A Non-randomised, Open-label, Sequential, Three-part, Phase I Study to Assess the Effect of Itraconazole (a CYP3A4 Inhibitor) on the Pharmacokinetics of Olaparib Following Oral Dosing of a Tablet Formulation, and to Provide Data on the Effect of Olaparib on QT Interval Following Oral Dosing of a Tablet Formulation to Patients with Advanced Solid Tumours

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The primary objective of this study is to investigate the effect of itraconazole on thepharmacokinetics (PK) of olaparib following oral dosing of the tablet formulation inpatients with advanced solid tumours.The secondary objectives are: to...

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

Summary

ID

NL-OMON40540

Source
ToetsingOnline

Brief title
Ph1 Olaparib tablet QT Itraconazole 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: Intraconazole, Olaparib tablets, Phase 1, QT interval

Outcome measures

Primary outcome

Primary objective:

To investigate the effect of itraconazole on the PK

of olaparib following oral dosing of the tablet

formulation in patients with advanced solid

tumours

Primary outcome variable(s):

Maximum plasma olaparib concentration (Cmax)

Olaparib area under the plasma concentration time curve from zero to infinity (AUC) (or area under the plasma concentration time curve from zero to the last measurable time point, AUC0-t, if AUC is not adequately estimable)

PK pharmacokinetics

Secondary outcome

Secondary objectives:

To characterise the PK of olaparib following oral dosing of the tablet formulation in the presence and absence of itraconazole

To demonstrate exposure to itraconazole and hydroxy-itraconazole

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

To investigate further the safety and tolerability of olaparib tablets in patients with advanced solid tumours

Secondary outcome variables:

Time to reach maximum plasma concentration for

olaparib (tmax),

Olaparib area under the plasma concentration

time curve from zero to the last measurable time

point (AUC0-"),

Olaparib apparent clearance (CL/F),

Olaparib apparent volume of distribution (Vz/F),

Olaparib terminal half-life (t1/2)

Itraconazole Cmax, AUC0-", tmax, and CL/F;

hydroxy-itraconazole Cmax, AUC0-", and tmax

ECG intervals (including QT and QTc interval)

Assessment of AEs, graded by CTCAE v4.03,

physical examination (including BP and pulse),

and evaluation of laboratory parameters (clinical

chemistry, haematology, and urinalysis)

Study description

Background summary

This study has been designed as a 2-part sequential study to allow the investigation of the
effect of itraconazole, a CYP3A4 inhibitor, on the PK of olaparib within each patient. 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 intended to be used in Phase III studies conducted
in the monotherapy maintenance setting.

Study objective

The primary objective of this study is to investigate the effect of itraconazole on the
pharmacokinetics (PK) of olaparib following oral dosing of the tablet formulation in
patients with advanced solid tumours.
The secondary objectives are: to characterise the PK of olaparib following oral dosing of the tablet formulation in the presence and absence of itraconazole, to demonstrate exposure to itraconazole and hydroxy-itraconazole, 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 tablets in patients with
advanced solid tumours (Part C).

Study design

This is a 3-part study in patients with advanced solid tumours: Part A will assess the effect of
itraconazole on the PK parameters of olaparib and will determine the effect of olaparib on the
QT interval following single oral dosing; Part B will determine the effect of olaparib on the
QT Interval following multiple oral dosing; Part C will allow patients continued access to
olaparib after the PK and QT phases and will provide for additional safety data collection. A
total of 48 patients are planned to be enrolled; at least 42 evaluable patients will be required to
complete the study. Patients will participate as a single cohort in all parts of the study.
Part A is a non-randomised, open-label, 2-treatment design. Patients will receive the
following 2 study treatments: a single oral dose of olaparib alone (tablet formulation), and a
single oral dose of olaparib administered concomitantly with itraconazole.

