# Pharmacokinetic boosting of olaparib to improve exposure, tolerance and cost-effectiveness (PROACTIVE-study)

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This study has been transitioned to CTIS with ID 2024-516414-38-00 check the CTIS register for the current data. Part APrimary objective1. To determine the equivalence of the Area-Under-the-Curve (AUC) of the reduced, boosted dose of olaparib and…

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Ovarian and fallopian tube disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON54399

**Source**
ToetsingOnline

**Brief title**
PROACTIVE

### Condition

- Ovarian and fallopian tube disorders

**Synonym**
ovarian cancer, Ovarian carcinoma

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Radboud Universitair Medisch Centrum
**Source(s) of monetary or material Support:** ZonMw

## Intervention

**Keyword:** Boosting, Cobicistat, Olaparib

## Outcome measures

### Primary outcome

Part A

1. AUC0-12h for the regular and boosted olaparib will be determined using non-compartmental analysis for the primary objective. Hereto, multiple PK samples will be collected after one week of each treatment regimen at the following times: pre-dose, *, 1, 1*, 2, 3, 4, 6, 8 hours after olaparib intake. If possible, additional PK samples will be taken after 10 and 12 hours.

Part B

1. Progression-free survival is defined as the time from randomization until the date of either objective radiological disease progression or biochemical progression combined with clinical progression or death;

o Objective radiological disease progression will be assessed according to RECIST version 1.11

o Biochemical disease progression will be assessed with serum CA-125 according to the GCIG criteria;

o Clinical progression will be assessed by treating physician;

2. The number of patients who require a dose reduction due to toxicity will be registered.

### Secondary outcome

Part A

1. Inter- and intrapatient variability in olaparib pharmacokinetics with and without cobicistat is calculated using non-compartmental analysis of PK data;

2. Adverse events and laboratory safety will be monitored and scored according to the CTCAEv5.0 to describe the safety of boosted olaparib treatment.

Part B

1. Health status and satisfaction of patients will be monitored with the CTSQ and EQ-5D-5L questionnaires;

2. ctDNA will be determined from plasma samples;

3. Adverse events and laboratory safety will be monitored and scored according to the CTCAEv5.0 to describe the safety of boosted olaparib treatment;

4. Costs for the cost-effectiveness analysis will be assessed by the iMTA Productivity Cost Quetstionnaire (iPCQ) and iMTA Medical Consumption Questionnaires (iMCQ). Health status will be monitored with the EQ-5D-5L questionnaire.

# Study description

**Background summary**

Olaparib (Lynparza®) is a poly-adenosine diphosphate ribose polymerase (PARP) inhibitor, originally used for the maintenance treatment of women with platinum-sensitive relapsed Breast Cancer gene (BRCA)-mutated high grade serious epithelial ovarian, fallopian tube, or peritoneal cancer, who are in response to platinum-based chemotherapy. Over the last two years, several therapeutic indications have been added to the drug label, such as first-line platinum-sensitive BRCA-mutated high grade serious epithelial ovarian, fallopian tube, or peritoneal cancer, germline BRCA1/2-mutated, Human Epidermal growth factor Receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer and BRCA1/2-mutated metastatic castration-resistant prostate cancer, who

have progressed following prior therapy. Since olaparib is very expensive (~¤5700/month), this increase of treatment population will have a significant impact on health care expenditures.
To keep healthcare affordable and accessible for all patients, innovative strategies are warranted to reduce the dose of expensive drugs, without reduction of efficacy. For olaparib, pharmacokinetic (PK) boosting can be applied. PK boosting is the lay term for administering a non-therapeutic active strong inhibitor of a metabolic enzyme, for example cytochrome P450 3A (CYP3A), together with a therapeutic drug that is metabolized by the same enzyme. Boosting thus increases the concentration of the therapeutic drug and allows lower doses to be administered to patients. Hence, coadministration of a reduced dose of olaparib with cobicistat (Tybost®), a non-therapeutic, strong inhibitor of the CYP3A can lead to equivalent exposure to olaparib. Furthermore, inhibition of CYP3A could lead to less PK variability since metabolic capacity is a prominent cause for (intra- and inter-individual) variability in systemic exposure. Predictable olaparib exposure will reduce the number of patients who are unintentionally under- or overtreated. Lastly, tumor tissue itself may express CYP3A as a detoxification or resistance mechanism. Theoretically, PK boosting may also overcome CYP3A-mediated drug resistance.

**Study objective**

This study has been transitioned to CTIS with ID 2024-516414-38-00 check the CTIS register for the current data.

Part A
Primary objective
1. To determine the equivalence of the Area-Under-the-Curve (AUC) of the reduced, boosted dose of olaparib and the regular dose.

