A drug-drug interaction study between the novel anti-HCV agent daclatasvir and the antiretroviral agents atazanavir/ritonavir or atazanavir/cobicistat in healthy volunteers.

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Primary objective:To compare the effect of multiple dose atazanavir/cobicistat on the multiple dose phar-macokinetics of daclatasvir with the effect of atazanavir/ritonavir on the multiple dose of daclatasvir by intra-subject comparison in healthy...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON42827

Source
ToetsingOnline

Brief title
DATE-4

Condition

- Viral infectious disorders

Synonym
HCV, Hepatitis C, HIV

Research involving

Human

Sponsors and support

Primary sponsor: Apotheek
Source(s) of monetary or material Support: Bristol-Myers Squibb Pharma EEIG

Intervention

Keyword: atazanavir, cobicistat, daclatasvir, hepatitis C

Outcome measures

Primary outcome

To compare the effect of multiple dose atazanavir/cobicistat (300/150mg QD) on the multiple dose pharmacokinetics (AUC, Cmax, Ctrought) of daclatasvir (30mg) with the effect of atazanavir/ritonavir on the multiple dose of 30mg daclatasvir, by intra-subject com-parison, in healthy subjects. The endpoints are geometric mean ratio*s (GMR) of daclatasvir AUC, Cmax, Ctrought with atazanavir/cobicistat compared to atazanavir/ritonavir co-treatment.
GMR of atazanavir AUC, Cmax, Ctrought with daclatasvir + cobicistat compared to daclatasvir + ritonavir co-treatment

Secondary outcome

Adverse events will be described and compared (including clinically relevant laboratory abnormalities) of the control treatments (atazanavir/ritonavir) and of the intervention treatment (atazanavir/cobicistat).

Study description

Background summary

Approximately 20-25% of the total number of HIV-infected pa-tients is

co-infected with HCV which translates to 6-8 million per-sons worldwide. Combined treatment of HIV and HCV is compli-cated by the risk of drug-drug interactions as both the direct act-ing antiviral agents (DAAs) for HCV as the antiretroviral agents for HIV are substrates of cytochrome P450 (CYP450) or various membrane transporters, and also have the capacity to influence these systems. A careful selection of the appropriate regimens and if needed adjusted doses is key for optimal treatment of both viral infections.

Daclatasvir is a recently approved anti-HCV agent that is a CYP3A4 substrate but does not affect CYP450 itself. It is also a moderate inhibitor of various membrane transporters such as organic anion-transporting polypeptide (OATP1B1), P-glycoprotein (P-gP), and organic cation transporters (OCT2).

Atazanavir/ritonavir is one of the preferred antiretroviral agents in all international guidelines. Ritonavir is used as a boosting agents based on its inhibitory effects on CYP3A. This also inhibits CYP3A-mediated metabolism of daclatasvir and when atazanavir/ritonavir is combined with daclatasvir, it is recom-mended to reduce the dose of daclatasvir from 60mg QD to 30mg QD.

Cobicistat has recently been approved as an alternative booster of atazanavir at a dose of 150mg QD. It is expected that cobicistat will inhibit CYP3A mediated metabolism of daclatasvir in a similar manner as ritonavir does, but there are no clinical data to support this. As cobicistat lacks some of the adverse events associated with ritonavir use, the use of cobicistat, including as a booster of atazanavir, is likely to increase.
This study aims to provide the evidence that 150mg of cobicistat will have the same effect on the pharmacokinetics of daclatasvir 30mg QD as 100mg of ritonavir, when given together with atazanavir 300mg.

Study objective

Primary objective:
To compare the effect of multiple dose atazanavir/cobicistat on the multiple dose phar-macokinetics of daclatasvir with the effect of atazanavir/ritonavir on the multiple dose of daclatasvir by intra-subject comparison in healthy subjects.

Secondary objective:
To evaluate the safety and tolerability of co administration of daclatasvir with atazanavir/cobicistat and atazanavir/ritonavir in healthy subjects.

Study design

This is a prospective open-label, 2-period, randomized, cross-over, single-centre, phase-I, multiple dose trial in 16 healthy volunteers.

