The pharmacokinetics of two generic co-formulations of lopinavir/ritonavir for HIV-infected children: a pilot study of Lopimune vs. the branded product

Published: 17-03-2008
Last updated: 11-05-2024

Primary objective: To determine the pharmacokinetic profile of lopinavir and ritonavir in two differ-ent co-formulations (Lopimune granules and Lopimune tablets) after single-dose in HIV-negative, healthy adult subjects, and to compare this to the…

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

Summary

ID

NL-OMON33781

Source
ToetsingOnline

Brief title
SURF

Condition

- Viral infectious disorders

Synonym
AIDS, HIV-infection

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: generic, HIV infected children, lopinavir/ritonavir, pharmacokinetics

Outcome measures

Primary outcome

Pharmacokinetics

Individual and mean plasma concentrations will be presented. Overlay presentations will be given to illustrate inter-subject variability.

Descriptive statistics will be calcu-lated for the plasma concentrations at each sampling time.

The primary comparison will be made between AUC0-inf, Tmax and Cmax values of lopinavir and ritonavir after intake of the Reference regimen vs. after intake of the two Test regimens. Non-parametric analysis (Wilcoxon*s signed rank test) will be done for AUC, Cmax and Tmax values between the three different regimens.

Secondary outcome

Demographics, Treatment Compliance, Concomitant Medication and Safety

Data on demographics, treatment compliance, concomitant medication and safety of all subjects (including drop-outs) will be included in the clinical trial report.

Demographics (including weight) and safety data at screening, laboratory safety

data and concomitant medication will be listed.

Descriptive statistics will be calculated for the subject characteristics.

Adverse events and serious adverse events will be listed per treatment and the

inci-dence (number of subjects with at least one AE) will be presented. Special

attention will be given to subjects who discontinued because of AEs.

Study description

Background summary

Highly Active Anti-Retroviral Therapy (HAART) has resulted in a major reduction of morbidity and mortality of HIV-infected adults and children. HIV mortality in children has decreased 70% since the introduction of protease inhibitor containing combinations. Important factors in the treatment of children are the availability of pharmacokinetic information on appropriate dosing and the availability of appropriate drug formulations for pediatric use. The *Guidelines for the use of antiretroviral agents in Pediatric HIV infection* recommend to start with 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs) in combination with a Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) or a Protease Inhibitor (PI) in treatment-naïve children. The preferred PI-based regimen consists of 2 NRTIs with lopinavir/ritonavir. The World Health Organization recommends for the developing countries that the PI class of drugs be reserved for second-line therapy. This is because use of PIs in an initial treatment regimen compromises any subsequent second-line regimen. Also, the use of PIs other then lopinavir/ritonavir and nelfinavir is more problematic in children because of a lack of suitable pediatric formulations or a lack of appropriate dosing information for other ritonavir-boosted PIs. Other limitations include the requirement and the poor tolerance of ritonavir. In 2005, a tablet formulation of lopinavir/ritonavir not requiring a cold chain (in contrast with the oral solution) became available but the tablets cannot be split in smaller parts and the tablet has not yet been studied in children. Still, lopinavir/ritonavir remains the preferred PI for use in children.

Another problem are the costs of antiretroviral therapy in resource-limited countries. Fortunately, during recent years more attention has been paid to access to care for patients in these countries. Pharmaceutical companies have reduced drug costs through separate pricing and the G8 & United Nations have created the Global Fund to fight global poverty-related diseases, including

HIV. Generic manufacturers have been allowed to produce HAART combinations at much lower costs without facing patent claims.

Cipla Pharmaceuticals is a generic manufacturer residing in India that has success-fully launched Triomune Baby, consisting of stavudine (6mg), lamivudine (30mg) and nevirapine (50mg) and Triomune Junior, consisting of stavudine (12mg), lamivudine (60mg) and nevirapine (100mg). These products, recently approved by the FDA, are used as first-line therapy in children in developing countries (FDC-Ped, Protocol ID UMCN-AKF 04.04). Cipla has now developed two co-formulated forms of lopi-navir/ritonavir for second-line antiretroviral therapy for children: Lopimune granules and Lopimune tablets. They contain 100mg lopinavir and 25mg ritonavir.

The pharmacokinetics and dosing requirements of the two Lopimune formulations will be tested in a large pharmacokinetic study in HIV-infected children in Zambia, as part of a protocol funded by the European and Developing countries Clinical Trial Partnership (EDCTP) (see www.EDCTP.org). Before this study will be started, information is required regarding the absorption of the two agents from these newly developed Lopimune products. Cipla Pharmaceuticals will conduct a formal bio-equivalence study that is required for registration purposes as well as to meet pre-qualification criteria set by WHO.

