Mass Balance Study of PM01183 (lurbinectedin) Administered as 1-hour Intravenous Infusion to Patients with Advanced Cancer

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

Summary

ID

NL-OMON45543

Source
ToetsingOnline

Brief title
PM1183-A-015-16

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
advanced cancer, solid tumors

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Advanced cancer, Lurbinectedin, Mass balance

Outcome measures

Primary outcome

- To obtain the mass balance and the time course of excretion of PM01183 in

adult patients with advanced cancer.

- To identify PM01183 metabolites formed in adult patients with

advanced cancer.

Secondary outcome

- To determine, if feasible, the concentration of as many PM01183 metabolites

as possible in body fluids.

- To evaluate, if possible, whether cytochrome P450 (CYP) and/or nuclear

receptors and drug transporter genotypes, responsible for PM01183 metabolism,

are related to major differences in the patient*s exposure to PM01183.

- To characterize the safety profile and feasibility of PM01183 in patients

with advanced cancer.

Study description

Background summary

PM01183 (lurbinectedin) is a novel synthetic tetrahydroisoquinoline structurally related to ecteinascidins. PM01183 is a new Chemical Entity that binds the DNA leading to the formation of DNA double-strand breaks (DSBs). The

binding to DNA is likely occurring in the minor groove region and induces apoptosis and delayed progression through the cellular phase S/G2. PM01183 also induces the specific degradation of transcribing RNA Pol II in several human tumor cell lines.
In vitro, PM01183 demonstrated cytotoxic effects against a broad selection of tumor types with half maximal inhibitory concentration (IC50) values in the range of 1-10 nM. Although selectivity was also seen, a clustering of sensitive tumors has not been identified. PM01183 also exhibited antitumor activity against different murine models of xenografted human-derived tumor types. PM01183 has been tested as a single agent or in combination with different drugs in solid tumors; while antitumor activity in hematological tumors was deemed negligible, PM01183 has shown activity in different solid tumors; some of the most responsive tumor types were breast, small cell lung cancer (SCLC), ovarian and endometrial cancer.
Based on current clinical data, the toxicity of PM01183 is predictable, reversible and manageable. The most relevant toxicity is reversible myelosuppression with a nadir occurring in the middle of the second week after Day 1 infusion in an every-three-week cycle; overall, the incidence of febrile neutropenia (FN) is below 20% in all ongoing Phase II trials.

Study objective

The present study is aimed at identifying the specific routes of PM01183 excretion and elimination following its administration to patients with advanced tumors. Also, the study design may allow the identification and quantification, if possible, of any potential PM01183-related metabolites formed in patients with advanced tumors.

Study design

This is a Phase I, open-label, uncontrolled, pharmacology study to characterize the mass balance of PM01183 administered as 1 hour (h) intravenous (i.v.) infusion every three weeks (q3wk) (one cycle = three weeks). The patient will have to stay in the research unit up to a minimum of eight days. The first dose of PM01183 will be radiolabeled with 14C1; subsequent doses of PM01183, up to a maximum of eight cycles, will not be radiolabeled. PM01183 will be administered to six evaluable patients for the primary endpoint and for a maximum of eight cycles, while considered to be on the patient*s best interest or until: disease progression (PD), unacceptable toxicity, intercurrent illness of sufficient magnitude to preclude safe continuation of the study, patient*s refusal and/or non-compliance with study requirements, a protocol deviation with an effect on the
risk/benefit ratio of the clinical study, more than two PM01183 dose reductions due to AEs related to PM01183 (unless clear benefit has been documented and always with the Sponsor*s agreement) or any other reason at the physician*s judgment that precludes PM01183 continuation.

If the patient responds to treatment or achieves stable disease (SD) after eight treatment cycles, treatment with PM01183 may continue outside this study under a Compassionate Use Program at the same dose based on Investigator*s decision and upon agreement with the Sponsor. Should the patient continue under a Compassionate Use Program, the treating center must request authorization to the relevant Health Authorities and notify the Sponsor in due time.

