



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 |
|-----------------------|--------|

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 |
| Scientific contact | Dr Alastair Teague, Guy's & St. Thomas' NHS Foundation Trust, 0044 02071887188, alastair.teague@gstt.nhs.uk |

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 combination¹. 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:

| 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) | 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 |
|-----------|----------------------|

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

| Number of subjects in period 1 | 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 ^[1] |
| 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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Group 1 ATRIPLA |
|-----------------------|-----------------|

Reporting group description:

Atripla 1 tablet od for 48 weeks

| | |
|-----------------------|---------------|
| Reporting group title | Group 2 DRV/r |
|-----------------------|---------------|

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 %

| Non-serious adverse events | 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 | |
|---|---------------------|---------------------|--|

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:

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:

Online references

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