



Clinical trial results:

A phase IV, open-label, single centre, single-arm, pilot study to assess Cerebrospinal fluid INflammatory markers after Addition of Maraviroc to MONotherapy darunavir/ritonavir – The CINAMMON Study SSAT046

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2012-000649-11 |
| Trial protocol | GB ES |
| Global end of trial date | 19 November 2015 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 28 October 2017 |
| First version publication date | 28 October 2017 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | SSAT046 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01680536 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | St Stephens Aids Trust |
| Sponsor organisation address | Chelsea Chambers, 262a Fulham Road, London, United Kingdom, SW10 9EL |
| Public contact | Marita Marshall, Head of Project Management, St Stephen's Clinical Research, 44 0203 828 0567, marita.marshall@ststcr.com |
| Scientific contact | Professor Brian Gazzard, St Stephen's Centre, Chelsea & Westminster Hospital, 44 020 8746 8239, brian.gazzard@chelwest.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 | 22 July 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 19 November 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 November 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To investigate changes from week 12 to week 36 in inflammatory markers in CSF when maraviroc (150mg qd) is added to stable darunavir/ritonavir (800/100mg qd) monotherapy for 24 weeks

Protection of trial subjects:

The protocol was written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice, E6 and the principles of the Declaration of Helsinki. The protocol was approved by the National Regulator and an Independent Ethics Committee as required by national legislation.

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were encouraged to ask questions concerning all portions of the conduct of the study to ensure understanding. The purpose of the study together with the procedures benefits and risks of the study; any discomforts and the precautions taken was described during the consent process; allowing subject to make an informed decision about participation. Subjects were also informed of their right to discontinue from the study at any time without any detriment.

The inclusion/exclusion criteria were designed to eliminate subjects who may have been put at risk by participating in the study. Women of childbearing potential were required to use effective birth control methods during the trial and for at least 30 days after the end of the trial (or after last intake of investigational Anti Retrovirals. Sexually active males were also required to use effective birth control methods during the trial. Safety and tolerability of medications were assessed by questions, physical examination and laboratory parameters. Any changes in health status during the study were recorded and followed up by the clinical team.

Background therapy:

Darunavir/Ritonavir (800/100mg qd) monotherapy

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 07 December 2012 |
| 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 | Spain: 8 |
| Country: Number of subjects enrolled | United Kingdom: 11 |
| Worldwide total number of subjects | 19 |
| EEA total number of subjects | 19 |

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) | 18 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from two centres (UK & Spain). FPI UK 07 Dec 2012; Spain 29 Oct 2014. A total of 19 subjects were recruited and the last subject to be recruited to the study was 12 Jan 2015. Last subject last visit was 18 Nov 2015.

Pre-assignment

Screening details:

HIV-1 positive aged between 18 and 65 years receiving single agent antiretroviral therapy (ritonavir boosted darunavir once daily) for at least three months with an undetectable viral load (<40 copies) in plasma.

Subjects were excluded if they were infected with HIV-2, using any concomitant therapy disallowed as per SPC for the study drugs.

Period 1

| | |
|------------------------------|-----------------------------------|
| Period 1 title | Experimental Arm (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|------------------|
| Arm title | Experimental Arm |
|-----------|------------------|

Arm description:

All subjects as this was a two centre, open-label, single arm pilot study

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Maraviroc |
| Investigational medicinal product code | J05AX09 |
| Other name | CESENTRI |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

150mg qd from week 12 to week 36

| Number of subjects in period 1 | Experimental Arm |
|--------------------------------|------------------|
| Started | 19 |
| 12 weeks | 16 |
| 36 week | 15 |
| Completed | 15 |
| Not completed | 4 |
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal | 3 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Experimental Arm |
|-----------------------|------------------|

Reporting group description:

All subjects as this was a two centre, open-label, single arm pilot study

| Reporting group values | Experimental Arm | Total | |
|--|------------------|-------|--|
| Number of subjects | 19 | 19 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 18 | 18 | |
| From 65-84 years | 1 | 1 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| median | 45.4 | | |
| full range (min-max) | 27.2 to 65.1 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 2 | 2 | |
| Male | 17 | 17 | |
| Ethnicity | | | |
| Subjects self description | | | |
| Units: Subjects | | | |
| Caucasian/White | 13 | 13 | |
| Mixed | 1 | 1 | |
| Pakistani | 1 | 1 | |
| Black African | 1 | 1 | |
| Other | 3 | 3 | |
| HIV Risk | | | |
| Subjects self description | | | |
| Units: Subjects | | | |
| Bisexual | 1 | 1 | |
| Homosexual | 10 | 10 | |
| Intravenous Drug Use | 2 | 2 | |
| Other | 6 | 6 | |

