An Open-Label, Non-Randomized, Single-Center Study to Determine the Metabolism and Elimination of Carbon-14 labeled Eribulin Acetate (14C-Eribulin) in Patients with Advanced Solid Tumors

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The primary objective of this study is to determine the excretion balance and to elucidate the metabolic pathway of eribulin in vivo after a single dose of carbon-14 radio-labeled eribulin (14C-eribulin), inpatients with advanced solid tumors.

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

Summary

ID

NL-OMON32470

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: Carbon-14 labeled Eribulin, Elimination, Metabolism, Solid Tumors

Outcome measures

Primary outcome

Excretion balance and metabolic pathway of 14C-eribulin as determined by PK

analysis of 14C-eribulin and parent eribulin mesylate in blood, plasma, urine

and faeces..

Secondary outcome

Safety, tolerability and efficacy of eribulin.

Study description

Background summary

E7389 (eribulin) is a synthetic analogue of a natural product isolated from the marine sponge Halichondria okadai. It has potent anticancer effects in cell-based and animal models of cancer. Eribulin exerts its chemotherapeutic effect by inhibiting microtubule dynamics, which differs from those of other known tubulin targeted-agents. The maximum-tolerated dose and dosing schedule has been determined in Phase 1 studies. Phase 2 studies investigating the efficacy and toxicity profile of eribulin in advanced metastatic breast cancer, non-small cell lung cancer and prostate cancer have been completed. In addition further phase II studies in multiple other tumor types and two phase III studies in advanced breast cancer are ongoing. Eribulin is a complex molecule whose metabolism and route of elimination in man has not been fully evaluated. By performing a mass balance study with radio-labeled drug information on the metabolic pathway and elimination can be obtained.

Study objective

The primary objective of this study is to determine the excretion balance and

to elucidate the metabolic pathway of eribulin in vivo after a single dose of carbon-14 radio-labeled eribulin (14C-eribulin), inpatients with advanced solid tumors.

Study design

Open Label, Single-Arm

Intervention

At Cycle 1, Day 1 patients will receive a single 2 mg flat dose of 14C-eribulin (approximately 80 - 90 µCi) as an intravenous infusion over 2 - 5 minutes. Thereafter patients will be given 1.4 mg/m2 non-radiolabeld eribulin on Day 8 of Cycle 1 and then on Days 1 and 8 every 21 days.

Study burden and risks

Common (5% or more, may occur in more than one person in 20) side-effects from eribulin are a temporary decrease of the body*s white and red blood cells.
• Decrease in the numbers of white blood cells (leukopenia and neutropenia) may increase the risk of infections, including pneumonia and urinary tract infections. Infections in patients with low numbers of white blood cells in some circumstances can be life-threatening. Neutropenia has occurred in patients treated with eribulin, and is associated with infection in some patients.
• A decrease in the number of red blood cells (anaemia) may result in a feeling of tiredness.
• Eribulin could also decrease the number of platelets (thrombocytopenia) and this may result in an increased risk of bleeding and bruising.
Other common side-effects of eribulin might include:
• Gastrointestinal problems such as nausea, vomiting, diarrhoea, constipation, indigestion, abdominal pain, a bad taste in the mouth and the development of sensitive areas like an ulcer in the mouth and throat.
• Neuropathy
• Respiratory problems including difficulty breathing and cough
• Other common effects include dry mouth, eyes watering, joint pain, muscle pain or weakness, fluid retention, weight loss, loss of appetite, dizziness, fatigue, headache and hair loss
• Some patients experienced an elevated temperature, which may be associated with an infection.
Other uncommon (less than 5%, less than one person in 20, but may be serious in some patients) possible side-effects of eribulin might include:
• Increased heart rate
• Infections, including pneumonia (infection of the lungs or chest), cellulitis (infection of the skin) and urinary tract infections (bladder infections)
• Confusion

• Kidney failure
• Seizure (like an epileptic fit)
• Dehydration
• Low blood pressure
• Deep vein thrombosis and pulmonary embolism (blood clots in the legs and lungs)
• During prior clinical studies some patients have died. The cause of death is often due to the patients known cancer, or a serious infection. In a few cases the cause of death was not established.
• During prior clinical studies a few patients have experienced allergic reactions during or after receiving this drug.
As these possible uncommon side effects have not occurred very often and are often seen in patients with cancer it can be difficult to establish if these are a true side effect of the drug.

