A Kaletra ONCE daily Randomised Trial of the pharmacokinetics, safety and efficacy of twice-daily versus once-daily lopinavir/ritonavir tablets dosed by weight as part of combination antiretroviral therapy in HIV-1 infected children (PENTA 18).

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Evaluating the current dosing guidelines in children taking the half-strength paediatric tablets will provide reassurance that the recommended lopinavir/ritonavir dose provides adequate drug exposure and maintains efficacy.This trial will evaluate...

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

Summary

ID

NL-OMON34553

Source
ToetsingOnline

Brief title
KONCERT

Condition

- Viral infectious disorders

Synonym
HIV infection

Research involving
Human

Sponsors and support

Primary sponsor: PENTA Foundation
Source(s) of monetary or material Support: PENTA foundation

Intervention

Keyword: Kaletra, Randomised, Trial

Outcome measures

Primary outcome

In order to compare the proportion of children ever recording plasma RNA *50

copies/ml

(confirmed within 4 weeks) on QD compared to BID therapy over 48 weeks, HIV-1

viral load will

be measured at screening, week 0 and at all follow-up protocol visits. If at

any time the HIV-1

viral load is >50 copies/ml, the family should be contacted so the HIV-1 viral

load can be remeasured

as soon as possible and within 4 weeks after the raised value. Samples will be

taken and

stored for confirmatory HIV-1 viral load testing in a centralised laboratory at

the end of the trial.

In order to evaluate the pharmacokinetics of twice-daily lopinavir/ritonavir half strength formulation tablets based on body weight a minimum of the first 16 children in each weight band (P15 to Q25kg, >25 to Q35kg, >35kg) will have an intensive PK day while on BID half strength formulation (day 0). Plasma concentrations of lopinavir and ritonavir will be determined by a validated high performance liquid chromatography assay with UV detection in a central laboratory (Radboud University Nijmegen).
To compare the pharmacokinetics of twice-daily lopinavir/ritonavir tablets with once-daily dosing in the same children, children who have undergone an intensive PK day and have been subsequently randomised to QD dosing will have a second intensive PK day four weeks after starting QD dosing of lopinavir/ritonavir tablets.

Secondary outcome

The stage of children*s HIV disease by CDC classification (Appendix 8) will be recorded at entry to the trial and at each protocol visit, disease progression will be recorded on the follow-up CRF as well as any adverse events. Efficacy of twice- and once-daily dosing of

lopinavir/ritonavir tablets

will also be compared through analysis of HIV-1 viral load and T cell subsets

measured locally at

each protocol visit, and the presence of HIV mutations conferring resistance to

drugs taken at

randomisation or during the trial.

Study description

Background summary

Several issues complicate treatment of HIV-1 infection in children and adolescents. One challenge is to give the correct antiretroviral dose to provide adequate drug exposure as a child grows to minimise toxicity and maintain efficacy. Dosing guidelines typically use weight or body surface area to adjust doses for children. As drug pharmacokinetics in children differ greatly from that in adults due to age-related variations in renal, hepatic and gastric function, which result in altered drug absorption and metabolism, it is important to conduct studies in children to inform dosing guidelines rather than extrapolate from adult data.

The protease inhibitor (PI) lopinavir/ritonavir (Kaletra) is recommended by European and American guidelines for treatment of children with HIV-1 infection and has been approved for use in children by the European Medicines Agency (EMEA) (age 2 years and older) and the United States Food and Drug Administration (FDA) (age 14 days and older). Lopinavir/ritonavir is available as oral solution or tablets in dosage strengths of 200/50 mg and 100/25 mg. The 200/50 mg tablet replaced the original soft-gel capsule in 2006, and the half-strength lopinavir/ritonavir tablet (100/25 mg) was approved by the EMEA and FDA in 2008, designed to provide flexible dosing for paediatric patients. Lopinavir/ritonavir tablets are approved for paediatric use, to be taken twicedaily. The number of tablets to be taken as the child grows is based on body weight bands under FDA approval whereas it is based on body surface area (BSA) by the EMEA. This leads to some differences in the number of tablets recommended for a child (see section 2.2.1), e.g. a child who weighs 40kg, which is approximately equivalent to a BSA of 1.3m2, would be recommended to take three 100/25mg tablets twice-daily under the EMEA approval compared to four 100/25mg tablets twice-daily under FDA approval.

No studies have been conducted to evaluate these dosing guidelines in children taking the half strength paediatric tablets.