End points

End points reporting groups

| | |
|---|------------------|
| Reporting group title | Experimental Arm |
| Reporting group description: All subjects as this was a two centre, open-label, single arm pilot study | |

Primary: S100b

| | |
|------------------------|----------------------|
| End point title | S100b ^[1] |
| End point description: | |

| | |
|--|---------|
| End point type | Primary |
| End point timeframe: Comparison of CSF marker levels at week 12 and week 36 | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were planned for this end point - descriptive statistics only were included in the protocol.

| End point values | Experimental Arm | | | |
|---------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 ^[2] | | | |
| Units: pg/ml (shown here x10-2) | | | | |
| median (full range (min-max)) | | | | |
| Baseline to Week 12 | -44 (-61 to 38) | | | |
| Week 12 to Week 36 | 14 (-124 to 170) | | | |

Notes:

[2] - Baseline to week 12= 3

Week 12 to week 36= 11

Due to missing samples

Statistical analyses

No statistical analyses for this end point

Primary: NfH

| | |
|------------------------|--------------------|
| End point title | NfH ^[3] |
| End point description: | |

| | |
|--|---------|
| End point type | Primary |
| End point timeframe: Comparison of CSF marker levels at week 12 and week 36 | |

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were planned for this end point - descriptive statistics only were included in the protocol.

| | | | | |
|---------------------------------|-------------------|--|--|--|
| End point values | Experimental Arm | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 ^[4] | | | |
| Units: pg/ml (shown here x10-2) | | | | |
| median (full range (min-max)) | | | | |
| Baseline to Week 12 | -4 (-5 to 1) | | | |
| Week 12 to Week 36 | -1 (-4 to 8) | | | |

Notes:

[4] - Baseline to week 12= 3

Week 12 to week 36= 11

Due to missing samples

Statistical analyses

No statistical analyses for this end point

Primary: Ferrotin

| | |
|-----------------|-------------------------|
| End point title | Ferrotin ^[5] |
|-----------------|-------------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Comparison of CSF marker levels at week 12 and week 36

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were planned for this end point - descriptive statistics only were included in the protocol.

| | | | | |
|---------------------------------|-------------------|--|--|--|
| End point values | Experimental Arm | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 11 ^[6] | | | |
| Units: ng/ml (shown here x10-1) | | | | |
| median (full range (min-max)) | | | | |
| Baseline to week 12 | 1 (1 to 3) | | | |
| Week 12 to week 36 | 1 (0 to 1) | | | |

Notes:

[6] - Baseline to week 12= 3

Week 12 to week 36= 11

Due to missing samples

Statistical analyses

No statistical analyses for this end point

Primary: Neopterin

| | |
|-----------------|--------------------------|
| End point title | Neopterin ^[7] |
|-----------------|--------------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Comparison of CSF marker levels at week 12 and week 36

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were planned for this end point - descriptive statistics only were included in the protocol.

| | | | | |
|-------------------------------|----------------------|--|--|--|
| End point values | Experimental Arm | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 ^[8] | | | |
| Units: nmol/L | | | | |
| median (full range (min-max)) | | | | |
| Baseline to Week 12 | 0.04 (-0.56 to 0.65) | | | |
| Week 12 to Week 36 | 0.09 (-0.81 to 0.17) | | | |

Notes:

[8] - Baseline to week 12= 3

Week 12 to week 36= 3

Due to missing samples

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From subject consent until the subjects final study visit.

Adverse event reporting additional description:

In addition to any events occurring between consent and that subject's last visit; any untoward event that may occurring subsequent to the reporting period, that the Investigator assessed as possibly, probably or definitely related to the study drug medication was also be reported as an Adverse Event.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Experimental Arm |
|-----------------------|------------------|

Reporting group description:

All subjects as this was a two centre, open-label, single arm pilot study

| Serious adverse events | Experimental Arm | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

