Clinical trial results:
A study of the effects of Simvastatin on neutrophil function in elderly subjects

Summary

EudraCT number	2011-002082-38
Trial protocol	GB
Global end of trial date	01 September 2013

Results information

Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019

Trial information

Trial identification

Sponsor protocol code	RG_11-123

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TT
Public contact	Clinical Trials Coordinator, Queen Elizabeth Hospital Birmingham NHS Trust, 44 01214721311, anita.pye@uhb.nhs.uk
Scientific contact	Clinical Trials Coordinator, Queen Elizabeth Hospital Birmingham NHS Trust, 44 01214721311, anita.pye@uhb.nhs.uk
Sponsor organisation name	University of Birmingham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TH
Public contact	Dr Elizabeth Sapey, University of Birmingham,, 44 1212462000, e.sapey@bham.ac.uk
Scientific contact	Dr Elizabeth Sapey, University of Birmingham,, 44 1212462000, e.sapey@bham.ac.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	09 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Hypothesis. The age-related loss of neutrophil function contributes to delayed resolution of infection and inflammation. These changes in neutrophil function with advanced age are a result of alterations in signal transduction pathways due to altered membrane cholesterol levels and can be corrected using simvastatin. In vitro studies have confirmed that neutrophils isolated from elderly subjects respond differently to those from young donors in terms of migration, phagocytosis and superoxide production when pre-treated with physiological concentrations of Simvastatin. Question: Is this clinically relevant in vivo? Does a course of treatment with simvastatin improve migratory dynamics, phagocytosis and superoxide generation of neutrophils isolated from the peripheral blood of older subjects and is this associated with altered membrane cholesterol levels?

Protection of trial subjects:

As per EU and UK law with monitoring and safety checks as per the protocol

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	3
From 65 to 84 years	12
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

24 participants were recruited but only 21 had the CTIMP or placebo, and 20 completed the full cross-over period. 20 were included in the analysis

Pre-assignment

Screening details:

Healthy old (OH) subjects, identified from among the Birmingham 1000 Elders cohort, had never smoked, had no evidence of acute or chronic disease, had normal spirometry, were medication free, and had no previous episodes of hospitalized sepsis.

Pre-assignment period milestones

Number of subjects started	24
Number of subjects completed	24

Period 1

Period 1 title	Period 1 in cross over
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Study drugs (simvastatin or placebo) were prepared, randomised, and packaged identically by Bilcare Ltd (Powys, UK). Computer-based block randomisation was performed in a 1:1 ratio by a centralised service (Bilcare Ltd, UK) ready for period 2

Arms

Arm title	CTIMP

Arm description:

Simvastatin

Arm type	Experimental
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	MA-PL0075/017
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

80mg once daily for 2 weeks

Number of subjects in period 1	CTIMP
Started	24
Completed	20
Not completed	4
Consent withdrawn by subject	4

Period 2

Period 2 title	Placebo cross over period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Study drugs (simvastatin or placebo) were prepared, randomised, and packaged identically by Bilcare Ltd (Powys, UK). Computer-based block randomisation was performed in a 1:1 ratio by a centralised service (Bilcare Ltd, UK)

Arms

Arm title	Placebo

Arm description:

Placebo in cross over

Arm type	Placebo
Investigational medicinal product name	DBAAe capsule shells filled with Microcrystalline cellulose.
Investigational medicinal product code	MA-10284
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Once daily for 2 weeks

Number of subjects in period 2	Placebo
Started	20
Completed	20

Baseline characteristics

Reporting groups

Reporting group title	Period 1 in cross over

Reporting group description: -

Reporting group values	Period 1 in cross over	Total	
Number of subjects	24	24	
Age categorical Units: Subjects			
Adults (18-64 years)	3	3	
From 65-84 years	12	12	
85 years and over	9	9	
Gender categorical Units: Subjects			
Female	15	15	
Male	9	9	

Subject analysis sets

Subject analysis set title	Baseline characteristics
Subject analysis set type	Per protocol

Subject analysis set description:

As this was a comparison of a change in neutrophil function, only those who completed the study were include din the analysis

Subject analysis set title	CTIMP
Subject analysis set type	Per protocol

Subject analysis set description:

As this was a comparison of changes in neutrophil function, only those who completed the study were included

Subject analysis set title	Placebo
Subject analysis set type	Per protocol

Subject analysis set description:

As this was a comparison of changes in neutrophil function, only those who completed the study were included

Reporting group values	Baseline characteristics	CTIMP	Placebo
Number of subjects	20	20	20
Age categorical Units: Subjects			
Adults (18-64 years)	2	2	2
From 65-84 years	10	10	10
85 years and over	8	8	8
Gender categorical Units: Subjects			
Female	11	11	11
Male	9	9	9

