A Two-part, Randomised, Open-label, Multicentre, Phase I Study to Determine the Effect of Food on the Pharmacokinetics of Olaparib Following Single 400 mg Doses of the Capsule Formulation in Patients with Advanced Solid Tumours

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON40586

Source
ToetsingOnline

Brief title
Phase 1-Olaparib/Capsules

Condition

- Other condition

Synonym
Cancer, Solid tumour

Health condition

Cancer: Solid tumour (Malignant solid tumour)

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Industry: Astra Zeneca

Intervention

Keyword: Food, Olaparib capsules, oncology, Phase 1

Outcome measures

Primary outcome

Pharmacokinetics

In Part A, the following variables will be calculated for olaparib where the

data allow: maximum plasma concentration (Cmax), time to reach maximum plasma

concentration (tmax), area under the plasma concentration time curve from zero

to the last measurable time point (AUC0-t), area under the plasma concentration

time curve from zero to infinity (AUC), apparent clearance following oral

administration (CL/F), apparent volume of distribution (Vz/F), terminal rate

constant (*z), and terminal half-life (t*). Other parameters may be determined

if deemed appropriate.

PK will not be measured in Part B.

Secondary outcome

Safety

Assessment of adverse events (AEs) graded by Common Terminology Criteria for

Adverse Events (CTCAE) v4.0, standard 12 lead electrocardiograms (ECGs), physical examination, vital signs (including blood pressure, pulse), and evaluation of laboratory parameters (clinical chemistry, haematology, and urinalysis).

Study description

Background summary

Olaparib is a drug that works by suppressing an enzyme called PARP that increases tumour growth; the suppression of this enzyme leads to the death of tumour cells. More than 1700 patients with ovarian, breast, pancreatic, gastric, and other solid tumours have received treatment with olaparib.

Study objective

The primary objective of this study is to investigate the effect of food on the pharmacokinetics (PK) of olaparib following oral dosing of the capsule formulation in patients with advanced solid tumours.
The secondary objective is to further investigate the safety and tolerability of olaparib following oral dosing of the capsule formulation in patients with advanced solid tumours.

Study design

This is a 2-part study: Part A will determine the effect of food on olaparib; Part B will allow patients continued access to olaparib after the PK phase. Approximately 30 patients with advanced solid tumours are planned to be enrolled, with at least 24 evaluable patients required to complete Part A.
Part A is a randomised, open-label, 3-period crossover PK study. Each patient will receive a single oral dose of olaparib (400 mg given via the capsule formulation) in each of 3 treatment periods (once in the overnight fasted state, once immediately following a high-fat meal and once immediately following a standard meal), with at least 5 and no more than 14 days (washout) between doses. Patients will check into the clinic on the evening prior to dosing in each treatment period, remain resident until 24 hours after each dose of olaparib, and then return to the clinic for assessments on Days 3 and 4 of each treatment period.
On completion of Part A, patients may be entered into Part B and continue to take olaparib capsules (400 mg twice daily [bd]) if they and the investigator agree that this is appropriate, providing the baseline safety assessments for

Part B are in accordance with the study inclusion and exclusion criteria. Patients must start Part B within 2 weeks (minimum 5 days, maximum 14 days) of the last dose received in Part A. Patients will have weekly clinic visits for the first 4 weeks; thereafter visits will be every 4 weeks. Part B will be of 6 months* duration from the date the last patient enters this part of the study. During and after Part B, patients may continue to take olaparib, if they and the investigator deem it appropriate, until such time as their disease progresses, the investigator believes they are no longer deriving clinical benefit, or they stop taking the olaparib for any other reason. After the end of Part B, patients will be seen as per their normal routine clinical schedule and no clinical data will be collected, other than serious adverse events (SAEs).
Patients will return to the clinic for follow-up assessments either 30 days (±7 days) after their last dose in the last treatment period in Part A or 30 days (±7 days) after discontinuation of olaparib in Part B. If a patient discontinues IP during Part B, they will also attend a study treatment discontinuation visit.

Statistical methods
The study has been sized to provide an estimate of the difference between olaparib PK parameters in the fed (standard meal or high-fat meal) and fasted states. Based on the estimate of within-patient standard deviation (SD) for log AUC from Study D0810C00024 of 0.296, and assuming a true food effect difference of 30% (estimated from pre-clinical in vivo data), 24 evaluable patients (4 per sequence, for the 6 sequences of the 3 treatment [food condition] periods) will give 90% power of showing that the 90% confidence interval (CI) for the food effect (ratio of geometric least-squares means of AUC or Cmax in the fed state [standard meal or high-fat meal] to the fasted state) lies entirely within the range of 0.59 and 1.70, ie, to exclude the possibility of a 70% increase in AUC or Cmax. Approximately 30 patients (5 per sequence) will be entered to ensure that at least 24 evaluable patients complete the study. nQuery v7.2 was used for the sample size calculations.
The goal of the statistical analysis is to estimate the effect of food on the PK of olaparib. Following log-transformation, Cmax and AUC (or AUC0-t, if AUC is not adequately estimable) of olaparib will be separately analysed by mixed-effect analysis of variance (ANOVA), fitting terms for treatment (food condition: fasted, high fat meal or standard meal), sequence, and treatment period. Patient within sequence will be treated as a random effect in the model. Point estimates and adjusted 90% CIs for the difference in treatment (standard meal or high fat meal compared to fasted) will be constructed. The point estimate and adjusted 90% CIs will then be exponentially back transformed to provide point and CI estimates for the ratio of interest (eg, Cmax or AUC of olaparib for the high fat meal to Cmax or AUC of olaparib in the fasted state). If the upper limit of the 90% CIs for the ratios of AUC (or AUC0-t as previously noted) and Cmax are <1.70, the magnitude of the effect of food will not be considered to be of clinical concern based upon exposure and tolerability data generated in the olaparib development programme.