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

| Non-serious adverse events | Experimental Arm | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 19 (89.47%) | | |
| Investigations | | | |
| Hipergliceridemia | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Chest Pain | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| Headache | | | |
| subjects affected / exposed | 5 / 19 (26.32%) | | |
| occurrences (all) | 6 | | |
| Migraine | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 2 | | |
| Paresthesias | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Paresthesias (right arm) | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Immune system disorders | | | |
| Common cold and fever | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Detectable viral load (49 copies/ml) | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Hayfever | | | |
| subjects affected / exposed | 2 / 19 (10.53%) | | |
| occurrences (all) | 2 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Rhinitis (allergy) | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Throat infection | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |

| | | | |
|---|----------------------|--|--|
| Vertiginous Syndrome subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Gastrointestinal disorders Anus Pain seen in Kobler clinic subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Dental infection subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Nausea subjects affected / exposed occurrences (all) | 2 / 19 (10.53%) 2 | | |
| Respiratory, thoracic and mediastinal disorders Hypertension subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Skin and subcutaneous tissue disorders Aphtha subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Inflammatory lesion (insect bite) subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Strongyloidiasis subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Warty Lesions (scrotum) subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | | |
| Anxiety (occasional) | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Unable to sleep (Insomnia) | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 19 (10.53%) | | |
| occurrences (all) | 2 | | |
| Cervicalgia | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Lumbago | | | |
| subjects affected / exposed | 2 / 19 (10.53%) | | |
| occurrences (all) | 2 | | |
| Non specific arthralgias (Hands) | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Right knee effusion | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Tendinitis (hand) | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal pain (back) | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Fungal infection | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |
| Genital herpes | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 2 | | |
| Nevus Bleeding in Lumbar region | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 12 July 2012 | <p>Clarification of payment to patients who undergo lumbar puncture</p> <p>Inc. criteria 8 for estimated glomerular filtration rate updated to >60 ml/min.</p> <p>PIS & PIC updated to refer to participants not subjects throughout.</p> <p>PIS clarification: participants will not be withdrawn without prior discussion.</p> <p>PIS re worded to clarify Maraviroc is licensed for HIV treatment & has shown good results when taken by people whose HIV virus has developed resistance to previous HIV treatments.</p> <p>Wording added to PIS to clarify that participants can ask their study doctors for any additional info.</p> <p>Contraception & pregnancy moved to a separate section of PIS.</p> <p>Details of the role and procedures of neurocognitive tests added the PIS.</p> <p>Upper age limit of 65 added to inc. criteria 1.</p> <p>Inc. criteria 7 amended for clarity, specifying subject should be on darunavir/ritonavir regimen 800/100mg once daily.</p> <p>Change of lab address.</p> <p>Clarification to sample processing instructions for CSF Inflammatory marker.</p> <p>Inc. criterion 6 corrected to: CD4 cell count at screening >200 cells/mm³ & exc. criteria 3 removed to avoid duplication.</p> <p>Urine dip, drugs of abuse and pregnancy tests were added to screening visit to protocol & PIS.</p> <p>Clarification on Drugs of abuse test to be carried out at baseline and week 36, as well as at week 12 only if NCI testing were carried out at that visit. Protocol and PIS updated.</p> <p>Addition of keeping a back up CSF sample for storage at each timepoint for future analysis.</p> <p>Change to the facility performing the MRI scanning. Clarification on the details of the MRI scans involved, imaging schedule and duration of scans, data storage as well as data analysis included protocol & PIS</p> <p>PIS updated with locations of the laboratories where their samples were sent.</p> <p>Fasting period requirement was changed from 10 hours to 8 hours PIS. 20.</p> <p>Exception of cannabinoids for any illegal drugs was removed from point 1 in Section 5.2 Prior and Concomitant Therapy.</p> |
| 12 September 2012 | <p>Change in the number of MRI brain scans and to make some corrections to the protocol and participant information sheet due to administrative changes</p> |
| 28 March 2013 | <p>Change in tablet strength of one of the IMPs used in this trial. From 400mg Prezista tablets to the newly approved 800mg Prezista tablet, so patients were prescribed 1x 800mg Prezista tablet rather than 2x 400mg Prezista tablets.</p> |
| 07 October 2013 | <ol style="list-style-type: none">1. To add an additional investigator site, Hospital Bellvitge in Barcelona, Spain, and to add PICs to help recruit in the UK2. To increase the sample size from 30 to 40 participants3. To decrease the total number of study lumbar punctures from 3 to 2. |
| 20 November 2014 | <p>This amendment applied to the Spanish site only. One or two healthy volunteers to be scanned at the Vall d'Hebron MRI imaging site. These volunteers had already been scanned under the ethically approved protocol "MRI Protocol Optimisation" in the UK at the Imperial College site. This was because different equipment was used at the different MRI centres and there was a need to ensure that scanning programs are optimised and comparable, to allow analysis of the data.</p> |

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.

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|--|
| Insufficient MRI data for analysis, due to recruitment and drop out issues. PI/r monotherapy is now a less utilised strategy. Low MVC dose used. Low numbers for paired data comparison More cog tests looked at non-exec than exec function |
|--|

Notes: