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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2012	Clarification of payment to patients who undergo lumbar puncture Inc. criteria 8 for estimated glomerular filtration rate updated to >60 ml/min. PIS & PIC updated to refer to participants not subjects throughout. PIS clarification: participants will not be withdrawn without prior discussion. 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. Wording added to PIS to clarify that participants can ask their study doctors for any additional info. Contraception & pregnancy moved to a separate section of PIS. Details of the role and procedures of neurocognitive tests added the PIS. Upper age limit of 65 added to inc. criteria 1. Inc. criteria 7 amended for clarity, specifying subject should be on darunavir/ritonavir regimen 800/100mg once daily. Change of lab address. Clarification to sample processing instructions for CSF Inflammatory marker. Inc. criterion 6 corrected to: CD4 cell count at screening >200 cells/mm3 & exc. criteria 3 removed to avoid duplication. Urine dip, drugs of abuse and pregnancy tests were added to screening visit to protocol & PIS. 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. Addition of keeping a back up CSF sample for storage at each timepoint for future analysis. 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 PIS updated with locations of the laboratories where their samples were sent. Fasting period requirement was changed from 10 hours to 8 hours PIS. 20. Exception of cannabinoids for any illegal drugs was removed from point 1 in Section 5.2 Prior and Concomitant Therapy.
12 September 2012	Change in the number of MRI brain scans and to make some corrections to the protocol and participant information sheet due to administrative changes
28 March 2013	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.
07 October 2013	1. To add an additional investigator site, Hospital Bellvitge in Barcelona, Spain, and to add PICs to help recruit in the UK 2. To increase the sample size from 30 to 40 participants 3. To decrease the total number of study lumbar punctures from 3 to 2.
20 November 2014	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.

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.

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: