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SMILE: Strategy for Maintenance of HIV suppression with dolutegravir + darunavir /ritonavir in children (PENTA 17)

Submission date
19/02/2015

Recruitment status
No longer recruiting

Registration date
06/03/2015

Overall study status
Completed

Last Edited
12/06/2023

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The human immunodeficiency virus (HIV) is a virus that attacks the immune system, making an affected person less able to fight infection and disease. It can be caught though unprotected sex, sharing drug needles, via transfusions of contaminated blood and blood products and from the mother to her baby during pregnancy, birth and breastfeeding. There is no cure for the condition, but there are a number of drug treatments that enable HIV+ people to live a long and healthy life. Acquired immune deficiency syndrome (AIDS) is the last stage of HIV infection, at which point the immune system is unable to fight life-threatening infections. With early diagnosis and effective treatment, most people with HIV do not go on to develop AIDS. SMILE is a study that will compare two different HIV (antiretroviral) medicine combinations. Taking antiretroviral medicines every day without missing a dose is important. This is to stop the virus becoming resistant which can happen if the virus levels in the blood are not low enough. However, some young people experience difficulty in taking several medications every day, particularly if this is more than once a day, and so doctors and scientists are now working towards easier ways for people to take the medicines. Newer antiretrovirals which are taken once daily include Prezista (darunavir) which is taken with a small dose of Norvir (ritonavir) and dolutegravir. In SMILE we will examine whether it is safe and effective to take Prezista + Norvir + dolutegravir compared to continuing to take current antiretroviral medications. Also, NRTIs are a particularly prone to cause adverse side effects. Therefore it may be important to reduce cumulative NRTI exposure in children.

Who can participate?
HIV+ children aged between 6-18 years

What does the study involve?
Children participating in the study are randomized by age (6 to <12 years, 12 to <18 years) and region (Africa vs non Africa). In each randomised arm, at least 70 children by age group are included. Those in group 1 receive the NRTI-sparing regimen - dolutegravir + darunavir/ritonavir

(DRV/r) (DUAL). Those in group 2 receive the usual standard of care (triple anti-retroviral therapy including 2 NRTIs + boosted PI/NNRTI) (TRIPLE). All participants are followed until the last patient recruited reaches week 48. The period of recruitment is 72 weeks.

What are the possible benefits and risks of participating?
As the study medicines only need to be taken once a day, it is expected that participants will find it easier to remember to take their medicines and suffer fewer long term side-effects. Possible disadvantages include the participants having to take more trips to the clinic, and, for patients in group 1, taking Prezista and dolutegravir together with the low dose of Norvir will not be as effective as their usual medicine at keeping the level of virus low. Side effects not previously experienced could also occur such as headache, tummy pain, nausea, rash, cough or insomnia.

Where is the study run from?
A total of 96 hospitals internationally are taking part in the study.

When is the study starting and how long is it expected to run for?
January 2013 to July 2018

Who is funding the study?
PENTA Foundation (Italy)

Who is the main contact?
Mr Luigi Comacchio
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2013-001476-37

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
PENTA 17

Study information

Scientific Title
A two-arm, Phase 2/3 multicentre, open-label, randomised study evaluating safety and antiviral effect of current standard antiretroviral therapy compared to once daily integrase inhibitor administered with darunavir/ritonavir (DRV/r) in HIV-1 infected, virologically suppressed paediatric participants.

Acronym
SMILE

Study objectives
Current hypothesis as of 06/08/2019:
Children with chronic HIV infection on ART with suppressed viral load will maintain similar levels of suppression with once daily integrase inhibitor (INSTI) + darunavir/r compared to continued standard of care triple ART.

Previous hypothesis:
Children with chronic HIV infection on ART with suppressed viral load will maintain similar levels of suppression with elvitegravir + darunavir/r compared to continued standard of care triple ART.

Ethics approval required
Old ethics approval format

Ethics approval(s)
French Ethics Committee - submitted

Study design
A two arm parallel group, non-inferiority, open-label, multi-centre, randomised controlled trial.

Primary study design
Interventional

Secondary study design

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
HIV infection

Interventions

Current intervention as of 06/08/2019:
Eligible participants will be randomised in a 1:1 ratio to switch to once daily INSTI + DRV/r or continue triple therapy. Randomisation will be stratified by age (6 to <12 years, 12 to <18 years) and region (African sites vs non-African sites) using permuted blocks of randomly varying sizes. The once-daily INSTI to be used is dolutegravir. Children weighing 40 kg or more will receive 800 mg darunavir, 100 mg ritonavir and 50 mg dolutegravir.