Intervention

This is a Phase I, open-label, uncontrolled, pharmacology study to characterize the mass balance of PM01183 administered as 1 hour (h) intravenous (i.v.) infusion every three weeks (q3wk) (one cycle = three weeks). The patient will have to stay in the research unit up to a minimum of eight days. The first dose of PM01183 will be radiolabeled with 14C1; subsequent doses of PM01183, up to a maximum of eight cycles, will not be radio-labelled.

Study burden and risks

Everyone taking part in the study may have side effects and will be carefully watched. However, doctors do not know all side effects that may happen. Not all patients will experience them and they may be mild or very serious. Many will resolve soon after the patient stops taking PM01183. In some cases, they can be serious, long lasting, or may not resolve. There is also a very small risk of death.
During previous clinical studies, the following side effects related to PM01183 have been observed, usually moderate in intensity and reversible:

Very common (observed in >= 10% of patients):
- Anemia: A condition in which there is a lower-than-normal number of red blood cells. It may result in symptoms like fatigue, palpitations, dizziness or malaise. It might require red blood cell transfusions.
- Thrombocytopenia: A condition in which there is a lower-than-normal number of platelets in the blood. It may result in easy bruising and excessive bleeding from wounds or bleeding in mucous membranes and other tissues.
- Leukopenia: A condition in which there is a lower-than-normal number of white blood cells (leukocytes) in the blood. It may increase the risk of infection.
- Neutropenia: A condition in which there is a lower-than-normal number of neutrophils (a type of white blood cell). It may increase the risk of potentially serious infections.
- Febrile neutropenia or neutropenic infection (severe infection while your defenses are low, which may require hospitalization and intravenous antibiotic therapy).
- Abnormal blood tests related to liver function. Usually not associated with clinical symptoms.
- Nausea: A feeling of sickness or discomfort in the stomach that may come with an urge to vomit.

- Vomiting.
- Fatigue: A condition marked by extreme tiredness and inability to function due to lack of energy and strength, weakness.
- Diarrhea: Frequent and watery bowel movements.
- Constipation: A condition in which stool becomes hard, dry and difficult to pass, and bowel movements do not happen very often. Other symptoms may include painful bowel movements and feeling bloated, uncomfortable, and sluggish.
- Anorexia: An abnormal loss of appetite.
- Abdominal pain or discomfort.

Common (observed in >= 1% but < 10% of patients):
- Sores (stomatitis) in the mouth or inflammation within your digestive system (mucositis) that may or may not be painful. Associated pain, if any, may result in difficulty eating and drinking.
- Fever, chills or the sensation of temperature increase without fever.
- Headache.
- Dyspnea: Difficulty in breathing or shortness of breath.
- Weight loss.
- Liquid/fluid retention (edemas).
- Changes in the taste of food (dysgeusia).
- Peripheral neuropathy: Numbness or diminished sensation to pressure, which may hamper normal daily activities such as dressing and undressing.
- Skin alterations: Such as rash and/or dry skin.
- Insomnia.
- Phlebitis or local infusion site reactions: Inflammation (redness, swelling, pain, and heat) of a vein through which PM01183 is administered.
- Alopecia: Hair loss may occur; however, it is rarely extensive with PM01183 treatment alone; hair usually grows again after treatment discontinuation.
- Hiccups.
- Cough.
- Epistaxis (nose bleeds).
- Dyspepsia (indigestion or heartburn).
- An increased risk in the frequency and/or duration of common infections due to a transient decrease in the ability of your immune system to fight microorganisms (bacterial, virus, fungi). It may include infections such as nasopharingitis, rhinitis, pneumonia, vaginitis and urinary infections, among others.
- Hypotension (low blood pressure) with or without dizziness or malaise when you change posture rapidly.
- Tachycardia (faster-than-normal heart rate) with or without palpitations (feeling the beats of your heart).
- Musculoskeletal and/or joint pain.
- Changes in blood laboratory parameters (e.g., glucose, sodium, potassium, magnesium, calcium, creatinine or uric acid) might be found in some cases and may require specific management.

