A Randomised, Open-label, Three-part, Phase I Study to Determine the Effect of Food on the Pharmacokinetics of Olaparib and to Provide Data on the Effect of Olaparib on QT Interval Following Oral Dosing of a Tablet 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-OMON40265

Source
ToetsingOnline

Brief title
Ph1 Olaparib tablet QT study

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 tablets, Phase 1, QT interval

Outcome measures

Primary outcome

To investigate the effect of food on the

pharmacokinetics (PK) of olaparib following oral

dosing of the tablet formulation in patients with

advanced solid tumours

Primary outcome variable(s):

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 (t1/2). Other parameters may be determined if deemed appropriate.

Secondary outcome

To investigate the effect of olaparib on the QT interval following oral dosing of the tablet formulation in patients with advanced solid tumours

Secondary outcome variables:
ECG intervals (including QT and QTc interval)

To assess the safety and tolerability of olaparib following oral dosing of the tablet formulation in patients with advanced solid tumours

Secondary outcome variables:
Assessment of AEs, graded by CTCAE (v4.03), physical examination (including BP and pulse), and evaluation of laboratory parameters (clinical chemistry, haematology, and urinalysis)

AE adverse event; BP blood pressure; CTCAE Common Terminology Criteria for

Adverse Event; ECG

electrocardiogram

Study description

Background summary

The food-effect part of this study has been designed as a 2-treatment period crossover study to
allow the investigation of the effect of food within each patient and in a randomised manner.
A crossover design is the recommended design for food effect studies to reduce inter-patient
variability.
Due to existing pre-clinical data it is not possible to use healthy volunteers for this study. It is
therefore relevant to use patients with advanced solid tumours.
The tablet dose chosen will deliver exposure that has been previously demonstrated to be
tolerated in cancer patients, and is the dose to be used in the monotherapy maintenance setting
in Phase III.

This study is robustly designed to assess the primary objective while minimising the number
of patients exposed to olaparib. AstraZeneca considers that olaparib continues to demonstrate
an overall acceptable benefit-risk balance to support its further clinical development.
Pre-clinical and emerging clinical tolerability data from patients indicate that olaparib is
generally well tolerated by patients with advanced cancer (please refer to the IB for details).
All AE, vital sign, and laboratory data will be collected and reviewed by the Principal
Investigator (PI) and clinical research staff on an ongoing basis.
Although patients may not initially gain any benefit from participation in Part A or Part B of
the study due to the short dosing periods, some benefit may be gained in Part C. If the
investigator believes it is in the patient*s interest, the patient may continue

treatment with
olaparib tablets until such time as their disease progresses, the investigator believes they are
no longer deriving clinical benefit, or they stop taking the olaparib tablets for any other
reason.
The data generated from this study will support further development of olaparib for the
treatment of cancer. The benefit/risk assessment for the conduct of this study of olaparib
tablets in patients is acceptable.

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 tablet formulation in patients with advanced
solid tumours.
The secondary objectives are to investigate the effect of olaparib on the QT interval corrected
for heart rate (QTc) following single (Part A) and multiple (Part B) oral doses of the tablet
formulation, and to investigate further the safety and tolerability of olaparib following oral
dosing of the tablet formulation in patients with advanced solid tumours.

Study design

This is a 3-part study in patients with advanced solid tumours: Part A will determine the effect
of food on the pharmacokinetics of olaparib and the effect of olaparib on QT interval
following a single oral dose of olaparib tablets; Part B will determine the effect of olaparib on
the QT interval following multiple oral dosing of olaparib tablets; Part C will allow patients continued access to olaparib tablets after PK and QT phases and will provide for additional
safety data collection. A total of 48 patients are planned to be enrolled, with at least
42 evaluable patients required to complete the study.
Part A of this study is a randomised, open-label, 2-treatment period crossover design. Each
patient will receive a single oral dose of olaparib tablets 300 mg in each of 2 treatment periods
(once in the overnight fasted state and once immediately following a high-fat

meal), with at
least 5 and no more than 14 days (washout) between doses. Digital electrocardiogram
(dECG), PK assessments, and safety assessments will be obtained for up to 72 hours post-dose
in each treatment period. Additionally, during the first treatment period, patients will undergo
baseline dECG assessments on Day -1 (ie, the day prior to dosing) at clock times matched to
planned/scheduled dECG assessment times on the dosing day (Day 1). Patients will check
into the clinic on the evening of Day -2 (first treatment period) or on the evening of Day -1
(second treatment period) and remain resident until 24 hours after each dose of olaparib
tablets. The dECGs performed on Day 1 of each treatment period will be clock-time matched
to the actual times that the Day -1 dECGs are performed in the first treatment period. Patients
will return to the clinic for assessments on Days 3 and 4 of each treatment period. On Day 1 of
Part A patients should be fasted over the same time period as Day -1.
Part B is an open-label study in the same patients who participated in Part A. Upon
completion of Part A, providing the patient continues to meet the study inclusion and
exclusion criteria and, following a washout period of at least 5 days and no more than 14 days
between the last dose in Part A and Day -1 of Part B, each patient will receive olaparib tablets
300 mg twice daily (bd) for 5 days. Patients will check into the clinic in the evening of
Day -2. On Day -1, baseline dECG assessments will be performed at clock times matched to
planned/scheduled dECG assessment times on Day 5. Patients will be discharged from the
clinic on the evening of Day -1. Patients will self-administer their olaparib doses under fasted
conditions (from 1 hour prior to 2 hours after dosing) from Day 1 up to the morning of Day 4
on an outpatient basis. On the evening of Day 4, patients will check back into the clinic, and
will receive their Day 4 evening dose. On the morning of Day 5, patients will receive their
Day 5 morning dose after an overnight fast and will remain fasting for 4 hours post-dose.
Patients will undergo dECG and PK assessments pre-dose and for 12 hours

