A Phase 1 Trial to Assess the Mass Balance and Pharmacokinetics of 14C-Guadecitabine in Subjects with AML, MDS, or Solid Tumors

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This study will provide an estimate of basic PK parameters for guadecitabine, an assessment of the routes and rates of elimination of radioactivity, and identification of metabolites and metabolic pathways.

Ethical review	Approved WMO
Status	Pending
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON46860

Source
ToetsingOnline

Brief title
14C-Guadecitabine ADME and Mass Balance Study

Condition

- Leukaemias

Synonym
blood- and bone marrow cancer

Research involving
Human

Sponsors and support

Primary sponsor: Astex Pharmaceuticals, Inc

Source(s) of monetary or material Support: Astex Pharmaceuticals;Inc

Intervention

Keyword: Acute myeloid leukemia (AML), Guadecitabine, Mass balance study, Myelodysplastic syndrome (MDS)

Outcome measures

Primary outcome

Primary objectives:

To evaluate the cumulative amounts and mass balance, and the time course of excretion of, 14C-radiolabeled drug material in urine and feces after subcutaneous administration of 14C-radiolabeled guadecitabine in subjects with AML, MDS, or solid tumors.

To identify the major route(s) of elimination and excretion after subcutaneous administration of 14C-radiolabeled guadecitabine in subjects with AML, MDS, or solid tumors.

Secondary outcome

Secondary objectives:

To determine total 14C-radioactivity in whole blood and plasma, blood/plasma ratio and protein binding after subcutaneous administration of 14C-radiolabeled guadecitabine in subjects with AML, MDS, or solid tumors.

To determine the pharmacokinetic profile of guadecitabine and active metabolite

decitabine in plasma after subcutaneous administration of 14C-radiolabeled guadecitabine in subjects with AML, MDS, or solid tumors.

To measure and identify, if applicable, the metabolites of guadecitabine (and secondary metabolites of decitabine) in plasma, urine and feces in subjects with AML, MDS, or solid tumors.

To assess the safety and tolerability after subcutaneous administration of guadecitabine administered once daily for 5 consecutive days in 28-day cycles to subjects with AML, MDS, or solid tumors.

Study description

Background summary

The need for mass balance trials in anticancer drug development has recently been emphasized by both the Food and Drug Administration and the European Medicines Agency in the ICH S9 guideline on the evaluation of anticancer medicinal products. The rationale for this trial is to satisfy Agency requirements for mass balance evaluation for guadecitabine.

Study objective

This study will provide an estimate of basic PK parameters for guadecitabine, an assessment of the routes and rates of elimination of radioactivity, and identification of metabolites and metabolic pathways.

Study design

This is a Phase 1, single-center, open-label, non-controlled, mass balance study with 14C-radiolabeled guadecitabine.

Intervention

Subjects will receive at least one cycle of 45mg/m2 of guadecitabine as once

daily doses on Days 1 to 5 of a 28-day cycle, of which the 5th (last) dose in the first cycle will be spiked with approximately 46.25 kBq/mg (1.25 microCi/mg) of 14C-radiolabeled guadecitabine. Additional cycles will be with unlabeled guadecitabine. For the extension part of the study (Cycle 2 and beyond), an adaptation of the dose (higher or lower doses) will be allowed pending safety, tolerability and efficacy outcomes. Subjects with AML or MDS may receive a dose of 60 mg/m2 from Cycle 2 on.

Study burden and risks

The reported serious adverse events (SAEs) associated with guadecitabine are myelosuppression-induced pancytopenia with typical sequelae: adverse events (AEs) of infectious nature (eg, infection progressing to sepsis or pneumonia). Other organ systems may be affected by resultant hypotension and hypoxia. In the setting of AML/MDS, it is difficult to separate the risks associated with guadecitabine from those of the disease. The risk for serious SAEs from the untreated disease appears to be virtually the same as from treatment with guadecitabine. The benefit of response from the disease outweighs any incremental risk since there are preliminary data demonstrating some clinical activity in the AML and MDS patient populations.

For patients with solid tumors, hypomethylating agents have shown some clinical activity, and guadecitabine is currently being evaluated in both hepatocellular cancer and ovarian cancer.

Using guadecitabine in conjunction with other myelosuppressive agents will increase the likelihood of currently expected AE/SAEs.

Radiolabeled molecules are commonly used to ascertain information on the elimination routes and metabolic fate of a compound. The effective radiation burden after a single SC radioactivity dose of 3.7 MBq 14C radiolabeled SGI-110 was estimated to be approximately 0.05 mSv, using assumptions made on the basis of absorption, distribution, metabolism and excretion and quantitative whole-body autoradiography data in cynomolgus monkeys. Approximately 85% of this dose is delivered to the bone marrow.

For biomedical investigations in small groups of human volunteers an effective dose below 0.1 mSv is considered trivial.