Uncommon but potentially serious adverse events (observed in approximately 1%

of patients):
- Pneumonia or pneumonitis (pulmonary infection or inflammation).
- Hypertension.
- Serious infections and/or sepsis (severe infection caused by microorganisms, especially bacteria, in the blood or tissues), which require intravenous antibiotic treatment and hospital admission for adequate management.
- Liver, renal, respiratory or multi organ impairment, which may require ICU admission in order to adequately manage it.
- Cardiac impairment, which may result in liquid retention, less tolerance to exercise and difficulty breathing, especially when lying in bed at night (orthopnea).
- Dehydration.
- Jaundice (yellowish coloration of the skin, eyes and mouth with or without darker coloration of urine).
- Muscular pain and/or weakness associated with abnormal muscular function blood tests.
- Extravasation, the spread of the drug out of the vein during its administration, may result in redness and pain in less serious cases or may lead to serious tissue injury and ulceration, at least theoretically. Only one patient has reported extravasation with PM01183, which resulted in a mild reaction and was successfully treated with anti-inflammatory treatment without requiring any surgery; the patient recovered completely without complications.

Some of these adverse events have been observed rarely; however, they might be serious and some might even be life-threatening, and thus require prompt hospitalization for adequate management. Most patients suffering these adverse events have recovered completely with adequate treatment; however, there is a risk that some patients may not fully recover or that recovery might take several weeks.

Reproductive risks: Because the effects of PM01183 during pregnancy have never been addressed formally in animals or in humans, we cannot exclude at this time whether its use may be harmful or deleterious in this situation. Therefore, the patient should not become pregnant or have a baby while participating in this study, and for at least six months after discontinuation of study treatment. Patient should not nurse (breast-feed) a baby while on this study and also for six months after treatment discontinuation. Consequently, the patient and their partner must agree on using a highly effective method of contraception to avoid pregnancy throughout the treatment period and for six months after treatment discontinuation. Highly effective methods of contraception include intrauterine device (IUD), oral contraceptives, subdermal implant, bilateral tubal occlusion or vasectomy.
Should pregnancy of their female partner occur, she will be asked to sign a release of information form to allow the collection of information on the progress of the pregnancy and its outcome. The study doctor will make this information available to the Sponsor of the study for safety monitoring

(follow-up).

Contacts

Public
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Pharma Mar

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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) Voluntarily signed and dated written informed consent (IC) obtained from the patient prior to any specific study procedure.
2) Patient*s availability to stay in the research unit up to a minimum of eight days.
3) Patients with histologically/cytologically confirmed solid malignant disease (not recorded in the exclusion criteria), for which no standard therapy would reasonably be expected to result in cure or palliation.
4) Age >= 18 years.
5) Body Surface Area (BSA) >= 1.56 m2.
6) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) <= 2.

7) Adequate organ function as reflected by:
a) Neutrophil count >= 1.5 x 10^9/L.
b) Platelet count >= 100 x 10^9/L.
c) Hemoglobin >= 9 g/dL (5.6 mmol/L).
d) Albumin >= 3.0 g/dL.
e) Calculated creatinine clearance (CrCL) >= 30 mL/min (using the Cockcroft and Gault*s formula).
f) Serum total bilirubin <= upper limit of normality (ULN) or, direct bilirubin < ULN if total bilirubin is > ULN and as long as total bilirubin <= 1.5 ULN.
g) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <= 3.0 x ULN.
h) Creatinine phosphokinase (CPK) <= 2.5 x ULN.
i) Left ventricular ejection fraction (LVEF) by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan within normal range (according to institutional standards).
8) Recovery to grade < 1 from any adverse event (AE) derived from previous treatment (alopecia of any grade and peripheral neuropathy [PN] grade < 2 are allowed).
9) Women of childbearing potential must have a negative serum pregnancy test before entering the study. Both women and men must agree to use a highly effective method of contraception throughout the treatment period and for six months after treatment discontinuation. Highly effective methods of contraception include intrauterine contraceptive device (IUD), oral contraceptives, subdermal implant, bilateral tubal occlusion or vasectomy.
10) Patients must carry a central venous catheter.

