



## Clinical trial results:

### The metabolic impact of Darunavir/ritonavir maintenance monotherapy after successful viral suppression with standard Atripla in HIV-1-infected patients (MIDAs).

#### Summary

EudraCT number	2010-022120-72
Trial protocol	GB
Global end of trial date	17 September 2013

#### Results information

Result version number	v1 (current)
This version publication date	06 October 2018
First version publication date	06 October 2018
Summary attachment (see zip file)	FINAL STUDY REPORT (AVT-15-OA-3622_Hamzah_Web.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	JF-001
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##### Additional study identifiers

ISRCTN number	ISRCTN11504121
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Guy's and St Thomas' NHS Foundation Trust
Sponsor organisation address	Great Maze Pond, London, United Kingdom, SE19RT
Public contact	Dr Alastair Teague, Guy's & St. Thomas' NHS Foundation Trust, 0044 02071887188, alastair.teague@gstt.nhs.uk
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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	01 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 September 2013
Global end of trial reached?	Yes
Global end of trial date	17 September 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

This project aims to assess the potential long-term advantages of switching HIV patients from the standard therapy (Atripla) to a different regime of treatment (darunavir 800 mg / ritonavir 100 mg). This will be assessed by measuring Vitamin D levels, calcium and phosphate homeostasis (balance), kidney (tubular) function, bone turnover and bone mineralisation, and HIV disease progression in all the patients who take part in the study.

Protection of trial subjects:

Safety blood tests (FBC, Urea and electrolytes and liver function tests) and adherence review are incorporated into the visit schedule. Any abnormalities or concerns will be addressed immediately and reported.

Background therapy: -

Evidence for comparator:

While Highly Active Anti-Retroviral Therapy (HAART) has dramatically reduced AIDS-related morbidity and mortality, the absence of HIV eradication with those drugs requires their prolonged use for a lifetime, making long-term toxicity a critical issue in the management of HIV-infected patients. Protease inhibitor (PI) monotherapy maintains plasma HIV-RNA suppression in a large proportion of patients already suppressed on a standard triple combination<sup>1</sup>. However, the more frequent occurrence of low-level viremia does not allow the use of such a strategy outside of clinical studies at this time. Darunavir has a high genetic barrier and low propensity to induce resistance-conferring mutations in cases of virologic failure. Early results showed non-inferiority with Darunavir/ritonavir monotherapy when compared to 2 NRTIs/ritonavir/darunavir [MONET and MONOI]. However, it remains unclear which patient populations might benefit most, and the potential risks and benefits associated with this therapeutic strategy remain to be defined.

Hypothesis for this trial is that oosted Darunavir, given once a day as monotherapy, confers less toxicity than Atripla while maintaining undetectable HIV RNA levels

Actual start date of recruitment	02 May 2011
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	United Kingdom: 70
Worldwide total number of subjects	70
EEA total number of subjects	70

Notes:

<b>Subjects enrolled per age group</b>	
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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	70
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Inclusion Criteria

1. Males and Females aged between 18 and 65
2. Documented Positive HIV 1-antibody test
3. Plasma HIV RNA <100 copies/ml and on Atripla for at least six months prior to study start
4. Agreeable NOT take vitamin D supplements for the duration of the study
5. Ability to give informed consent

### Pre-assignment

Screening details:

Inclusion Criteria

- Males and Females aged between 18 and 65  
Documented Positive HIV 1-antibody test  
Plasma HIV RNA <100 copies/ml and on ATP for at least six months prior to study start  
Agreeable NOT take vitamin D supplements for the duration of the study  
Ability to give informed consent

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Randomization will take place on a 1:1 basis, with randomisation/allocation to study arm being determined using the MS Excel RAND() function

### Arms

Are arms mutually exclusive?	Yes
Arm title	Atripla

Arm description:

Atripla 1 tablet once daily for 48 weeks

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

Dosage and administration details:

Atripla® is efavirenz 600mg, emtricitabine 200mg with tenofovir disoproxil (as fumarate) 245mg. This will be taken orally once a day for 48 weeks.

Arm title	Darunavir/ ritonavir
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Arm description:

Participants were randomised to receive Darunavir 800mg / ritonavir 100mg orally once per day for 48 weeks.

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

Dosage and administration details:

Darunavir 800mg once daily taken orally for 48 weeks

Investigational medicinal product name	Ritonovir
Investigational medicinal product code	
Other name	Norvir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ritonovir 100mg taken orally once per day for 48 weeks

<b>Number of subjects in period 1</b>	Atripla	Darunavir/ ritonovir
Started	34	36
12 week visit	32	32
Completed	31	25
Not completed	3	11
Consent withdrawn by subject	1	6
Intolerance to IMP	-	2
Concomitant vitamin d therapy	2	-
Discontinued IMP	-	2
Adverse event, non-fatal	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Atripla
Reporting group description: Atripla 1 tablet once daily for 48 weeks	
Reporting group title	Darunavir/ ritonovir
Reporting group description: Participants were randomised to receive Darunavir 800mg / ritonovir 100mg orally once per day for 48 weeks.	

Reporting group values	Atripla	Darunavir/ ritonovir	Total
Number of subjects	34	36	70
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	34	36	70
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	41.6	43.8	
standard deviation	± 8.8	± 9.2	-
Gender categorical Units: Subjects			
Female	7	9	16
Male	27	27	54

## End points

### End points reporting groups

Reporting group title	Atripla
Reporting group description:	
Atripla 1 tablet once daily for 48 weeks	
Reporting group title	Darunavir/ ritonovir
Reporting group description:	
Participants were randomised to receive Darunavir 800mg / ritonovir 100mg orally once per day for 48 weeks.	