For two reasons we think that it is desirable to have additional information on the pharmacokinetics of these agents. First, it may take more than 6-12 months before data will be available from the company. Second, it may be wise to collect data inde-pendently from the manufacturer. In this way, the clinical study in Zambia may start earlier and consequently more children may benefit earlier from this co-formulated product.

In the main study the granules were compared to the Kaletra adult tablets. The bioavailability of the granules was much lower compared to the tablets. It is possible that the granules have a pharmacokinetic profile more similar to the Kaletra oral solution, and does a food effect play a role in absorption. To investigate whether the granules can be used in a study with children we would like to compare the granules to the oral solution. The oral solution and granules will be taken with food in the additional part of the study. To test the food effect on granules, the additional study will be performed in subjects who participated in the main study.

Study objective

Primary objective:
To determine the pharmacokinetic profile of lopinavir and ritonavir in two differ-ent co-formulations (Lopimune granules and Lopimune tablets) after single-dose in HIV-negative, healthy adult subjects, and to compare this to the branded product.

Secondary objectives:
To evaluate the safety of single-dose administration of the two generic co-formulations of lopinavir/ritonavir and compare this to the branded product.

Study design

This is a three-period, single dose, crossover, open label, comparative, single-centre phase-I trial in 12 HIV-negative adult subjects.

Subjects will be randomly divided to one of the following sequences, so each se-quence will be followed by two subjects

ABC; ACB; BCA; BAC; CAB; CBA

Reference regimen: Kaletra tablets (regimen A):
Lopinavir/ritonavir 200/50mg; 2 tablets

Test regimen 1: Lopimune granules (regimen B)
Lopinavir/ritonavir 100/25mg; 4 sachets with granules

Test regimen 2: Lopimune tablets (regimen C)
Lopinavir/ritonavir 100/25mg; 4 tablets

Additional part of the study (5 subjects)
DE; ED
D = Kaletra oral solution, with food
E = Lopimune granules, with food

Normal adult lopinavir/ritonavir dose
400/100mg, so 4 sachets Lopimune en 5 mL solution (80/20 mg)

9 days: 2 single doses with 1 week wash-out

Intervention

For the determination of plasma drug concentrations, blood samples of 5 mL to obtain at least 3.0 mL of plasma will be collected in heparinized hard plastic tubes at the following time points: 0 (predose), 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 24 and 32 hours post ingestion (11 samples) on Days 1, 8 and 15. The exact times of sampling will be recorded in the case report forms.
Subjects will receive a venous catheter (with NaCl lock) for blood sampling.

Additional part: Day 1 and 8 PK days, sample sample schedule.

Study burden and risks

Healthy volunteers may suffer from side-effects associated with the intake of studymedication. They will not directly benefit from the studyresults. When proven that the plasmaconcentrations of lopinavir are similar after intake of the generic formulations when compared to the branded product, a follow-up clinical study will be initiated in HIV infected children in Zambia. These subjects are the ones who will benefit from this study.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein 10
6500 HB Nijmegen
Nederland
Scientific
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein 10
6500 HB Nijmegen
Nederland

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 of age on the day of the first dosing.
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 a 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 (see Appendix A). If not, 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 Investiga-tor's judgement.
7. Female subject is either not of childbearing potential, defined as postmeno-pausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or is of childbearing potential and practicing one of the following methods of birth control: condoms, sponge, foams, jellies, diaphragm or copper intrauterine device (IUD); has a vasectomized partner; or total abstinence from sexual intercourse.

Exclusion criteria

1. Documented history of sensitivity/idiosyncrasy to medicinal products or excipi-ents.
2. Positive HIV test.
3. Positive hepatitis B or C test.
4. Therapy with any drug, including oral contraceptives (for two weeks preceding dosing), except for paracetamol
5. Relevant history or presence of pulmonary disorders (especially COPD), car-diovascular disorders, neurological disorders (especially seizures and mi-graine), gastro-intestinal disorders, renal and hepatic disorders, hormonal dis-orders (especially diabetes mellitus), coagulation disorders.
6. Relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion.
7. History of or current abuse of drugs, alcohol or solvents.
8. Inability to understand the nature and extent of the trial and the procedures required.
9. Participation in a drug trial within 60 days prior to the first dose.
10. Donation of blood within 60 days prior to the first dose.
11. Febrile illness within 3 days before the first dose
12. Pregnancy or breastfeeding

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):	14-04-2008
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Kaletra
Generic name:	Lopinavir/ritonavir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lopimune granules
Generic name:	Lopinavir/ritonavir
Product type:	Medicine
Brand name:	Lopimune tablets
Generic name:	Lopinavir/ritonavir

Ethics review

Approved WMO Date:	17-03-2008
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-01-2009
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
EudraCT	EUCTR2007-006142-18-NL
CCMO	NL21709.091.08