An analysis of tmax using the Wilcoxon Signed Rank Test, and the Lehman median estimator of difference (standard or high fat meal compared to fasted) and 90% CIs will also be presented.Safety data will be listed and summarised using descriptive statistics

Intervention

In Part A, each patient will receive a single 400 mg oral dose of olaparib, given as the capsule formulation, in each of 3 treatment periods (fasted, following a high-fat meal and following a standard meal). Each dose will comprise 8 x 50 mg capsules for oral administration.
In Part B, patients will receive 400 mg oral olaparib bd, given as the capsule formulation, for the duration of their participation.

Study burden and risks

The patient will be asked to get admitteed to the hospital (for 3 times) to eat 3 different kind of meals, beside of that to take investigational medication, while for the patient no curative treatment is possible.

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

For inclusion in the study patients must fulfil the following criteria:
1. Provision of written informed consent prior to any study specific procedures
2. Patients must be >18 years of age.
3. Able to eat a high fat meal within a 30 minute period, as provided by the site.
4. Histologically or, where appropriate, cytologically confirmed malignant solid tumour refractory or resistant to standard therapy and for which no suitable effective standard therapy exists.
5. Normal organ and bone marrow function measured within 28 days prior to administration of investigational product (IP) as defined below:
* Haemoglobin >=10.0 g/dL, with no blood transfusions in the previous 28 days
* Absolute neutrophil count (ANC) >=1.5 x 109/L
* White blood cells (WBC) >3 x 109/L
* Platelet count >=100 x 109/L
* Total bilirubin <=1.5 x institutional upper limit of normal (ULN) (except in the case of Gilbert*s disease)
* Aspartate aminotransferase or serum glutamic oxaloacetic transaminase (AST), alanine aminotransferase or serum glutamic pyruvic transaminase (ALT) <=2.5 x institutional ULN unless liver metastases are present in which case it must be <=5x ULN
* Serum creatinine <=1.5 x institutional ULN
6. Calculated serum creatinine clearance >50 mL/min (using Cockroft-Gault formula or by 24-hour urine collection).
7. Eastern Cooperative Oncology Group (ECOG) performance status <=2.
8. Patients must have a life expectancy >=16 weeks.
9. Evidence of non-childbearing status for women of childbearing potential, or postmenopausal status: negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on Day 1 of the first treatment period in Part A. Postmenopausal is defined as:
* Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
* Luteinising hormone and follicle-stimulating hormone levels in the postmenopausal range for women under 50 years of age
* Radiation-induced oophorectomy with last menses >1 year ago
* Chemotherapy-induced menopause with >1 year interval since last menses
* Surgical sterilisation (bilateral oophorectomy or hysterectomy).
10. Patients are willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.
11. Patients must be on a stable concomitant medication regimen, defined as no changes in medication or in dose within 2 weeks prior to start of olaparib dosing, except for

bisphosphonates, denosumab and corticosteroids, which should be stable for at least 4 weeks prior to start of olaparib dosing.

Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:
1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff, its agents and/or staff at the study site).
2. Previous enrolment in the present study.
3. Treatment with any investigational product (IP) during the last 14 days (or a longer period depending on the defined characteristics of the agents used).
4. Any previous treatment with a PARP inhibitor, including olaparib.
5. Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for >=5 years.
6. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 2 weeks prior to study treatment. The patient can receive a stable dose of bisphosphonates or denosumab for bone metastases before and during the study as long as these were started at least 4 weeks prior to treatment.
7. Patients who have received or are receiving inhibitors or inducers of CYP3A4
8. Toxicities (>=CTCAE Grade 2) caused by previous cancer therapy, excluding alopecia.
9. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. Patients with asymptomatic brain metastases or with symptomatic but stable brain metastases can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment.
10. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.
11. Patients unable to fast for up to 14 hours.
12. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, uncontrolled seizures, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive bilateral interstitial lung disease on high resolution computer tomography (HRCT) scan, or any psychiatric disorder that prohibits obtaining informed consent.
13. Patients with a history of heart failure or left ventricular dysfunction.
14. Patients with type I or type II diabetes.
15. Patients who have gastric, gastro-oesophageal or oesophageal cancer.
16. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the olaparib, and patients who have had previous gastrointestinal resection.
17. Breastfeeding women.
18. Immunocompromised patients, eg, patients who are known to be serologically positive for human immunodeficiency virus (HIV).

19. Patients with known active hepatic disease (ie, hepatitis B or C).
20. Patients with a known hypersensitivity to olaparib or any of the excipients of the product.
21. Resting ECG with measurable QTc >470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome.
22. Patients who receive a seasonal flu vaccine (including H1N1, H1N5) must defer enrolment for 28 days post vaccination.
23. Clinical judgment by the investigator that the patient should not participate in the study.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-07-2013
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Olaparib
Generic name:	AZD2281

Ethics review

Approved WMO

Date:	08-05-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	03-07-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2013-001255-13-NL
ClinicalTrials.gov	NCT01851265
CCMO	NL44481.068.13