post-dose. The
dECGs performed on Day 5 will be clock-time matched to the actual times that the Day -1
dECGs are performed. Patients will be discharged from the clinic after completing 12-hour
assessments on Day 5, and will self-administer their evening Day 5 dose of olaparib tablets.
On Day 5 of Part B patients should be fasted over the same time period as Day -1.
In both Parts A and B, patients are allowed to undergo the Day -1 (baseline) dECG
evaluations on Day -2 or Day -3, if necessary, as long as the washout period by the start of
baseline procedures for Part B has been at least 5 days since the previous treatment. If
baseline assessments are done earlier than Day -1, then the periods of in-house confinement
will be adjusted accordingly. For example, if baseline assessments are on Day -3, then
patients will check into the clinic in the evening of Day -4 and will leave the clinic the
morning of Day -2 after the 24-hour dECG measurement for Part A or the evening of Day -3 after the 12-hour dECG measurement for Part B. Patients will check back into the clinic in
the evening of Day -1.
On completion of Part B, patients may be entered into Part C and continue to take olaparib
tablets (300 mg bd) if they and the investigator agree that this is appropriate. Patients should
start Part C immediately after the last dose received in Part B. Patients will have weekly
clinic visits for the first 4 weeks; thereafter visits will be every 4 weeks. Part C will be of
12 months* duration from the date the last patient enters this part of the study.
During and after Part C, patients may continue to take olaparib tablets, 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 tablets for
any other reason. After the end of Part C (12 months after the last patient entered Part C),
patients will be seen as per their normal routine clinical schedule and no clinical data will be
collected, other than serious adverse events (SAEs) and drug dispensing/accountability.

Patients will return to the clinic for follow-up assessments 30 days (±7 days) after their last
dose (regardless of whether the last dose was in Part A, Part B, Part C, or the continued access
phase after Part C). If a patient discontinues olaparib tablets during Part C, they will also
attend a study treatment discontinuation visit.

Intervention

Taking Investigational product, eat high fat, normal or no breakfast and QT Interval measurements.

Study burden and risks

The patient will be asked to get admitteed to the hospital (for 3 times) to eat 3 different kind of breakfasts, 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

1. Provision of written informed consent prior to any study specific procedures
2. Patients aged >=18 years
3. Able to eat a high-fat meal within a 30-minute period, as provided by the study site
4. Histologically or, where appropriate, cytologically confirmed malignant solid tumour refractory or resistant to standard therapy or 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 (AST), alanine aminotransferase (ALT) <=2.5 x institutional ULN unless liver metastases are present in which case it must be <=5 x ULN
* Serum creatinine <=1.5 x institutional ULN
* Serum potassium, sodium, magnesium and calcium within the institutional normal range
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 of >=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 (with the exception of electrolyte supplements), 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

1. Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff, its agents, and/or staff at the study site)
2. Previous enrolment in the present study
3. Participation in another clinical study with an IP during the last 14 days (or a longer period depending on the defined characteristics of the agents used)
4. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 2 weeks prior to study treatment (or a longer period depending on the defined characteristics of the agents used). 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.
5. Patients who have received or are receiving inhibitors or inducers of CYP3A4 (see Section 5.6.1 for guidelines and washout periods)
6. Toxicities (>=CTCAE Grade 2) caused by previous cancer therapy, excluding alopecia
7. 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.
8. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.
9. Patients unable to fast for up to 14 hours
10. 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 computed tomography (HRCT) scan, or any psychiatric disorder that prohibits obtaining informed consent.
11. Patients with a history of poorly controlled hypertension with resting blood pressure (BP) >150/100 mm Hg in the presence or absence of a stable regimen of hypertensive therapy. Measurements will be made after the patient has been resting supine for a minimum of 5 minutes.
Two or more readings should be taken at 2-minute intervals and averaged. If the first 2 diastolic readings differ by more than 5 mm Hg, an additional reading should be obtained and averaged.
12. Patients with a history of heart failure or left ventricular dysfunction, and patients who require calcium channel blockers
13. Patients with type I or type II diabetes

14. Patients who have gastric, gastro-oesophageal or oesophageal cancer
15. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders or significant gastrointestinal resection likely to interfere with absorption of olaparib.
16. Breastfeeding women
17. Immunocompromised patients, eg, patients who are known to be serologically positive for human immunodeficiency virus (HIV)
18. Patients with known active hepatic disease (ie, hepatitis B or C)
19. Patients with a known hypersensitivity to olaparib or any of the excipients of the product
20. Mean QTc with Fridericia's correction (QTcF) >470 ms in screening ECG or history of familial long QT syndrome:
* a marked baseline prolongation of QT/QTc interval (eg, repeated demonstration of a QTc interval >470 ms)
* a history of additional risk factors for Torsade de pointes (eg, heart failure, hypokalaemia, family history of long QT syndrome)
21. The use of concomitant medications that prolong the QT/QTc interval
22. Clinical judgment by the investigator that the patient should not participate in the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-11-2013
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Olaparib

Generic name:	AZD2281

Ethics review

Approved WMO Date:	14-06-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-09-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-09-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-10-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-05-2014
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:	12-08-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-09-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-10-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-10-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-08-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-10-2019
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	EUCTR2013-001891-39-NL
Other	http://www.clinicaltrials.gov
CCMO	NL45021.068.13