Pharmacokinetic drug interaction study between rAltegraVIr and ATORvastatin (AVIATOR).

Published: 07-02-2013
Last updated: 23-04-2024

Primary objective:To assess the effect of multiple dose atorvastatin on the steady state pharmacokinetics of raltegravir and vice versa by intrasubject comparison in healthy subjects.• The comparison of steady state raltegravir (400 mg BID for 7…

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

Summary

ID

NL-OMON38561

Source
ToetsingOnline

Brief title
AVIATOR

Condition

- Viral infectious disorders
- Lipid metabolism disorders

Synonym
AIDS, HIV

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: farmaceutische industrie,Merck

Intervention

Keyword: atorvastatine, HIV, hypercholesterolemia, raltegravir

Outcome measures

Primary outcome

Geometric Mean Ratios and 90% confidence intervals of pharmacokinetic parameters (AUC0-t, Cmax, Ct) of raltegravir for raltegravir with atorvastatine vs. raltegravir alone and of atorvastatine for atorvastatine with raltegravir vs. atorvastatine alone.

Secondary outcome

The safety profile of the combined use of raltegravir and atorvastatin.

The comparison of change in LDL cholesterol of short-term atorvastatine use with or without raltegravir.

Study description

Background summary

Dyslipidemia is highly prevalent among patients with HIV infection and contributes to the increased cardiovascular disease risk in this patient population. Atorvastatin lowers plasma low-density lipoprotein (LDL) cholesterol levels and is used for prevention of artherosclerotic disease. Raltegravir, an HIV integrase inhibitor, could be one of the preferred antiretroviral agents in HIV patients with dyslipidemia because it has a beneficial lipid profile.
Theoretically, no clinically relevant drug interaction is expected between atorvastatin and raltegravir. However, atorvastatin and raltegravir share similar metabolic pathways which could be relevant in the occurrence of pharmacokinetic interactions. In order to be able to recommend raltegravir and atorvastatin concomitant use, a pharmacokinetic study in healthy volunteers is proposed.

Study objective

Primary objective:
To assess the effect of multiple dose atorvastatin on the steady state pharmacokinetics of raltegravir and vice versa by intrasubject comparison in healthy subjects.
• The comparison of steady state raltegravir (400 mg BID for 7 days) pharmacokinetics (AUC0-12h, Cmax, C12h) with atorvastatin (20 mg QD for 7 days) vs. raltegravir alone by intrasubject compari-son.
• The comparison of steady state atorvastatin (20 mg QD for 7 days) pharmacokinetics (AUC0-24h, Cmax, C24h) with raltegravir (400 mg BID for 7 days) vs. atorvastatin alone by intrasubject compari-son.

Secondary objective:
• To evaluate the safety and tolerability of co administration of raltegravir and atorvastatin in healthy subjects.
• To investigate the non-steady state changes in serum LDL cholesterol secondary to short-term atorvastatin use in the presence or absence of raltegravir.

Study design

The 24 subjects will be divided into 6 groups of 4 subjects.
Each group will take the following treatments, but in a different order.
Washout periods of 14 days will be scheduled between treatments.

Treatments:
A. Raltegravir 400 mg BID for 7 days
B. Atorvastatin 20 mg QD for 7 days
C. Raltegravir 400 mg BID + Atorvastatin 20 mg QD for 7 days

Treatment sequence per group:
• Group 1: ABC
• Group 2: ACB
• Group 3: BCA
• Group 4: BAC
• Group 5: CAB
• Group 6: CBA

On day 7 of each treatment periode blood samples will be collected for a pharmacokinetic plasmaconcentration-time curve of raltegravir and/or atorvastatin.

Intervention

Administration of raltegravir 400 mg BID for two times 7 days. Administration of atorvastatin 20 mg once daily for two tomes 7 days.

Study burden and risks

The study participants are healthy volunteers and will not benefit from the participation in this clinical trial.
Atorvastatin is widely used in clinical practice and generally well tolerated; adverse effects are mostly mild and not frequently observed. Common adverse effects are: nausea, abdominal discomfort, increased liver function (ASAT, ALAT) and headaches. To minimize the risk of concentration related adverse events, such as myopathy, a relatively low dose of atorvastatin (20 mg QD) will be used in this drug interaction trial.
Raltegravir has been tested in both treatment-naïve and -experienced pa-tients and has an excellent risk/benefit ratio. The most common adverse events (> 5% incidence) associated with raltegravir were gastro-intestinal-related effects, headeache and dizziness, which were generally transient, self-limiting and mild-to moderate in severity. The possible adverse events of the combination of raltegravir and atorvastatin are not yet known. Because both raltegravir and atorvastatin have been associated with cases of myopathy, this could be an additional risk factor when used in combination. Lab safety is performed regularly throughout the study and participants are asked about possible adverse events on each visit. Subjects are asked to notify the trial physician/investigator immediately when unexplained muscle ache occurs.

Participants will visit the clinical research centre for a screening visit, 12 short visits (1 hour) and 3 full days (13 hours). The duration of the entire trial (excluding screening period) is 50 days. Duration of treatment with study medication is 3 weeks.
For pharmacokinetic purposes 62 blood samples will be taken in total. For safety assessment (haematology and clinical chemistry), hCG bloodtest, blood glucose and pharmacogenetic testing a total of 34 blood samples will be collected. The total bloodvolume taken will be 485 mL maximum. 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 amount of venous punctions.

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. 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 the first dosing
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, electrocardiography, results of biochemistry, haematology and urinalysis testing within 4 weeks prior to the first dose. Results of biochemistry, haematology and urinalysis testing should be within the laboratory's reference ranges. 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 judgement.

Exclusion criteria

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, e.g. hysterec-tomy, 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.
5. Therapy with any drug (for two weeks preceding dosing), except for acetaminophen.
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, musculoskeletal and con-nective tissue disorders.
7. Relevant history or current condition that might interfere with drug ab-sorption, 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 the first dose.
11. Donation of blood within 60 days prior to the first dose.
12. Febrile illness within 3 days before the first dose.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-04-2013
Enrollment:	24
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Isentress
Generic name:	raltegravir

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lipitor
Generic name:	atorvastatin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-02-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-03-2013
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	EUCTR2012-005147-24-NL
CCMO	NL43180.091.13