Secondary objectives
1. To determine whether boosting reduces the inter- and intrapatient PK variability of olaparib;
2. To describe the safety of boosted olaparib.

Part B
Primary objectives
1. To determine if efficacy by progression-free survival (PFS) in patients with high grade ovarian cancer receiving olaparib maintenance therapy who are in response following completion of first-line platinum-based chemotherapy, treated with the lower boosted dose of olaparib is non-inferior to patients treated with the regular dose of olaparib;
2. To determine if tolerance by dose reductions due to toxicity in patients treated with the lower boosted dose of olaparib is non-inferior to patients treated with the regular dose of olaparib.

Secondary objectives

1. To investigate whether health status, tolerance and satisfaction of patients treated with the boosted low dose olaparib is comparable to patients treated with the regular dose of olaparib;
2. To evaluate whether treatment response of boosted versus regular olaparib can be determined with cell-free tumor nucleic acids (ctDNA) as pharmacodynamic biomarker;
3. To describe toxicity of the lower boosted dose of olaparib compared to the regular dose of olaparib;
4. To compare cost-effectiveness of the lower boosted dose of olaparib compared to the regular dose of olaparib.

**Study design**

Part A
A multicenter, randomized, open-label, crossover, drug-drug interaction study in 18 patients.

Part B
A multicenter randomized, open-label, non-inferiority study in 142 patients.

**Intervention**

The comparator treatment is the regular dose of olaparib tablets 300 mg BID, 250 mg BID or 200 mg BID based on the patient's condition and physician's discretion.
The investigational treatment is the reduced dose of olaparib tablets 100 mg BID, 150 mg OD or 100 mg OD, combined with the PK booster cobicistat 150 mg BID.

**Study burden and risks**

A possible benefit of the intervention is less pharmacokinetic variability in the group treated with the boosted olaparib dose.
The risk associated with this study are limited, since both treatment regimens (comparator and intervention) are according to the drug label of olaparib. Although the exposure to olaparib is increased in the interventional treatment arm in part A compared to monotherapy, the boosted exposure was comparable to an average exposure to olaparib in an unselected pupation. Therefore, the additional risks due to side effects in the interventional treatment arm in part B is considered negligible. Many patients treated with olaparib experience side effects. These side effects are considered mild and easily manageable with dose reductions. The most common side effects are bone marrow depressions which - when adequately managed - do not interfere with the quality of life of patients. Since all patients will be adequately monitored in line with standard care, the additional risk for side effects in the interventional treatment arm is expected to be comparable to the comparator arm.

The burden for subjects participating in this study is mainly time-investment associated with the study visits, additional questionnaires, the additional number of blood samples in part A of the study and tumor biopsies if consented in part B of the study. The majority of participating will have to take an additional drug, cobicistat, which increases burden of medication intake. In these subjects, we will carefully evaluate potential drug interactions to guarantee safety.

## 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

Part A - proof of concept
• Subjects who start or are on treatment with olaparib tablets, according to the drug label and physician*s discretion;

• Subjects who are able and willing to provide written informed consent prior to screening;
• Age of 18 years or older;
• Able to measure the outcome of the study in this subject (e.g. patient availability; willing and being able to undergo repeated plasma sample collection);
• Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.

Part B - clinical evaluation
• Subjects who start on treatment with olaparib tablets, according to the drug label and physician*s discretion;
• Subjects who are able and willing to provide written informed consent prior to screening;
• Age of 18 years or older;
• Able to measure the outcome of the study in this subject (e.g. patient availability; willing and being able to undergo sample collection for PK and PD purposes);
• Expected to be on olaparib treatment for >= 3 months;
• Eastern Cooperative Oncology Group (ECOG) performance status of 0-3.

### Exclusion criteria

Part A + B
• Concurrent use of other anti-cancer therapies;
• Concurrent use of potent inducers or inhibitors of CYP3A4 as assessed with the KNMP *G-standaard*;
• Known contra-indications for treatment with cobicistat in line with the summary of product characteristics;

## Study design

### Design

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| Study phase: | 4 |
| Study type: | Interventional |
| Intervention model: | Crossover |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 02-02-2022 |
| Enrollment: | 160 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Lynparza |
| Generic name: | olaparib |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Tybost |
| Generic name: | cobicistat |
| Registration: | Yes - NL outside intended use |

# Ethics review

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|---|---|
| Approved WMO Date: | 24-08-2021 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 24-11-2021 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 19-12-2022 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 25-05-2023 |
| Application type: | Amendment |

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|---|---|
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 12-07-2023 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 25-07-2023 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 02-08-2023 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 16-08-2023 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 11-12-2023 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 21-12-2023 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |

# 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 |
|---|---|
| EU-CTR | CTIS2024-516414-38-00 |
| EudraCT | EUCTR2021-004032-28-NL |
| CCMO | NL78695.091.21 |