A phase I, open-label, two-stage, randomized, crossover, comparative pharmacokinetic and safety study of two formulations of CO-1.01 for injection in patients with advanced solid tumors.

Published: 06-01-2011
Last updated: 03-05-2024

Primary objective:•To compare the pharmacokinetic (PK) profiles of gemcitabine-5*-elaidate (parent compound) of two formulations of CO-1.01 in order to investigate whether the confidence interval (CI) for the ratio of the AUC0-* of the two...

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

Summary

ID

NL-OMON34352

Source
ToetsingOnline

Brief title
Phase I PK study of CO-1.01 in patients with advanced solid tumors.

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
advanced solid neoplasm, advanced solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Clovis Oncology Inc
Source(s) of monetary or material Support: Clovis Oncology Inc.

Intervention

Keyword: advanced solid tumors, CO-1.01, comparative, phase I

Outcome measures

Primary outcome

•Ratio of the AUC0-* of the two formulations of CO-1.01 given as a 30 min i.v.

infusion at 1250 mg/m2

Secondary outcome

Secondary endpoints:

•PK of CO-1.01 and metabolites in plasma and urine after 1250 mg/m2 CO-1.01

given as a single 30 min i.v. infusion

•QT/QTc interval of the ECG

•Relationship between plasma concentration of CO-1.01 and QT/QTc interval of

the ECG

•Drug tolerability and toxicity using clinical AE monitoring and clinical

laboratory testing

Exploratory

•Tumor response (according to RECIST 1.1)

•Blood concentrations of total cholesterol, LDL cholesterol, HDL cholesterol,

and triglycerides

Study description

Background summary

Gemcitabine-5*-elaidate is a fatty acid derivative of gemcitabine. Gemcitabine is used alone or in combination with other chemotherapy as a treatment for several solid tumor types, including pancreatic cancer, NSCLC, breast cancer, and ovarian cancer. Gemcitabine-5*-elaidate was synthesized to improve the clinical efficacy of gemcitabine by rendering cellular uptake independent of nucleoside transporters (which can be highly limiting in cancer cells) and prolonging the retention of the active metabolites, thus overcoming resistance mechanisms and schedule dependency that limits the efficacy of gemcitabine.

Nonclinical studies indicate that CO-1.01, a gemcitabine derivative, appears to be independent of nucleoside transporters (e.g., human equilibrative nucleoside transporter 1 [hENT1]) to exert its anticancer activity. Therefore, patients with low or no meaningful expression of hENT1 treated with CO-1.01 are predicted to show superior clinical outcomes compared with those given gemcitabine. Furthermore, the PK profiles of CO-1.01 and gemcitabine are different, and this may also favorably influence the in vivo antiproliferative effects of CO-1.01.

The formulation of CO-1.01 that is currently in clinical studies contains 15 mg/mL of gemcitabine-5*-elaidate solubilized in purified phospholipids. Recently, Clovis Oncology developed another formulation of CO-1.01, which contains 30 mg/mL of gemcitabine-5*-elaidate solubilized in purified phospholipids.

Study objective

Primary objective:
•To compare the pharmacokinetic (PK) profiles of gemcitabine-5*-elaidate (parent compound) of two formulations of CO-1.01 in order to investigate whether the confidence interval (CI) for the ratio of the AUC0-* of the two formulations is contained within 80 to 125%

Secondary objectives:
•To assess the PK of CO-1.01 and metabolites in plasma and urine after 1250 mg/m2 CO-1.01 given as a single 30 min intravenous (i.v.) infusion
•To evaluate the effects on the QT/QTc interval of the ECG of each formulation of CO-1.01
•To explore the relationship between the PK of CO-1.01 and the potential changes in QT/QTc
•To determine the tolerability and toxicity of CO-1.01

Exploratory:
•To evaluate tumor response of CO-1.01 in patients who enter the optional Treatment Extension Period of the study

Study design

This is a two-stage, open-label, randomized, two treatment period by two sequence crossover design study.

De study consist of two stages. In the first stage (Stage 1) the PK of CO-1.01 will be investigated. In the second stage of the study (Stage 2) the efficacy and safety of CO-1.01 will be further investigated. The second stage is optional.

An interim analysis of the PK data will be performed after completion of Stage I. A sample size re-estimation will be performed to determine the number of patients needed to have 80% power to meet the primary objective of the study. The required additional patients will then be enrolled. Stage I of the trial will enroll 12 patients and the total number of patients enrolled in both stages will not exceed 36 patients. The results from both stages will then be combined for the final analysis. It is anticipated that the detailed ECG assessments will be performed on patients who participate in Stage I of the study only; otherwise, the procedures in the two stages will be the same.

Patients will be randomly assigned to one of two following treatment sequences.
Treatment Sequence 1: Day 1 Formulation A, Day 8 Formulation B
Treatment Sequence 2: Day 1 Formulation B, Day 8 Formulation A

Each patient will be treated as follows:

• Pretreatment ECG visit: Triplicate standard ECGs and a 9-hour period of continuous ECG monitoring (Holter) during the Screening Period

• Pharmacokinetic Period: Patients will receive two different formulations of CO-1.01 at a dose of 1250 mg/m2 given over 30 min i.v. on Day 1 and Day 8. Patients will be randomly assigned to one of two treatment sequences. The randomization will be stratified by gender.

