Clinical trial results:
Simvastatin as adjuvant therapy to correct neutrophil dysfunction in older pneumonia patients - a randomised double blind placebo controlled trial

Summary

EudraCT number	2012-003343-29
Trial protocol	GB
Global end of trial date	30 December 2016

Results information

Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019
Summary attachment (see zip file)	Abridged protocol (Protocol SNOOPI abridged.pdf)

Trial information

Trial identification

Sponsor protocol code	RG_12-179

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, B152TT
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

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	06 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Pneumonia (severe lung infection) is one of the commonest causes of death and the death rate has not fallen for many years. Elderly patients are at greater risk of pneumonia and its complications such as sepsis. Usually the immune system works cooperatively to clear infection and prevent organ damage. Neutrophils are cells of the immune system that are critical in clearing bacteria. These cells are the foot soldiers of the immune system and move from the blood into infected tissues/organs to locate and kill the invading bacteria using an arsenal of toxic products. Sepsis occurs when the bodies normally helpful reaction to infection becomes harmful. As part of this process, neutrophils stop working properly, they become less able to clear bacteria and release their toxic products indiscriminately, causing organ damage. Defects in the efficiency of these cells is associated with a poor outcome from pneumonia and sepsis. We have undertaken a pilot study in patients, which

Protection of trial subjects:

As per EU CTIMP law and under MHRA guidance.
Daily review by research team and safety bloods taken for creatine kinase, liver function tests and renal function, as stipulated in the protocol.

Background therapy:

Patients were treated as per British Thoracic Society Community acquired pneumonia with the patients physician directing care. Contraindicated drugs were stipulated in protocol inclusion and exclusion criteria.

Evidence for comparator:

This was an additional therapy

Actual start date of recruitment	07 January 2013
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: 62
Worldwide total number of subjects	62
EEA total number of subjects	62

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)	8
From 65 to 84 years	33
85 years and over	21

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from a secondary care hospital. They were eligible if they met The British Thoracic Society guidelines for community acquired pneumonia, and the 2012 Surviving Sepsis Campaign Guidelines

Pre-assignment

Screening details:

Chest radiograph review, bloods and observations.

Period 1

Period 1 title	Within 48 hours of admission (overall period)
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:

The randomization sequence was pre-determined by Sharp Clinical Services, designed to provide a 1:1 randomization pattern.

Arms

Are arms mutually exclusive?	Yes
Arm title	Statin treatment

Arm description:

Simvastatin 80mg OD PO

Arm type	Experimental
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	MA - PL0075/0017
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

80mg orally once daily

Arm title	Placebo

Arm description:

Placebo tablet

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	MA10284
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

DBAAe capsule shells filled with Microcrystalline cellulose taken once a day

Number of subjects in period 1	Statin treatment	Placebo
Started	32	30
Completed	28	25
Not completed	4	5
Consent withdrawn by subject	1	2
Lost to follow-up	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Statin treatment
Reporting group description: Simvastatin 80mg OD PO	
Reporting group title	Placebo
Reporting group description: Placebo tablet	

Reporting group values	Statin treatment	Placebo	Total
Number of subjects	32	30	62
Age categorical			
Adults aged over 50 years of age			
Units: Subjects			
Adults (18-64 years)	4	4	8
From 65-84 years	19	14	33
85 years and over	9	12	21
Age continuous			
Study was for people aged 50 and over			
Units: years			
median	78.1	83.8	
inter-quartile range (Q1-Q3)	70 to 88	68 to 90	-
Gender categorical			
Units: Subjects			
Female	13	14	27
Male	19	16	35

Subject analysis sets	
Subject analysis set title	All randomised subjects
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subject data analysed on intention to treat basis	
Subject analysis set title	Simvastatin Day 4 - Day 0
Subject analysis set type	Intention-to-treat
Subject analysis set description: All analysis on intention to treat basis	
Subject analysis set title	Placebo Day 4 - Day 0
Subject analysis set type	Intention-to-treat
Subject analysis set description: All analysis on intention to treat basis	

Reporting group values	All randomised subjects	Simvastatin Day 4 - Day 0	Placebo Day 4 - Day 0
Number of subjects	62	32	30
Age categorical			
Adults aged over 50 years of age			
Units: Subjects			

Adults (18-64 years)	8	4	4
From 65-84 years	33	19	14
85 years and over	21	9	12
Age continuous			
Study was for people aged 50 and over			
Units: years			
median	79.4	78.1	83.8
inter-quartile range (Q1-Q3)	70.2 to 87.0	70 to 88	68 to 90
Gender categorical			
Units: Subjects			
Female	27	13	14
Male	35	19	16

End points

End points reporting groups	
Reporting group title	Statin treatment
Reporting group description: Simvastatin 80mg OD PO	
Reporting group title	Placebo
Reporting group description: Placebo tablet	
Subject analysis set title	All randomised subjects
Subject analysis set type	Intention-to-treat
Subject analysis set description: All subject data analysed on intention to treat basis	
Subject analysis set title	Simvastatin Day 4 - Day 0
Subject analysis set type	Intention-to-treat
Subject analysis set description: All analysis on intention to treat basis	
Subject analysis set title	Placebo Day 4 - Day 0
Subject analysis set type	Intention-to-treat
Subject analysis set description: All analysis on intention to treat basis	