Another challenge for the treatment of HIV-1 infection in children and adolescents is to improve medication adherence in particular for children who rely on caregivers for medication administration, and for adolescents undergoing the transition to adulthood. Adherence is related to several factors, including palatability and number of pills or volume of medication, complexity of medication schedules and interference with the child or caregiver*s daily activities. Decreasing the frequency of dosing is likely to increase convenience and enhance adherence to antiretroviral therapy in HIV-1 infected children and adolescents.

Study objective

Evaluating the current dosing guidelines in children taking the half-strength paediatric tablets will provide reassurance that the recommended lopinavir/ritonavir dose provides adequate drug exposure and maintains efficacy.

This trial will evaluate whether once-daily dosing of lopinavir/ritonavir is comparable to twice-daily dosing in terms of virological suppression over 48 weeks and to compare the pharmacokinetics of twice-daily lopinavir/ritonavir tablets with oncedaily dosing in the same children.

(2.7 protocol)

Study design

KONCERT is a prospective, open label, multicentre, randomised (1:1) phase II/III trial. Children
will be randomised 1:1 into two groups:
1. Twice-daily lopinavir/ritonavir (BID arm)
2. Once-daily lopinavir/ritonavir (QD arm)
Randomisation will be stratified by body weight band (P15 to Q25kg, >25 to Q35kg, >35kg).
It is planned to recruit 160 young people over 18 months. All participants must be followed until
the last participant has completed 48 weeks of follow-up.

Intervention

3 additional visits are required for the trial above the normal 3-monthly clinic visit schedule
(screening, week 4 and week 8). This may involve children taking extra time out of school
and parents having to take time off work

* Children in the PK group will undergo one (or two if assigned to once-daily lopinavir/ritonavir) 12-hour blood sampling visits at weeks 0 and 4. This may involve an
overnight stay prior to blood sampling. This may present problems in terms of taking time
out of work, childcare issues for siblings and wellbeing of the children in the trial

Study burden and risks

There is a small risk that the viral load will become detectable for those children
randomised on trial. If a raised viral load is confirmed on repeat testing (to be done within
4 weeks) for a participant randomised to once-daily lopinavir/ritonavir consideration should
be given to switching QD-dosed subjects to BID therapy, and BID-dosed subjects to
alternative treatment options as appropriate.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

inclusiecriteria:
* Aged <18 years (up to 18th birthday) with confirmed HIV1
infection
* Weight *15 kg
* Able to swallow tablets
* Stable (i.e. CD4 not declining) on a combination antiretroviral regimen that has included lopinavir/ritonavir for at least 24 weeks
* Taking lopinavir/ritonavir dosed twicedaily and be willing at the screening visit to change to tablet formulation (if not currently taking tablets) and to change the lopinavir/ritonavir dose to follow the recommended FDA dosing plan based on body weight bands as necessary; if participating in the PK study*, be willing at the screening visit to change to lopinavir/ritonavir half strength formulation tablets (100/25mg) only, dosed twicedaily and change the lopinavir/ritonavir dose to follow the recommended FDA dosing plan based on body weight bands as necessary
* Viral suppression (HIV1 RNA <50 copies/ml) for at least the prior 24 weeks (minimum of 2 measurements).
* Children and caregivers willing to participate in the PK study if they are among a minimum of the first 16 children enrolled in each body weight band in the trial, including a second PK assessment if randomised to switch to oncedaily lopinavir/ritonavir.
* Parents/carers and children, where applicable, give informed written consent;* a minimum of the first 16 children per weight band will be entered into the PK study and must be willing to change to taking halfstrength formulation lopinavir/ritonavir tablets (100/25mg) only, dosed according to the FDA recommended dosing plan based on their body weight, at the screening visit. Once it has been confirmed that the PK study has full evaluable PK data evaluable PK data has been obtained on 16 children in each weight band on twicedaily dosing and 8 in each weight band on oncedaily dosing, it will no longer be necessary for children entering the trial to be willing to take half strength formulation lopinavir/ritonavir tablets only

Exclusion criteria

Exclusion criteria
* children on an antiretroviral regimen that includes a NNRTI, fosamprenavir or nelfinavir
* children who have previously failed virologically on a PI containing regimen (where virological failure is defined as two successive HIV-1 RNA results>1000 copies/ml

(confirmed) more than 24 weeks after starting HAART, i.e changes for toxicity are not counted as failure)* acute illness
* abnormal renal or liver function (grade 3 or above)
* receiving concomitant therapy except for prophylaxis; Some treatments may be allowed, but must first be discussed with a trial medical expert
* pregnancy or risk of pregnancy in females of child bearing potential

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-07-2010
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kaletra
Generic name:	lopinavir/ritonavir
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	27-07-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2009-013648-35-NL
CCMO	NL32178.018.10