Upon completion of the Pharmacokinetic Period (Stage 1)(i.e., through Day 10), patients may continue to participate in an optional Treatment-Extension Period which begins with Cycle 1, Day 15. CO-1.01 will be administered on Days 1, 8, and 15 of a 28-day cycle during the Treatment Extension Period. For patients who continue treatment with CO-1.01, the dose may be delayed or decreased for drug-related toxicity, and treatment may continue until tumor progression or intolerable toxicity

During the first cycle of treatment (Pharmacokinetic Period), patients will

undergo PK assessments and cardiac assessments (12-lead ECG and Holter monitor) on Days 1 to 3 and Days 8 to 10. Central/core laboratories will be used for ECG interpretation and PK assay. Local imaging assessments for antitumor efficacy (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria) will be performed at Screening and after completion of every two cycles. AEs will be assessed from the time informed consent (IC) is obtained through 28 days after the last dose of CO-1.01. Other safety tests (vital signs, clinical laboratory tests, Eastern Cooperative Oncology Group [ECOG], and physical exam) will be collected as scheduled in the protocol.

Intervention

CO-1.01 will be administered as a 30 ± 3 min i.v. infusion under medical supervision. All treatment cycles are 28 days long with CO-1.01 doses administered on Days 1, 8 and 15.

CO-1.01 Formulation A: The current formulation of C0-1.01, which contains 15 mg/mL of gemcitabine-5*-elaidate solubilized in purified phospholipids

CO-1.01 Formulation B: New formulation of CO-1.01, which contains 30 mg/mL of gemcitabine-5*-elaidate solubilized in purified phospholipids

Patients will be randomized to two different treatment schedules and will receive each of the CO-1.01 formulations on opposite weeks of treatment as follows:

•Treatment Sequence 1: 1250 mg/m2/day of CO-1.01 Formulation A on Day 1 and Formulation B on Day 8
•Treatment Sequence 2: 1250 mg/m2/day of CO-1.01 Formulation B on Day 1 and Formulation A on Day 8

The optional Treatment Extension Period will start on Day 15 of Cycle 1. CO-1.01 will be dosed on Days 1, 8, and 15 of a 28-day cycle during the Treatment Extension Period. Where possible, Formulation B (new formulation) will be used for the Treatment Extension Period, although Formulation A (current formulation) may also be used as determined by the sponsor.

Study burden and risks

Study assessments will be performed at screening, C1D1, C1D2, C1D3, C1D8, C1D9, C1D10, C1D15, and CXD1, CXD8, CxD15, CxD22 (only the even numbered cycles) of every consecutive cycle. Treatment duration will continue until disease progression, Intercurrent illness that prevents administration of CO-1.01, unacceptable toxicity, patient withdrawal of consent, major noncompliance that may affect patient safety, pregnancy, death, or discontinuation from the study for any other reason, whereupon all patients will complete the End of Treatment

visit ± 28 days after last study medication.

Please refer to Table 4, page 46-47 of the protocol.

Risks:
• Toxicity due to the use of CO-1.01
• Reaction to the use of contrast fluid (used for CT scans
• Side effects of blood sampling

Contacts

Public
Clovis Oncology Inc

2525 28th Street
CO 80301 Boulder
US
Scientific
Clovis Oncology Inc

2525 28th Street
CO 80301 Boulder
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients must satisfy all of the following criteria:
• Diagnosis with a histologically confirmed solid tumor malignancy that is metastatic or

unresectable for which there are no standard curative or palliative treatment options available and for which CO-1.01 treatment would be appropriate
• Life expectancy of at least 3 months
• Performance Status (ECOG) 0 or 1
• Age >=18 years
• Adequate hematological and biological function, confirmed by the following laboratory values:
Bone Marrow Function
* Absolute neutrophil count (ANC) >=1.5 × 109/L
* Platelets >100.0 × 109/L
* Hemoglobin >=9 g/dL (or 5.6 mmol/L)
Hepatic Function
* AST <= 3 × upper limit of normal (ULN); if liver metastases, <=5 × ULN
* Bilirubin <=2 × ULN
* Albumin >3 g/dL (or 30 g/L)
Renal Function
*Serum creatinine <=1.5 × ULN
• Written consent on an Institutional Review Board/Independent Ethics Committee-approved IC Form prior to any study-specific evaluation

Exclusion criteria

Any of the following criteria will exclude patients from study participation:
• Clinically significant abnormal 12-lead ECG or QTcF >450 msec (males) or >470 msec (females), PR >240 msec, or a QRS >110 msec
• Family history of long QT syndrome
• Implantable pacemaker or implantable cardioverter defibrillator
• Symptomatic brain metastases
• Concomitant treatment with prohibited medications (e.g., concurrent anticancer therapy including other chemotherapy, radiation, hormonal treatment [except corticosteroids and megesterol acetate], or immunotherapy) <=14 days prior to CO-1.01
• Treatment with a previous regimen of CO-1.01 within 30 days of randomization
• Treatment with any medication known to produce QT prolongation (see Appendix 4)
• Surgical procedures are not allowed <=14 days prior to administration of CO 1.01. in all cases, the patient must be sufficiently recovered and stable
• History of allergy to gemcitabine or eggs
• Females who are pregnant or breastfeeding
• Refusal to use adequate contraception for fertile patients (females and males) for 6 months after the last dose of CO-1.01
• Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study (e.g., substance abuse, psychiatric disturbance, uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism)
• Any other reason the investigator considers the patient should not participate in the study

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-04-2011
Enrollment:	21
Type:	Actual

Ethics review

Approved WMO Date:	06-01-2011
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-03-2011
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-05-2011
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	EUCTR2010-023818-31-NL
CCMO	NL34852.031.10