Exclusion criteria

1) Concomitant diseases/conditions:
a) History or presence of unstable angina, myocardial infarction, valvular heart disease or congestive heart failure within the last 12 months.
b) Symptomatic arrhythmia or any arrhythmia requiring ongoing treatment, and/or prolonged QT-QTc grade >= 2.
c) Active uncontrolled infection.
d) Limitation of the patient*s ability to comply with the treatment or follow-up protocol.
e) Any other major illness that, in the Investigator*s judgment, will substantially increase the risk associated with the patient*s participation in this study. This includes but is not limited to, any significant disease such as significant cardiovascular, pulmonary, endocrine, renal, neurological or psychiatric disorder.
2) Symptomatic, progressive or corticosteroid-requiring documented brain metastases or leptomeningeal disease (controlled and stable or non-progressing brain metastases without steroids are allowed).
3) Patients with the following tumors:
1) Concomitant diseases/conditions:
a) History or presence of unstable angina, myocardial infarction, valvular heart disease or congestive heart failure within the last 12 months.

b) Symptomatic arrhythmia or any arrhythmia requiring ongoing treatment, and/or prolonged QT-QTc grade >= 2.
c) Active uncontrolled infection.
d) Limitation of the patient*s ability to comply with the treatment or follow-up protocol.
e) Any other major illness that, in the Investigator*s judgment, will substantially increase the risk associated with the patient*s participation in this study. This includes but is not limited to, any significant disease such as significant cardiovascular, pulmonary, endocrine, renal, neurological or psychiatric disorder.
2) Symptomatic, progressive or corticosteroid-requiring documented brain metastases or leptomeningeal disease (controlled and stable or non-progressing brain metastases without steroids are allowed).
3) Patients with the following tumors:
a) Colorectal cancer.
b) Primary CNS tumors.
4) Women who are pregnant or breast-feeding.
5) High transfusion requirements (> two packages or units of red blood cells and/or one platelet transfusion) within 30 days prior to inclusion in the study.
6) Chemotherapy, radiotherapy, immunotherapy or molecular targeted cancer therapy within four weeks prior to the start of PM01183 administration (six weeks for mitomycin C, nitrosourea therapy, temozolomide and other minor groove binders). This restriction does not apply to steroids and/or
bisphosphonates.
7) Major surgical procedure within the last eight weeks prior to the first PM01183 administration.
8) Wide-field radiotherapy (> 25% of bone marrow [BM] reserve) within 12 months prior to administration of PM01183 (pelvic radiation is considered 25% BM reserve).
9) Known hypersensitivity to any of the excipients used.
10) Participation in another clinical study or concomitant treatment with any investigational product in the 30-day period prior to inclusion in the study and/or participation in a 14C study within the last six months prior to screening for the current study. Total radioactivity exposure from the
current study and any previous 14C study must not exceed 5 mSv.
11) Tumoral or other conditions affecting the gastrointestinal (GI) tract or near the GI tract expected to induce total or partial occlusion of the GI transit.
12) Presence or history of inflammatory bowel disease or digestive tract fistulae.
13) Significant constipation (defined as < one deposition every two days or need of laxatives).
14) Any condition resulting in clinically evident obstruction of the urinary tract.
15) A history of regular use of tobacco or nicotine-containing products within three months prior to screening.
16) Consumption of red wine, Seville oranges, grapefruit or grapefruit juice from two days prior to the first dose of study medication.
17) Consumption of Hypericum perforatum (Saint John*s wort) herbal extracts from at least seven days prior to the first dose of study medication.
18) History of alcoholism.
19) Any condition that could interfere with the accurate assessment and recovery of radiocarbon 14C.

20) Prior allogenic, syngeneic or autologous BM transplantation or stem cell transplantation.
21) Unwillingness or inability to follow the procedures outlined in the protocol.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-05-2017
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PM01183
Generic name:	Lurbinectedin
Product type:	Medicine
Brand name:	radiolabeled PM01183
Generic name:	radiolabeld 14C1-lurbinectedin

Ethics review

Approved WMO

Date:	17-11-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	09-03-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-08-2017
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	EUCTR2016-000800-27-NL
CCMO	NL59571.031.16

Study results

Date completed:	08-05-2018
Results posted:	18-05-2020

First publication
04-09-2019