Primary: Change in fMLP induced NETosis	
End point title	Change in fMLP induced NETosis
End point description: Neutrophil extracellular traps	
End point type	Primary
End point timeframe: Change from Day 0 to day 4	

End point values	Statin treatment	Placebo	Simvastatin Day 4 - Day 0	Placebo Day 4 - Day 0
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	32	30	32	30
Units: Arbitrary units				
median (inter-quartile range (Q1-Q3))	-230.0 (-1187.0 to 53.7)	46.2 (-430.8 to 679.8)	-230.0 (-1187 to 53.7)	46.2 (-430.8 to 679.8)

Attachments (see zip file)	Change in NETosis/Snoopi-Blue 201812-2320C-Figure 3.tiff

Statistical analyses

Statistical analysis title	Change in netosis
Statistical analysis description: Day 4 - Day 0 results	

Comparison groups	Simvastatin Day 4 - Day 0 v Placebo Day 4 - Day 0
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	90 %
sides	2-sided

Secondary: Change in neutrophil migration

End point title	Change in neutrophil migration
End point description:	
End point type	Secondary
End point timeframe:	
Day 4 - Day 0	

End point values	Simvastatin Day 4 - Day 0	Placebo Day 4 - Day 0		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	30		
Units: um/min				
median (inter-quartile range (Q1-Q3))	0.36 (-0.43 to 0.86)	-0.04 (-0.74 to 0.32)		

Statistical analyses

Statistical analysis title	Change in chemotaxis
Comparison groups	Simvastatin Day 4 - Day 0 v Placebo Day 4 - Day 0
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033
Method	Wilcoxon (Mann-Whitney)

Secondary: Systemic neutrophil elastase activity

End point title	Systemic neutrophil elastase activity
End point description:	
End point type	Secondary

End point timeframe: Day 4 - Day 0

End point values	Simvastatin Day 4 - Day 0	Placebo Day 4 - Day 0		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	20		
Units: nM				
median (inter-quartile range (Q1-Q3))	-2.55 (-5.23 to -1.15)	0.25 (-2.13 to 1.92)		

Statistical analyses

Statistical analysis title	Change in neutrophil elastase activity
Comparison groups	Simvastatin Day 4 - Day 0 v Placebo Day 4 - Day 0
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in SOFA score

End point title	Change in SOFA score
End point description:	
End point type	Secondary
End point timeframe: Day 4 - Day 0	

End point values	Simvastatin Day 4 - Day 0	Placebo Day 4 - Day 0		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	30		
Units: Score				
median (inter-quartile range (Q1-Q3))	-2 (-3 to -1)	-1 (-2 to 0)		

Statistical analyses

Statistical analysis title	Change in SOFA score from day 0 to day 4
Comparison groups	Simvastatin Day 4 - Day 0 v Placebo Day 4 - Day 0
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Wilcoxon (Mann-Whitney)

Post-hoc: Hospitalisation free survival

End point title	Hospitalisation free survival

End point description:

End point type	Post-hoc

End point timeframe:

Analysis of readmission and survival as a composite endpoint at 180-days

End point values	All randomised subjects	Simvastatin Day 4 - Day 0	Placebo Day 4 - Day 0	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	62	32	30	
Units: Odds ratio				
number (not applicable)	62	32	30	

Statistical analyses

Statistical analysis title	Odds ratio
Comparison groups	Placebo Day 4 - Day 0 v Simvastatin Day 4 - Day 0 v All randomised subjects
Number of subjects included in analysis	124
Analysis specification	Post-hoc
Analysis type	superiority[1]
P-value	= 0.03
Method	Odds ratio

Notes:

[1] - Analysis of readmission and survival as a composite endpoint demonstrated a significant increase in hospitalization free survival at both 180-days Odds ratio: 0.45; 95% CI 0.22 to 0.93

Post-hoc: Hospitalisation free survival 365 days

End point title	Hospitalisation free survival 365 days

End point description:

End point type	Post-hoc

End point timeframe:

Analysis of readmission and survival as a composite endpoint at 365-days

End point values	All randomised subjects	Simvastatin Day 4 - Day 0	Placebo Day 4 - Day 0	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	62	32	30	
Units: Odds ratio				
number (not applicable)	62	32	30	

Statistical analyses

Statistical analysis title	Odds ratio for hospitalisation free survival
Statistical analysis description: Comparing those on CTIMP to placebo	
Comparison groups	Simvastatin Day 4 - Day 0 v Placebo Day 4 - Day 0
Number of subjects included in analysis	62
Analysis specification	Post-hoc
Analysis type	superiority[2]
P-value	= 0.03
Method	odds ratio

Notes:

[2] - Odds ratio: 0.45, 95% CI 0.22 to 0.90

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All SAEs irrespective of the causal relationship with the trial medications will be reported to the Sponsor within 24 hours of awareness by the investigator.	
Assessment type	Systematic

Dictionary used	
Dictionary name	ICD
Dictionary version	10

Reporting groups	
Reporting group title	Only 1 Adverse event reported
Reporting group description:	
One adverse event- myalgia in the simvastatin arm	

Serious adverse events	Only 1 Adverse event reported		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)		
number of deaths (all causes)	20		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Only 1 Adverse event reported		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 32 (3.13%)		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2014	5 amendments in total. 2 prior to study start (1 of these stipulated by MHRA to add more contraindicated medications). Last amendment 2014.

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/31206313