Previous intervention:
Arm 1: NRTI-sparing regimen - elvitegravir (EVG) + darunavir/ritonavir (DRV/r)
Arm 2: Standard of care (triple anti-retroviral therapy including 2 NRTIs + boosted PI/NNRTI)

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Current drug names as of 06/08/2019: 1. Dolutegravir 2. Darunavir 3. Ritonavir Previous drug names: 1. Elvitegravir 2. Darunavir 3. Ritonavir

Primary outcome measure
Percentage of patients with HIV-1 RNA ever ≥50 copies/ml (confirmed within 4 weeks) at any time up to week 48

Secondary outcome measures
Percentage of patients with HIV-1 RNA ever ≥ 50 c/mL (confirmed within 4 weeks) at any time up to week 48
1. Percentage of patients with HIV-1 RNA < 50 c/mL at week 48
2. Percentage of patients with HIV-1 RNA ≥ 50 c/mL at week 24
3. Percentage of patients withHIV-1 RNA ≥ 400c/mL at week 24 and week 48
4. All grade 3 or 4 clinical adverse events (particularly lipodystrophy)
5. All grade 3 or 4 laboratory adverse events
6. Any adverse event at least possibly related to study drugs or leading to treatment modifications
7. Occurrence of new resistance mutations
8. Changes in CD4 (absolute and percentage) from baseline to weeks 24 and 48
9. Change in ART (defined as any change from the ART regimen at randomisation)
10. New or recurrent CDC/WHO stage C or severe stage B event or death
11. Blood lipids
12. Adherence as measured by questionnaire and visual analogue scale
13. Acceptability and quality of life over 48 weeks as assessed by patient completed questionnaires
14. Height and weight
15. Tanner scales (in participants aged over 8 years)
16. Date of first menses

Overall study start date
01/01/2013

Completion date

30/09/2020

Eligibility

Key inclusion criteria
1. HIV-1 infected children weighing ≥ 17 kg at the screening visit
2. Aged 6 to < 18 years old
3. Parents or guardians, and children where appropriate, willing and able to give informed consent and to adhere to the protocol
4. Children must have all HIV-1 RNA viral load <50c/mL for at least 12 months with a minimum of two separate results before screening.
5. Children on a 3-drug PI/r or NNRTI containing regimen for at least 6 months.
6. Children/parents/guardians prepared to switch if randomised to elvitegravir + darunavir /ritonavir arm
7. Children and parents prepared to restart the current ART regimen after simplification if viral load restart criteria are met (see Section 5.5)
8. For children aged 6-12 either:
8.1. Children and caregivers are willing to participate in the lead-in PK study if the child is aged 6-12 and the PK study is still enrolling children in their weight band* OR
8.2. Data from the lead-in PK study have been analysed and children aged 6-12 can be enrolled directly into the main study

* only children randomised to Arm 1 will take part

Participant type(s)
Patient

Age group
Child

Lower age limit
6 Years

Upper age limit
18 Years

Sex
Both

Target number of participants
300

Total final enrolment
318

Key exclusion criteria
1. Receiving or requiring agents with interactions with darunavir, RTV, or EVG
2. Evidence of resistance to DRV or integrase inhibitors (for participants in clinical sites where resistance testing is standard of care)
3. Previous exposure to integrase inhibitors for more than 2 weeks

4. History of previous encephalopathy
5. Intercurrent illness (randomisation can take place after the illness resolves)
6. Creatinine, AST or ALT of grade 3 or above at screening.
7. Diagnosis of tuberculosis and on anti-tuberculosis treatment (children can be enrolled after successful tuberculosis treatment)
8. Hepatitis B or Hepatitis C co-infection
9. Pregnancy or risk of pregnancy in girls of child-bearing potential unless committed to taking effective contraception

Date of first enrolment
01/09/2015

Date of final enrolment
31/07/2018

Locations

Countries of recruitment
Argentina

Belgium

Brazil

Denmark

England

France

Germany

Greece

Ireland

Italy

Mexico

Netherlands

Poland

Portugal

Romania

South Africa

Spain

Sweden

Switzerland

Thailand

Uganda

United Kingdom

Study participating centre
Hospital Robert-Debré
48 Bd Sérurier
Paris
France
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Study participating centre
Heartlands Hospital
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B9 5SS

Study participating centre
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Study participating centre
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Sponsor information

Organisation
PENTA Foundation

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Sponsor type
Research organisation

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ROR
https://ror.org/00d7mpc92

Funder(s)

Funder type
Research organisation

Funder Name
PENTA Foundation (Italy)

Results and Publications

Publication and dissemination plan
Regarding publications: we intend to publish the study results at the end of the trial and will present the trial at several conferences throughout its duration

Intention to publish date

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Basic results	22/12/2021	20/05/2022	No	No
Results article	02/06/2023	12/06/2023	Yes	No