Treatment period Group 1:
A Daclatasvir 30 mg QD + atazanavir/ritonavir 300/100mg QD from Day 1 to 10 (refer-ence ATV/r)
Day 11-21 wash-out
B Daclatasvir 30mg QD + atazanavir/cobicistat 300/150mg QD from Day 22-31 (test ATV/c)

Treatment period Group 2:
B Daclatasvir 30 mg QD + atazanavir/cobicistat 300/150mg QD from Day 1 to 10 (test ATV/c)
Day 11-21 wash-out
A Daclatasvir 30mg QD + atazanavir/ritonavir 300/100mg QD from Day 22-31 (reference ATV/r)

Intervention

See study design:
Daclatasvir 30 mg QD + atazanavir/ritonavir 300/100mg QD from Day 1 to 10 (reference ATV/r)

Daclatasvir 30mg QD + atazanavir/cobicistat 300/150mg QD from Day 22-31 (intervention ATV/c)

Study burden and risks

This study will be performed in healthy volunteers instead of HCV-infected patients. The study participants will not benefit from the participation in this clinical trial. The study participants are healthy subjects between 18 and 55 years, these subjects are repre-sentative for HCV-infected patients. In our opinion it is not ethical to perform this study in patients, as we are going to study an unknown interaction and we potentially do not give optimal HCV treatment.

On the other hand one could argue that a study in healthy volunteers might be unethical if severe adverse events cannot be excluded. However, as mentioned before, daclatasvir, atazanavir, cobicistat, and ritonavir are authorized products which are well tolerated by both patients and healthy volunteers.

Participants will visit the clinical research centre for a screening visit, 2 full day visits and 10 short visits. Eight short visits are scheduled to control safety/adverse events, and two for PK-sampling. The duration of the entire trial (excluding screening period) is 32 days. Duration of treatment with study medication is 20 days.

The overall risk is judged to be minimal.

Contacts

Public
Selecteer

Geert Grooteplein-Zuid 10
Nijmegen 6525 GA
NL
Scientific
Selecteer

Geert Grooteplein-Zuid 10
Nijmegen 6525 GA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject is at least 18 and not older than 55 years at screening.
2. Subject does not smoke more than 10 cigarettes, 2 cigars, or 2 pipes per day for at least 3 months prior to Day 1.
3. Subject has a Quetelet Index (Body Mass Index) of 18 to 30 kg/m2, extremes included.
4. Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.
5. Subject is in good age-appropriate health condition as established by medical history, physical examination, and electrocardiography, results of biochemistry, hematology and urinalysis testing within 4 weeks prior to day 1. Results of biochemistry, hematology and urinalysis testing should be within the laboratory's reference ranges (see Appendix A). If laboratory results are not within the reference ranges, the subject is included on condition that the Investigator judges that the deviations are not clinically relevant. This should be

clearly recorded.
6. Subject has a normal blood pressure and pulse rate, according to the Investigator's judgment.

Exclusion criteria

1. Creatinine clearance below 60mL/min.
2. Documented history of sensitivity/idiosyncrasy to medicinal products or excipients.
3. Positive HIV test.
4. Positive hepatitis B or C test.
5. Pregnant female (as confirmed by an hCG test performed less than 4 weeks before day 1) or breastfeeding female. Female subjects of childbearing potential without adequate contraception, e.g. hysterectomy, bilateral tubal ligation, (non-hormonal) intrauterine device, total abstinence, double barrier methods, or two years post-menopausal. They must agree to take precautions in order to prevent a pregnancy throughout the entire conduct of the study.
6. Therapy with any drug (for two weeks preceding Day 1), except for acetaminophen (maximal 2 gram/day).
7. Relevant history or presence of pulmonary disorders (especially COPD), cardiovascular disorders, neurological disorders (especially seizures and migraine), psychiatric disorders, gastro-intestinal disorders, renal and hepatic disorders (clinically relevant increased ALAT/ASAT or hyperbilirubinemia) hormonal disorders (especially diabetes mellitus), coagulation disorders.
8. Relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion.
9. History of or current abuse of drugs, alcohol or solvents.
10. Inability to understand the nature and extent of the study and the procedures required.
11. Participation in a drug study within 60 days prior to Day 1.
12. Donation of blood within 60 days prior to Day 1.
13. Febrile illness within 3 days before Day 1.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-11-2015
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Daklinza
Generic name:	Daclatasvir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Etovaz
Generic name:	Atazanavir/Cobicistat
Product type:	Medicine
Brand name:	Norvir
Generic name:	Ritonavir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Reyataz
Generic name:	Atazanavir
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-06-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-09-2015
Application type:	First submission
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
EudraCT	EUCTR2015-001354-15-NL
CCMO	NL53380.091.15
Other	nog niet beschikbaar, wordt op Clinical trials.gov geregistreerd