Pharmacokinetic Evaluation of POSaconazole boosted Fosamprenavir (EPOS)

Published: 06-11-2008
Last updated: 05-05-2024

Primary: To determine the influence of posaconazole on unboosted fosamprenavir pharmacokinetics, and vice versa, in healthy volunteersSecondary: To determine the safety of combined use of fosamprenavir with posaconazole in healthy vol-unteers

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

Summary

ID

NL-OMON32580

Source
ToetsingOnline

Brief title
EPOS

Condition

- Fungal infectious disorders

Synonym
HIV, human immunodeficiency virus

Research involving
Human

Sponsors and support

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

Intervention

Keyword: drug interaction, fungal infection, HIV, pharmacokinetics

Outcome measures

Primary outcome

-To determine the effect of posaconazole on fosamprenavir pharmacokinetics

(AUC, Cmax, Cmin)

-To determine the effect of fosamprenavir on posaconazole pharmacokinetics

(AUC, Cmax, Cmin)

Secondary outcome

-Adverse effects which are either due to posaconazole, fosamprenavir/ ritonavir

or combined use of posaconazole and

fosamprenavir.

Study description

Background summary

Infections with fungi and yeast frequently occur in patients infected with the human immu-nodeciency virus type 1 (HIV-1). Oropharyngeal candidiasis (OPC) and candida esophagitis (CE) have been reported to occur in up to 90% of the subjects infected with HIV and these are therefore the most common encountered opportunistic infections in these patients (1-3). As a result of highly active antiretroviral therapy (HAART), the incidence and prevalence of most opportunistic infections has decreased (4;5). OPC remains however the most frequent HIV-associated oral disease in resource limited settings or in non-compliant patients (6).
The occurrence of OPC and CE is associated with low CD4 T-lymphocyte counts, high viral loads and disease progression (2;4), but at the same time OPC tends to be one of the earliest opportunistic infections seen in patients with CD4 T-lymphocyte counts > 200 cells/mm3. As HIV infection progresses with declining CD4+ cells and increasing HIV viral loads, the se-verity of OPC increases with more frequent relapses, for which systemic therapy may be nec-essary (7).

Azole antifungal drugs are first line therapy in the treatment of oropharyngeal candidiasis and invasive fungal infections. Fluconazole is first line therapy to treat fungal infections in HIV positive patients with oral candidiasis. However, with the emergence of resistant strains, fluconazole might not provide adequate protection in all patients (8-10). Posaconazole is a second generation triazole with antifungal activity against a broad range of yeast and moulds that has been proven to be a valid alterna-tive for fluconazole (11;12).
The combination of antiretroviral drugs (either non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs)) with azole antifungal drugs is not without risk. NNRTIs may reduce the efficacy of many azole antifungals due to induction of hepatic me-tabolism (13). PIs themselves are influenced to a large extent when combined with potent inhibitors of enzymatic pathways (such as the azoles) leading to increased exposure to the PI with possible increased toxicity (13).

Fosamprenavir is a PI that is used to treat HIV-infection in combination with ritonavir. Once hydrolyzed to amprenavir, this substance is a substrate for CYP3A4. Ritonavir is an ex-tremely potent inhibitor of CYP3A4 and serves as a booster of the pharmacokinetics of am-prenavir (14). Posaconazole is a very potent CYP3A4 inhibitor and therefore might enhance amprenavir pharmacokinetics in a similar way as ritonavir.

The current study is designed to test this hypothesis. When there is an indication for antifun-gal therapy in an HIV-infected patient, temporal replacement of ritonavir by posaconazole would be an attractive option for combined treatment of HIV and fungal infection.

Study objective

Primary:
To determine the influence of posaconazole on unboosted fosamprenavir pharmacokinetics, and vice versa, in healthy volunteers

Secondary:
To determine the safety of combined use of fosamprenavir with posaconazole in healthy vol-unteers

Study design

This is an open-label, sequential, 3-period, cross-over, single-centre, phase-I, multiple-dose trial in 24 healthy volunteers.

Intervention

During this study, which lasts 67 days in total, subjects have to take study medication during three treatment-periods which last 10 days each.

The 24 participants will be divided into 6 groups that receive the three treatments in a different order.
There are two wash-out periods of 17 days between these three treatment periods.

Study burden and risks

Both posaconazole and fosamprenavir/ ritonavir are well tolerated.
Participants are monitered frequently for adverse events.
Intake of medication is for a limited time period only (10 days). Also combined intake is for a limited period (10 days).
On the day of dosing an indwelling Venflon I.V. cannula will be inserted in a peripheral vein of each subject by a physician or an authorised nurse to facilitate repeated blood sampling. The use of these needles might cause some degree of dyscomfort. The risk for the patient is very limited.

For specific, drug related, side effects, we refer to the study protocol.

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

-Subject is at least 18 and not older than 55 years of age on the day of the first dosing.
- 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.
- Subject has a Quetelet Index (Body Mass Index) of 18 to 30 kg/m2, extremes in-cluded.
- Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.
- 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, hae-matology 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.
- Subject has a normal blood pressure and pulse rate, according to the Investigator's judgement.

Exclusion criteria

- Documented history of sensitivity/idiosyncrasy to medicinal products or excipients.
- Positive HIV test.
- Positive hepatitis B or C test.
- Pregnant female (as confirmed by an HCG test performed less than 4 weeks before the first dose) or breast-feeding female.
-Therapy with any drug (for two weeks preceding dosing), except for paracetamol.
- Subjects with an ECG with QTc interval greater than 450 msec for men, and greater than 470 msec for women at screening.
-Relevant history or presence of pulmonary disorders (especially COPD), cardiovascu-lar disorders, neurological disorders (especially seizures and migraine), gastro-intestinal disorders, renal and hepatic disorders, hormonal disorders (especially diabe-tes mellitus), coagulation disorders.
-Relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion.
- History of or current abuse of drugs, alcohol or solvents.
- Inability to understand the nature and extent of the trial and the procedures required.
11. Participation in a drug trial within 60 days prior to the first dose.
12. Donation of blood within 60 days prior to the first dose.
13. 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):	02-03-2009
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Norvir
Generic name:	ritonavir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Noxafil
Generic name:	posaconazole
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Telzir
Generic name:	fosamprenavir
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-11-2008
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-01-2009
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	EUCTR2008-006243-39-NL
CCMO	NL25510.091.08