End points

End points reporting groups

Reporting group title	CTIMP
Reporting group description:	
Simvastatin	
Reporting group title	Placebo
Reporting group description:	
Placebo in cross over	
Subject analysis set title	Baseline characteristics
Subject analysis set type	Per protocol
Subject analysis set description:	
As this was a comparison of a change in neutrophil function, only those who completed the study were include din the analysis	
Subject analysis set title	CTIMP
Subject analysis set type	Per protocol
Subject analysis set description:	
As this was a comparison of changes in neutrophil function, only those who completed the study were included	
Subject analysis set title	Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
As this was a comparison of changes in neutrophil function, only those who completed the study were included	

Primary: Median change in neutrophil migration to fMLP

End point title	Median change in neutrophil migration to fMLP
End point description:	
End point type	Primary
End point timeframe:	
After 2 weeks of CTIMP therapy	

End point values	CTIMP	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: um/min				
median (inter-quartile range (Q1-Q3))	0.34 (0.05 to 0.72)	-0.05 (-0.38 to 0.08)		

Statistical analyses

Statistical analysis title	Change in chemotaxis from baseline values
Comparison groups	CTIMP v Placebo

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in chemotaxis towards CXCL8

End point title	Change in chemotaxis towards CXCL8

End point description:

End point type	Secondary

End point timeframe:

Compared to baseline after 2 weeks of therapy in cross over trial

End point values	CTIMP	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: um/min				
median (inter-quartile range (Q1-Q3))	0.26 (0.01 to 0.61)	0.03 (-0.73 to 0.34)		

Statistical analyses

Statistical analysis title	Change from baseline chemotaxis
Comparison groups	CTIMP v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in phagocytosis E Coli

End point title	Change in phagocytosis E Coli

End point description:

End point type	Secondary

End point timeframe:

After two weeks of CTIMP or placebo in cross over trial

End point values	CTIMP	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: arbitrary units				
median (inter-quartile range (Q1-Q3))	580 (-22.0 to 1347)	690 (-79.0 to 1207)		

Statistical analyses

Statistical analysis title	Change in phagocytosis E Coli
Comparison groups	CTIMP v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.404
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in phagocytosis staph aureus

End point title	Change in phagocytosis staph aureus

End point description:

End point type	Secondary

End point timeframe:

After 2 weeks of CTIMP or placebo in cross over trial

End point values	CTIMP	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: arbitrary units				
median (inter-quartile range (Q1-Q3))	257 (-616.7 to 1951)	1217 (-588.7 to 2048)		

Statistical analyses

Statistical analysis title	Change in phagocytic index
Comparison groups	CTIMP v Placebo

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.196
Method	Wilcoxon (Mann-Whitney)

Secondary: NETosis PMA

End point title	NETosis PMA

End point description:

End point type	Secondary

End point timeframe:

Two weeks of CTIMP or placebo in cross over study

End point values	CTIMP	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: Arbitrary Units				
median (inter-quartile range (Q1-Q3))	5985 (-24415 to 30189)	6964 (-17992 to 22048)		

Statistical analyses

Statistical analysis title	Change in PMA induced NETs
Comparison groups	CTIMP v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 729
Method	Wilcoxon (Mann-Whitney)

Secondary: NETosis to fMLP

End point title	NETosis to fMLP

End point description:

End point type	Secondary

End point timeframe:

After two weeks of CTIMP or Placebo

End point values	CTIMP	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: Arbitrary Units				
median (inter-quartile range (Q1-Q3))	1355 (-2133 to 6518)	1099 (-2818 to 2719)		

Statistical analyses

Statistical analysis title	Change in ketosis to fMLP
Comparison groups	CTIMP v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.216
Method	Wilcoxon (Mann-Whitney)

Secondary: Netosis to LPS

End point title	Netosis to LPS

End point description:

End point type	Secondary

End point timeframe:

After 2 weeks of CTIMP or placebo in cross over trial

End point values	CTIMP	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: Arbitrary Units				
median (inter-quartile range (Q1-Q3))	7115 (-839 to 9851)	4048 (2833 to 6279)		

Statistical analyses

Statistical analysis title	Change in Netosis to LPS
Comparison groups	CTIMP v Placebo

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.596
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: For up to two weeks after completion of study	
Assessment type	Systematic
Dictionary used	
Dictionary name	ICD
Dictionary version	10
Reporting groups	
Reporting group title	All subjects

Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)		
Musculoskeletal and connective tissue disorders			
Muscle ache	Additional description: Muscle ache in one subject with no change in blood tests and able to complete study		
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2012	Justification in protocol for giving 80mg Simvastatin, as requested by MHRA

Notes:

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/28657793