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

Subjects must fulfill all of the following inclusion criteria:;1. Male or female subjects, >=18 years of age at Screening;2. Body Mass Index (BMI) of 19.0 to 32.0 kg/m2, inclusive. Weight of at least 50 kg;3. For subjects with AML, MDS only:;a. Cytologically or histologically confirmed diagnosis of AML (except M3 acute promyelocytic leukemia) or MDS according to the 2008 World Health Organization (WHO) classification with the disease being refractory, relapsed, or unresponsive to standard treatment;b. Platelets >= 75,000/mm3;c. Absolute neutrophil count (ANC) >= 1000 cells/mm3;4. For subjects with solid tumors only:;a. Cytologically or histologically confirmed advanced solid tumor that is metastatic or unresectable, and for whom standard life-prolonging measures are not available.;b. Platelets >= 100,000/mm3;c. Absolute neutrophil >= 100 cells/mm3;5. Subjects with life expectancy of at least 16 weeks;6. Subjects with Eastern Cooperative Oncology Group (ECOG) performance status of 0-2;7. Subjects with acceptable organ function, as evidenced by laboratory data:;a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3x upper limit of normal (ULN);b. Total serum bilirubin <= 2 mg/dL (<= 35 µmol/L);c. Serum creatinine levels <= 1.25x ULN OR calculated by Cockcroft-Gault formula >=50 mL/min;d. International normalized ratio (INR) <=2.3;8. Subjects who sign an approved informed consent form for the study;9. Subjects who are willing and able to comply with the protocol and study procedures, in particular willingness to undergo hospitalization and collection of

blood and excreta after treatment with radiolabeled guadecitabine;10. Female subjects may be enrolled if they are:;a. documented to be surgically sterile or postmenopausal (amenorrhea >1 year and/or FSH >=40 mU/mL);or;b. practicing true abstinence for at least 28 days prior to dosing and agreeing to continue until 3 months after last study drug administration and having a negative urine pregnancy test at Screening and Day -1. Abstinence is acceptable only if it is consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of birth control.;or;c. using 2 forms of highly effective contraception, out of which one should be a physical barrier (condom or diaphragm or cervical cap with spermicidals), and another method such as adequate hormonal method (e.g. contraceptive implants, injectables, oral contraceptives) or non-hormonal methods (e.g. intrauterine device [IUD]) from Screening or at least 28 days prior to study drug administration (whichever is earlier) until 3 months after the last study drug administration and having a negative urine pregnancy test at Screening and Day -1. Contraceptive measures which may be considered highly effective comprise combined hormonal contraception (oral, vaginal, or transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, IUD, or intrauterine hormone-releasing system.;11. Males with partners of childbearing potential may be enrolled if they:;a. are documented to be surgically sterile (vasectomy) for at least 6 months before study drug administration;or;b. agree to practice true abstinence for at least 3 months after the last study drug administration (see also Inclusion Criterion 10b);or;c. agree to use 2 adequate forms of highly effective contraception, out of which one should be a physical barrier for 3 months after the last study drug administration (see also Inclusion Criterion 10c).

Exclusion criteria

Subjects meeting any of the following exclusion criteria will be excluded from the study:;1. Subjects who have known hypersensitivity to guadecitabine or decitabine;2. Subjects who have received radiation therapy, other locoregional therapy, or chemotherapy within 4 weeks prior to the first dose of study drug. Subjects must have recovered from any significant toxicities associated with previous therapies.;3. Subjects who have previously participated in human ADME studies and treated with radiolabeled drug.;4. Subjects who are at poor medical risk because of other systemic diseases or active uncontrolled infections;5. Subjects with a life-threatening illness, medical condition or organ system dysfunction, or other reasons which, in the Investigator*s opinion, could compromise the subject*s safety, interfere with the metabolism of guadecitabine, or compromise the integrity of the study outcomes;6. Subjects with abnormal left ventricular ejection fraction (<50%) on echocardiogram or multiple-gated acquisition scan (MUGA);7. Subjects with uncontrolled ischemic heart disease or a history of congestive cardiac failure of >=Grade 3 severity according to New York Heart Association (NYHA);8. Subjects with active hepatitis B infection should be on adequate antiviral therapy;9. Subjects with prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, non-metastatic prostate cancer with normal prostate specific antigen (PSA) or other cancer from which the subject has been disease free for at least three years;10. Subjects with known history or active disease of

human immunodeficiency virus (HIV) or hepatitis B or hepatitis C (HCV), unless there is evidence for cured hepatitis C;11. History of alcohol abuse or drug addiction (including soft drugs like cannabis products);12. Average intake of more than 24 units of alcohol per week for male subjects and 17 units per week for female subjects (1 unit of alcohol equals 10 mL of pure alcohol, i.e. approximately 250 mL of beer, 75 mL of wine or 25 mL of spirits);13. Participation in a drug study within 60 days prior to first study drug administration in the current study;14. Donation or loss of more than 500 mL of blood within 60 days prior to the first study drug administration.;15. Women of child-bearing potential must not be pregnant or breastfeeding and must have a negative pregnancy test at screening.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2016
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	[14C]-Guadecitabine
Product type:	Medicine
Brand name:	NA
Generic name:	Guadecitabine

Ethics review

Approved WMO Date:	30-05-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-08-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-09-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-12-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-05-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	07-12-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-12-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	08-01-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-04-2019
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	EUCTR2015-003083-36-NL
CCMO	NL57607.031.16