# Pharmacokinetics of single-dose dOLutegravir in HIV-serOnegative sub-jects with severe hepatic impairment compared to matched controls (POLO).

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The aim of the POLO study is to evaluate pharmacokinetics and safety of a single-dose of dolutegravir in patients with severe hepatic impairment (Child-Pugh score * 10) and compare these to matched controls.

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Will not start |
| **Health condition type** | Viral infectious disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON47050

**Source**
ToetsingOnline

**Brief title**
POLO

### Condition

- Viral infectious disorders

**Synonym**
HIV, human immunodeficiency virus

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Afdeling Apotheek

**Source(s) of monetary or material Support:** Fabrikant studiegeneesmiddel,ViiV Health Care

## Intervention

**Keyword:** dolutegravir, HIV, pharmacokinetics

## Outcome measures

### Primary outcome

Geometric Mean and the 95% classical confidence interval of AUC0-24h, Cmax,

C24h and median (range) of tmax for dolutegravir and dolutegravir glucuronide

in hepatic impaired subjects.

Geometric Mean and the 95% classical confidence interval of CUnbound DTG, t=3h

and CUnbound DTG, t=24h after administration.

### Secondary outcome

(Serious) Adverse Events

# Study description

### Background summary

Currently, there are no data on the pharmacokinetics of dolutegravir in patients with severe hepatic impairment. This is unfortunate as dolutegravir as part of combination antiretroviral therapy for treamtent of HIV-infection in patients with severe hepatic impairment has some advantages over other frequently used antiretroviral agents. For example, dolutegravir has a limited potential for causing drug-drug interactions, has a better tolerability profile and its metabolism is probably minimally affected by liver dysfunction.

### Study objective

The aim of the POLO study is to evaluate pharmacokinetics and safety of a single-dose of dolutegravir in patients with severe hepatic impairment (Child-Pugh score * 10) and compare these to matched controls.

## Study design

Open-label, parallel-group, nonrandomized, multi-centre, phase-I, single dose trial.

## Intervention

A single dose of 50mg of dolutegravir will be given to participants on an empty stomach around 8 AM. Breakfast will be provided 2h later. Plasma sampling will be done for 96h (at t=0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72 and 96 hours post ingestion). A final safety assessment will be scheduled 7 days after drug intake (Day 8 +/- 2 days).

## Study burden and risks

The study participants are all HIV-seronegative subjects and will not bene-fit from the participation in this clinical trial.
Participants will visit the clinical research centre or hospital for a screening visit, 1 full day (13 hours/24 hours) and 5 or 4 short visits (10 minutes). The duration of the entire trial (excluding screening period) is 8 (+/- 2 days) days maximum. Exposure to the study medication after a single dose is 2-5 days, depending on the elimination half-life.
Dolutegravir has a good benefit/risk ratio. Its safety was demonstrated in a study in 8 patients with moderate hepatic impairment and 8 matched controls (Song et al 2013). For pharmacokinetic purposes 17 blood samples will be taken in total. For safety assessment a total of 17 to 20 blood samples will be collected (depending on which group, matched controls or hepatic impairment group). The total blood volume taken during the entire study will be approximately 120-130 mL of blood. During the days that blood samples will be collected for a pharmacokinetic curve an intravenous cannula will be inserted to facilitate blood sampling and limit the number of venous punctions.

Risk assessment is *minimal*. The risk-classification based on NFU-guidelines is assessed as minimal to the subject population receiving study drug at the selected regimen. Patients with severe hepatic impairment are a vulnerable group. However, the study drug will be administered as a single dose only and subjects will be monitored closely. In addition, dolutegravir is considered to be safe and well tolerated in HIV-infected subjects and also in healthy volunteers with or without moderate hepatic impairment. The drug is licensed on the Dutch market for the dose administered (50mg QD). Also, a higher dolutegravir dose (50mg BID) is licensed. Therefore the risk is assessed as minimal to both matched controls and subjects with hepatic impairment.

# Contacts

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Selecteer

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**Scientific**
Selecteer

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Hepatic impairment group:
1. Subject is at least 18 and not older than 90 years at screening.
2. Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.
3. Child-Pugh score 10 or greater (Appendix A). Expected to be in clinical stable condition for at least 4 weeks as assessed by the subject*s own hepatologist. This assessment takes into account the following aspects: MELD score, fibroscan results (if available), life expectancy, recent history of decompensation events and the rate of progression of hepatic insufficiency.;Matched controls:
1. Subject is at least 18 and not older than 90 years at screening.
2. Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.

3. Subject is in good age-appropriate health condition as established by medical history, physical examination, electrocardiography, results of biochemistry, haematology and urinalysis testing within 4 weeks prior to Day 1. Results of biochemistry, haematology and urinalysis testing should be within the laboratory's reference ranges (see Appendix D). If laboratory results are not within the reference ranges, the subject is in-cluded on condition that the Investigator judges that the deviations are not clinically relevant. This should be clearly recorded.
4. Subject has a normal blood pressure and pulse rate, according to the Investigator's judgement.

## Exclusion criteria

Hepactic impairment group:
1. Inability to understand the nature and extent of the study and the pro-cedures required.
2. Gilbert*s syndrome or other underlying disease (other than hepatic impairment) that causes alterations in the Child-Pugh class components (bilirubin, albumin, protombin, encephalopathy and ascites).
3. Therapy with strong inducers or inhibitors of UGT1A1 or drugs that are contra-indicated with concomitant use of dolutegravir (see appendix B). (NB. there are restrictions for intake of magnesium/aluminium-containing antacids, iron and calcium supplements, multivitamins and other cation-containing supplements.
4. Positive HIV test.
5. Participation in a drug study within 60 days prior to Day 1.
6. Febrile illness within 3 days before Day 1.;Matched controls:
1. Documented history of sensitivity/idiosyncrasy to medicinal products or excipients.
2. Positive HIV test.
3. Positive hepatitis B or C test.
4. Pregnant female (as confirmed by an hCG test performed less than 4 weeks before Day 1) or breast-feeding female. Female subjects of childbearing potential without adequate contraception (see Appendix C).
5. Therapy with strong inducers or inhibitors of UGT1A1 or drugs that are contra-indicated with concomitant use of dolutegravir (see appendix B). (NB. there are restrictions for intake of magnesium/aluminium-containing antacids, iron- and calciumsupplements, multivitamins and other cation-containing supplements.
6. Relevant history or presence of pulmonary disorders (especially COPD), cardiovascular disorders, neurological disorders (especially seizures and migraine), psychiatric disorders, gastro-intestinal disor-ders, renal and hepatic disorders, hormonal disorders (especially dia-betes mellitus), coagulation disorders.
7. Relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion.
8. History of or current abuse of drugs, alcohol or solvents.
9. Inability to understand the nature and extent of the study and the pro-cedures required.
10. Participation in a drug study within 60 days prior to Day 1.
11. Donation of blood within 60 days prior to Day 1.
12. Febrile illness within 3 days before Day 1

13. UGT1A1 polymorphism (at least one *28, *37 or *6 allele)

# Study design

## Design

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

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Will not start |
| Enrollment: | 15 |
| Type: | Anticipated |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Tivicay (for use in clinical trials) |
| Generic name: | dolutegravir (for use in clinical trials) |

# Ethics review

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| Approved WMO Date: | 10-10-2017 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 02-05-2018 |

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| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 18-06-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 29-11-2018 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 29-07-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

# 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 | EUCTR2016-001349-21-NL |
| CCMO | NL57349.078.17 |