The effects of eribulin on the unborn child are currently not known. However it is likely that eribulin, like other anti-cancer medications, would harm an unborn child.

The additional radiation burden due to administration of approximately 100 µCi of 14 C-eribulin is approximately 0.187 mSv. This is about 11% of the average annual environmental background radiation burden in the Netherlands. Patients will not receive any additional tumor assessments involving exposure to radiation than in routine care. Patients are required to stay in hospital for a minimum of 8 days, during which time frequent blood samples will be taken and full urine and faeces collection is required.
It is not possible to determine whether a patient will benefit from receiving eribulin. Early indications of anticancer activity have been observed in phase 2 studies. Two phase 3 studies in patients with metastatic breast cancer are ongoing.

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. 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). Patients with measurable tumours according to RECIST are desirable but not essential for inclusion.
2. Patients must be aged >= 18 years
3. Patients must have an ECOG Performance Status of 0, 1, or 2
4. Patients must have adequate renal function as evidenced by serum creatinine <=135 µM/L (<= 1.5 mg/dL) or creatinine clearance >= 40 mL/minute (min)
5. Patients must have adequate bone marrow function as evidenced by absolute neutrophil count (ANC) >= 1.5 x 109/L and platelet count >= 100 x 109/L
6. Patients must have adequate hepatic function as evidenced by bilirubin <= 1.5 times the upper limit of normal (ULN) and alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) <= 3 x ULN (in the case of liver metastases <= 5 x ULN), unless there are bone metastases, in which case liver specific alkaline phosphatase must be separated from the total and used to assess the liver function instead of the total alkaline phosphatase
7. Resolution of all chemotherapy or radiation-related toxicities to Grade 1 severity or below, except for stable sensory neuropathy <= Grade 2 and alopecia
8. Patients must be willing and able to comply with the study protocol for the duration of the study
9. Patients must give written informed consent prior to any study-specific screening procedures with the understanding that the patient may withdraw consent at any time without prejudice

Exclusion criteria

1. Patients who have received any of the following treatments within the specified period before treatment start:
- chemotherapy, radiation, or biological therapy within three weeks
- hormonal therapy within one week
- any investigational drug within 4 weeks
- Systemic unconventional or alternative therapies including, but not limited to, herbal remedies within 4 weeks
2. Have had radiation therapy encompassing > 30% of marrow
3. Have received prior treatment with mitomycin C or nitrosourea
4. Have had major surgery within 4 weeks before starting study treatment
5. Patients with pulmonary lymphangitic involvement that results in pulmonary dysfunction requiring active treatment, including the use of oxygen
6. Patients with brain or subdural metastases are not eligible, unless they have completed local therapy and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (e.g. radiologic) and/or symptoms of brain metastases must be stable for at least 4 weeks
7. Patients with meningeal carcinomatosis
8. Patients who are receiving anti-coagulant therapy with warfarin or related compounds, other than for line patency, and cannot be changed to heparin-based therapy, are not eligible. If a patient is to continue on mini-dose warfarin, then the prothrombin time (PT) or international normalized ratio (INR) must be closely monitored
9. 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. Peri-menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential
10. Patients with severe/uncontrolled intercurrent illness/infection
11. Significant cardiovascular impairment (history of congestive heart failure > NYHA grade II, unstable angina or myocardial infarction within the past 6 months, or serious cardiac arrhythmia)
12. Patients with organ allografts requiring immunosuppression
13. Patients with known positive HIV status
14. Patients with pre-existing neuropathy > Grade 2
15. Patients with a hypersensitivity to halichondrin B and/or halichondrin B chemical derivative
16. Patients who participated in a prior eribulin clinical trial, whether or not they received eribulin (E7389).
17. 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):	01-01-2009
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Radio Labeled Eribulin Acetate (14C-eribulin)
Product type:	Medicine
Brand name:	NVT
Generic name:	Eribulin Mesylate

Ethics review

Approved WMO Date:	11-11-2008
Application type:	First submission
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)
Approved WMO Date:	14-10-2010
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	EUCTR2007-004703-35-NL
CCMO	NL24670.031.08