Patients will check into the clinic the evening of Day -2. Baseline digital electrocardiogram (dECG) assessments will be obtained on Day -1 at clock times matched to the planned/scheduled dECG assessment times on Day 1 of dosing. On Day 1, patients will receive a single oral dose of olaparib 100 mg in the morning after an overnight fast and will remain fasting for 4 hours post-dose.
Patients will remain resident until 24 hours after the dose of olaparib, during which time PK blood samples, dECGs, and other safety information will be collected. The dECGs performed on Day 1 and Day 9 will be clock-matched to the actual times that the Day -1 dECGs are performed. Patients will then return to the clinic on an outpatient basis for PK assessments on Days 3 and 4. On Day 5, patients will commence daily doses of itraconazole (200 mg once daily [od]) for 7 days. Itraconazole doses should be taken with a full meal, except for the dose on the morning of Day 9, which will be taken after an overnight fast. Patients will selfadminister their itraconazole doses on an outpatient basis from Day 5 until the morning of Day 8. On the evening of Day 8, patients will check into the clinic. On the morning of Day 9, patients will receive a single oral dose of olaparib 100 mg (administered concomitantly with the itraconazole dose) after an overnight fast and will remain fasting for 4 hours post-dose.
Patients will remain resident until 24 hours after the dose of olaparib, during which time PK blood samples, dECGs, and other safety information will be collected. Patients will then return to the clinic on an outpatient basis for PK assessments on Days 11 and 12. On Days 1 and 9 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 7 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 300 mg twice daily (bd) for 5 days. Patients will check into the clinic on the

evening of
Day -2. On Day -1, baseline dECG assessments will be performed at clock times matched to
the 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-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. 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 baseline dECG evaluations
(scheduled for Day -1) within 3 days prior to the start of dosing, if necessary, as long as the
washout period by the start of Day -1 procedures has been at least 7 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, eg, if baseline assessments are on Day -3, then
patients will check into the clinic the evening of Day -4 and will leave the clinic either 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, 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 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 during Part C, they will also attend a
study treatment discontinuation visit.

Intervention

Taking Investigational product, itraconazol and QT Interval measurements.

Study burden and risks

The patient will be asked to get admitteed to the hospital to take itraconazole, 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 should fulfil the following criteria:
1. Provision of written informed consent prior to any study-specific procedures
2. Patients aged *18 years
3. Histologically or, where appropriate, cytologically confirmed malignant solid tumour refractory or resistant to standard therapy and for which no suitable effective standard therapy exists
4. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of investigational product (IP) as defined below:
- Haemoglobin (Hb) * 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 * 5x ULN
- Serum creatinine * 1.5 x institutional ULN
- Serum potassium, sodium, magnesium, and calcium within the institutional normal range
5. Calculated serum creatinine clearance >50 mL/min (using Cockroft-Gault formula or by 24 hour urine collection)
6. Eastern Cooperative Oncology Group (ECOG) performance status *2
7. Patients must have a life expectancy of *16 weeks.
8. 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 Part A.
Post-menopausal 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)
9. Patients are willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.
10. 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 the 2 weeks prior to start of olaparib dosing, except for bisphosphonates, denosumab, and corticosteroids, which should be at a stable dose for at least 4 weeks prior to the start of olaparib dosing.

Exclusion criteria

Patients should 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 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. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days of the first administration of the IP until the end of Part A.
8. 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.
9. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery
10. Patients unable to fast for up to 14 hours
11. 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.
12. 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.
13. Patients with a history of heart failure, or left ventricular dysfunction, and patients who require calcium channel blockers
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 the absorption 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 itraconazole or any of the excipients of the product
20. Patients with a known hypersensitivity to olaparib or any of the excipients of the product
21. 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)
22. The use of concomitant medications that prolong the QT/QTc interval
23. Concomitant medication contraindicated for use with itraconazole (including, but not limited to): cisapride, oral midazolam, nisoldipine, pimozide, quinidine, dofetilide, triazolam, levacetylmethadol (levomethadyl), 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA)-reductase inhibitors metabolized by CYP3A4, such as lovastatin and simvastatin, ergot alkaloids metabolized by CYP3A4, such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine).
24. 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:	Intraconazole
Generic name:	Intraconazole
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Olaparib
Generic name:	AZD2281

Ethics review

Approved WMO Date:	18-06-2013
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:	18-09-2013
Application type:	Amendment
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:	12-09-2014
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:	19-06-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-04-2016
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	EUCTR2013-001892-18-NL
Other	http://www.clinicaltrials.gov.
CCMO	NL45022.068.13