Clinical trial results:
Once daily DArunavir/ritonavir in HIV-infected children 6-12 years old: a PHarmacokiNEtic validation of model-based dosing recommendations (DAPHNE)

Summary

EudraCT number	2014-001111-39
Trial protocol	NL
Global end of trial date	19 July 2017

Results information

Result version number	v1 (current)
This version publication date	21 September 2019
First version publication date	21 September 2019
Summary attachment (see zip file)	DAPHNE paper (00006454-201810000-00012.pdf)

Trial information

Trial identification

Sponsor protocol code	UMCN-AKF13.03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Radboudumc
Sponsor organisation address	Geert Grooteplein Zuid 10, Nijmegen, Netherlands,
Public contact	David Burger, Radboud University Medical Center, david.burger@radboudumc.nl
Scientific contact	David Burger, Radboud University Medical Center, david.burger@radboudumc.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 July 2016
Global end of trial reached?	Yes
Global end of trial date	19 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To validate FDA-approved dosing recommendation for once daily DRV/r in children 6-12 years old. This will be done by evaluating the pharmacokinetics of DRV/r given once daily (according to FDA dosing guideline) to children from 6 – 12 years

Protection of trial subjects:

The risk-classification is assessed as negligible to the patient population receiving study drug at the current regimens. The drug (darunavir) is licensed by the FDA for the use as investigated in this protocol. A rich sampling pharmacokinetic assessment, performed after switch to a once-daily regime, is part of current routine clinical practice for children who are treated with a antiretroviral drugs.
There are no real risks involved. Anaemia because of PK sampling is unlikely, because the amount of blood that will be taken solely for study purposes is within the limits of international standards.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	12
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twelve children were enrolled from four sites in the Netherlands.

Pre-assignment

Screening details:

Children (6–12 years of age) were eligible when they used darunavir/ritonavir once-daily for at least 2 weeks according to the approved dose.

Period 1

Period 1 title	screening
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	DRV/rtv QD

Arm description:

In this multicenter pharmacokinetic study in HIV-infected children (6–12 years of age), we validated the approved once-daily darunavir/ritonavir dosing recommendations.

Arm type	Active comparator
Investigational medicinal product name	darunavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

≥ 15 kg to < 30 kg DRV 600 mg with ritonavir 100 mg
≥ 30 kg to < 40 kg DRV 675 mg with ritonavir 100 mg
≥ 40 kg DRV 800 mg with ritonavir 100 mg

Number of subjects in period 1	DRV/rtv QD
Started	12
Completed	12

Period 2

Period 2 title	PK sampling DRV/rtv QD
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	DRV/rtv QD

Arm description:

Children were using DRV/rtv QD treatment dosed according to EMA approved SPC.

Arm type	Experimental
Investigational medicinal product name	darunavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

≥ 15 kg to < 30 kg DRV 600 mg with ritonavir 100 mg
≥ 30 kg to < 40 kg DRV 675 mg with ritonavir 100 mg
≥ 40 kg DRV 800 mg with ritonavir 100 mg

Number of subjects in period 2	DRV/rtv QD
Started	12
Completed	12

Period 3

Period 3 title	adult data
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	daruanvir adult

Arm description:

this is information from literature, therefore number of subjects is put in as 1 (start 12, as otherwise we get errors).

Arm type	Active comparator
Investigational medicinal product name	darunavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

DRV 800 mg with ritonavir 100 mg, adult dose

Number of subjects in period 3	daruanvir adult
Started	12
Completed	1
Not completed	11
not applicable, lit data	11

Baseline characteristics

Reporting groups	
Reporting group title	screening

Reporting group description: -

Reporting group values	screening	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	8.9		
full range (min-max)	6.3 to 11.7	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	5	5	

End points

End points reporting groups

Reporting group title	DRV/rtv QD
Reporting group description:	
In this multicenter pharmacokinetic study in HIV-infected children (6–12 years of age), we validated the approved once-daily darunavir/ritonavir dosing recommendations.	
Reporting group title	DRV/rtv QD
Reporting group description:	
Children were using DRV/rtv QD treatment dosed according to EMA approved SPC.	
Reporting group title	daruanvir adult
Reporting group description:	
this is information from literature, therefore number of subjects is put in as 1 (start 12, as otherwise we get errors).	
Subject analysis set title	DAPHNE
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients in the study	

Primary: AUC0-24

End point title	AUC0-24
End point description:	
End point type	Primary
End point timeframe:	
one day	

End point values	DRV/rtv QD	daruanvir adult		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	1[1]		
Units: mg*h/L				
geometric mean (geometric coefficient of variation)	63.1 (± 33)	81 (± 30)		

Notes:

[1] - literature data

Statistical analyses

Statistical analysis title	descriptive
Statistical analysis description:	
comparison of AUC values in children to adults.	
Comparison groups	DRV/rtv QD v daruanvir adult

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.05 [3]
Method	t-test, 1-sided
Parameter estimate	none

Notes:

[2] - comparison of AUC values in children to adults.

[3] - not applicable

Adverse events

Adverse events information	
Timeframe for reporting adverse events: entire study	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	none
Dictionary version	1
Reporting groups	
Reporting group title	DAPHNE

Reporting group description: -

Serious adverse events	DAPHNE		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	DAPHNE		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)		
Psychiatric disorders			
hallucinations	Additional description: One child suffered from anxiety starting 4 weeks after switch to drv/rtv and 2 weeks after PK assessment, resulting in hallucinations at 6 weeks after start. DRV/rtv was stopped and the child fully recovered wihtin 4 days after stop.		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29474261