### Primary: Mean change in Vitamin D level at Week 48 from baseline

End point title	Mean change in Vitamin D level at Week 48 from baseline
End point description:	
Change in 25(OH)D at week 48	
End point type	Primary
End point timeframe:	
From baseline to week 48	

End point values	Atripla	Darunavir/ ritonovir		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	25		
Units: mm/l				
arithmetic mean (standard deviation)	1.2 (± 6)	5 (± 5.9)		

### Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description:	
For sample size calculation, an increase of 15 nmol/L in 25(OH)D in the DRV/R arm compared to ATP was considered clinically relevant. With a 1:1 randomisation, 35 patients per arm and a continue-switch design, the study had 90% power to detect this difference. In addition, the study had 90% power to detect a fall in ALP of 10 IU/L in the DRV/r arm, compared with ATP. These calculations allowed for 5 patients in the DRV/r arm switching back to ATP for tolerability reasons.	
Comparison groups	Atripla v Darunavir/ ritonovir
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.2
Method	aa
Parameter estimate	Median difference (net)

Confidence interval	
Variability estimate	Standard deviation

Notes:

[1] - The study was not statistically powered to assess virological efficacy. In addition to the proportion of participants with two consecutive HIV viral load values > 50 copies/ml, an FDA snapshot analysis was performed at week 48. The frequencies of adverse events (AEs), AEs leading to discontinuation and laboratory test abnormalities were described by treatment arm.

All analyses were performed on an intention to treat basis and conducted using Stata (version12).



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Duration of the trial and 4 weeks post last dose of IMP.

Adverse event reporting additional description:

Darunavir is a licensed antiretroviral therapy which is well tolerated. The commonest side effects are nausea, headaches and diarrhoea which tend to be mild and self limiting. All side effects will be documented and Grade 2-4 AEs

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	Group 1 ATRIPLA
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Reporting group description:

Atripla 1 tablet od for 48 weeks

Reporting group title	Group 2 DRV/r
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Reporting group description:

Darunavir 800mg od/ ritonovir 100mg od for 48 weeks

Serious adverse events	Group 1 ATRIPLA	Group 2 DRV/r	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 34 (8.82%)	3 / 36 (8.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Seizure	Additional description: Seizures due to scar tissue after toxoplasmosis infection		
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Meningoencephalitis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Uveitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arthritic Sepsis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Group 1 ATRIPLA	Group 2 DRV/r	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 34 (88.24%)	31 / 36 (86.11%)	
Investigations			
High HIV Viral Load			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
High Alkaline Phosphatase			
subjects affected / exposed	0 / 34 (0.00%)	1 / 36 (2.78%)	
occurrences (all)	0	1	
High Cholesterol			
subjects affected / exposed	5 / 34 (14.71%)	6 / 36 (16.67%)	
occurrences (all)	5	6	
High LDL Cholesterol			
subjects affected / exposed	3 / 34 (8.82%)	4 / 36 (11.11%)	
occurrences (all)	3	4	
Low serum phosphate			

subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	3 / 36 (8.33%) 3	
Low white blood cells subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 36 (2.78%) 1	
High Gamma-GT subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 36 (2.78%) 1	
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	2 / 36 (5.56%) 2	
Dizziness subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 36 (2.78%) 1	
Neurosensory alteration subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	2 / 36 (5.56%) 2	
Syncope subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 36 (2.78%) 1	
Altered Mood subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 36 (0.00%) 0	
Cognitive & Behavioral change subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	0 / 36 (0.00%) 0	
General disorders and administration site conditions			
Chills subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 36 (2.78%) 1	
Eye disorders			
Altered vision subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 36 (2.78%) 1	
Gastrointestinal disorders			

Bloating subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 36 (2.78%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 0	5 / 36 (13.89%) 1	
Nausea subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 36 (2.78%) 1	
Vomiting subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	3 / 36 (8.33%) 0	
Bleeding Rectum subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 36 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 36 (2.78%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)  Fracture subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1  1 / 34 (2.94%) 1	2 / 36 (5.56%) 2  0 / 36 (0.00%) 0	
Infections and infestations Sexually transmitted disease subjects affected / exposed occurrences (all)  Gastroenteritis subjects affected / exposed occurrences (all)  Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0  3 / 34 (8.82%) 3  1 / 34 (2.94%) 1	1 / 36 (2.78%) 1  0 / 36 (0.00%) 0  0 / 36 (0.00%) 0	

Lower respiratory tract infection subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	0 / 36 (0.00%) 0	
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2011	Addition of 4 exclusion criteria. Additional lab tests added and change in CI and PI for the study
08 August 2011	Amendment to the inclusion criteria. Amendment to the DXA scan from partial to full body scan and amendment to data analysis section of the protocol.
13 March 2012	changes and clarifications have been made to both the inclusion and exclusion criteria. change in the CI and PI

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was not statistically powered to assess virological efficacy. In addition to the proportion of participants with two consecutive HIV viral load values > 50 copies/ml, an FDA snapshot analysis was performed at week 48. The frequencies of adv

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26460504>