platelet count >= 100 x 109/L
7. Patients willing and able to comply with the study protocol for the duration of the study
8. Written informed consent prior to any study-specific screening procedures with the understanding that the patient may withdraw consent at any time without prejudice
Additional Inclusion Criteria for the Group of Patients with No Hepatic Impairment
Patients must meet all the general inclusion criteria listed above plus have:
Normal hepatic function as evidenced by: International Normalized Ratio (INR), albumin, bilirubin, alanine transaminase (ALT) and aspartate transaminase (AST) within the institution*s normal laboratory ranges and alkaline phosphatase (ALP) <= 2.5 times the upper limit of normal range (ULN) and with no clinical signs of ascites.
Additional Inclusion Criteria for the Group of Patients with a History of Known Hepatic Impairment
Patients must meet all the general inclusion criteria listed above plus have either:
Mild hepatic dysfunction (Child-Pugh A) according to the Child-Pugh scoring system criteria, where patients with laboratory values within normal ranges will not be included in the Child-Pugh A category
Or, Moderate hepatic dysfunction (Child-Pugh B) according to the Child-Pugh scoring system criteria

Exclusion criteria

Exclusion Criteria
1. Patients who have received any of the following treatments within the specified period before eribulin mesylate (E7389) treatment start:
a Chemotherapy, radiation, biological therapy within 3 weeks
b Hormonal therapy within 1 week
c Any investigational drug within 4 weeks
2. Patients with any clinically significant laboratory abnormality except for those parameters influenced by hepatic impairment.
3. Patients with severe (Child-Pugh C) hepatic dysfunction according to the Child-Pugh scoring system
4. Patients with encephalopathy >= grade 1
5. Patients receiving any drug known to induce or inhibit CYP3A4 activity.
6. Patients, who require therapeutic anti-coagulant therapy other than for line patency with

warfarin or related compounds and cannot be changed to heparin-based therapy, are not eligible
7. Women who are pregnant or breast-feeding; women of childbearing potential with either a positive pregnancy test at screening or no pregnancy test; women of childbearing potential unless (1) surgically sterile or (2) using adequate measures of contraception in the opinion of the Investigator. Perimenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential.
8. Fertile men who are not willing to use contraception or fertile men with a female partner who are not willing to use contraception
9. Severe/uncontrolled intercurrent illness/infection
10. Significant cardiovascular impairment (history of congestive heart failure > NYHA grade II, unstable angina or myocardial infarction within the past six months, or serious cardiac arrhythmia)
11. Patients with organ allografts requiring immunosuppression (not including blood and blood components transfusions)
12. Patients with known positive HIV status
13. Patients with brain or subdural metastases are not eligible, unless they are stable and have completed local therapy and have discontinued the use of corticosteroids for this indication for at least four weeks before starting treatment with eribulin mesylate (E7389).
14. Patients with meningeal carcinomatosis
15. Patients with a hypersensitivity to halichondrin B and/or halichondrin B-like compounds
16. Patients who participated in a prior E7389 clinical trial
17. Patients with preexisting neuropathy > G2
18. Patients with other significant disease or disorders that, in the Investigator*s opinion, would exclude the patient from the study

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	28-11-2007
Enrollment:	18

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	NVT
Generic name:	Eribulin Mesylate

Ethics review

Approved WMO Date:	18-12-2007
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-10-2008
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-05-2009
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-03-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2007-002213-39-NL
CCMO	NL20248.031.07