Clinical trial results:
A SERIES OF RANDOMISED CONTROLLED N-of 1 TRIALS IN PATIENTS WHO HAVE DISCONTINUED OR WISH TO DISCONTINUE STATIN USE DUE TO MUSCLE-RELATED SYMPTOMS TO ASSESS IF ATORVASTATIN TREATMENT CAUSES MORE MUSCLE SYMPTOMS THAN PLACEBO

Summary

EudraCT number	2016-000141-31
Trial protocol	GB
Global end of trial date	08 August 2019

Results information

Result version number	v1 (current)
This version publication date	08 May 2021
First version publication date	08 May 2021
Summary attachment (see zip file)	StatinWISE BMJ Article (bmj.n135.full.pdf)

Trial information

Trial identification

Sponsor protocol code	ISRCTN30952488

Additional study identifiers

ISRCTN number	ISRCTN30952488
ClinicalTrials.gov id (NCT number)	NCT02781064
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	London School of Hygiene and Tropical Medicine
Sponsor organisation address	Keppel Street, London, United Kingdom, WC1e 7HT
Public contact	StatinWISE trial team, London School of Hygiene and Tropical Medicine, +44 02072994684, statinwise@lshtm.ac.uk
Scientific contact	StatinWISE trial team, London School of Hygiene and Tropical Medicine, +44 02072994684, statinwise@lshtm.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	08 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary research objective is to determine whether the muscle symptoms attributed to statin use by patients are caused by statins.

Protection of trial subjects:

This study was conducted in keeping with the principles of Good Clinical Practice and the ethical and regulatory guidelines and regulations of the Medicines & Healthcare products Regulatory Agency (MHRA) and research ethics committees in the United Kingdom where the trial was committed. Participant safety was monitored by the Clinical Trial Unit, the Sponsor, the participant's GP, the data monitoring committee and the MHRA.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	01 September 2016
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: 200
Worldwide total number of subjects	200
EEA total number of subjects	0

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)	56
From 65 to 84 years	138

85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Participants were recruited across 50 GP practices in England and Wales between December 2016 and April 2018.

Pre-assignment

Screening details:

Participants recruited were considering stopping their statin (recruited opportunistically when they complained of symptoms during a consultation) or had stopped taking a statin in the last three years because of muscle symptoms.

Period 1

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

Blinding implementation details:

All participants and clinical and research staff were blinded during baseline assessment as participants had not yet been randomised to a treatment sequence.

Arms

Arm title	N-of-1 trial

Arm description:

All participants were randomly assigned one of 8 sequences of alternating statin or placebo treatment as an N-of-1 trial.

Arm type	Experimental
Investigational medicinal product name	Atorvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20mg atorvastatin, administered orally once daily

Number of subjects in period 1	N-of-1 trial
Started	200
Completed	200

Period 2

Period 2 title	Treatment
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:

Randomisation codes were generated and held securely and confidentially by an information technology team and sponsor representative at the London School of Hygiene and Tropical Medicine Clinical Trials Unit who were independent of the StatinWISE trial management team and the general practitioner surgery staff. Codes were provided Sharp Clinical Services (UK), a good manufacturing practice certified clinical trial supply company, for treatment packs manufacturing.

Arms

Arm title	N-of-1 trial

Arm description:

Participants were allocated with equal probability to one of eight possible sequences which ensured that all participants received one period of statins and one period of placebo in their first two treatment periods (in random order) and no one was allocated to three sequential periods of the same treatment.

Arm type	N-of-1 trial
Investigational medicinal product name	Atorvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20mg atorvastatin, administered orally once daily

Number of subjects in period 2	N-of-1 trial
Started	200
Completed	114
Not completed	86
Adverse event, serious fatal	2
Consent withdrawn by subject	16
Physician decision	14
No reason stated	18
Lost to follow-up	4
Intolerable symptoms	32

Baseline characteristics

Reporting groups

Reporting group title	Baseline assessment

Reporting group description: -

Reporting group values	Baseline assessment	Total	
Number of subjects	200	200	
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)	56	56	
From 65-84 years	138	138	
85 years and over	6	6	
Age continuous Units: years			
arithmetic mean	69.1		
standard deviation	± 9.5	-	
Gender categorical Units: Subjects			
Female	85	85	
Male	115	115	
Ethnicity Units: Subjects			
Asian	11	11	
Black	8	8	
White	179	179	
Other	2	2	
Smoking status Units: Subjects			
Current smoker	14	14	
Ex-smoker	105	105	
Non-smoker	81	81	
Diabetes Units: Subjects			
Yes	33	33	
No	167	167	
Cardiovascular disease history Units: Subjects			
Yes	60	60	
No	140	140	
Statin status at recruitment			

Units: Subjects			
Stopped	151	151	
Considering stopping	49	49	
Cholesterol			
Units: mmol/L			
median	5.3		
inter-quartile range (Q1-Q3)	4.4 to 6.2	-	
QRISK2 score			
For participants with no history of 18.3 (9.6-28.8) cardiovascular disease			
Units: n/a			
median	18.3		
inter-quartile range (Q1-Q3)	9.6 to 28.8	-	

End points

End points reporting groups

Reporting group title	N-of-1 trial

Reporting group description:

All participants were randomly assigned one of 8 sequences of alternating statin or placebo treatment as an N-of-1 trial.

Reporting group title	N-of-1 trial

Reporting group description:

Participants were allocated with equal probability to one of eight possible sequences which ensured that all participants received one period of statins and one period of placebo in their first two treatment periods (in random order) and no one was allocated to three sequential periods of the same treatment.

Subject analysis set title	Primary outcome analysis - statin periods
Subject analysis set type	Full analysis

Subject analysis set description:

Of the 200 participants, 151 (76%) provided one or more visual analogue scale measurements in both a statin period and a placebo period and were included in the primary analysis. The 151 participants included in the primary analysis contributed 2638 measurements during 392 statin periods.

Subject analysis set title	Primary outcome analysis - placebo periods
Subject analysis set type	Full analysis

Subject analysis set description:

Of the 200 participants, 151 (76%) provided one or more visual analogue scale measurements in both a statin period and a placebo period and were included in the primary analysis. The 151 participants included in the primary analysis contributed 2576 symptom score measurements during 383 placebo periods.

Subject analysis set title	Secondary outcome analysis - statin compared to placebo period
Subject analysis set type	Full analysis

Subject analysis set description:

152 participants contributed at least one secondary outcome measurement in a statin period and one in a placebo period.

Subject analysis set title	Secondary outcome - location of muscle symptoms
Subject analysis set type	Full analysis

Subject analysis set description:

In total, there were 493 reports of muscle symptoms during a treatment period arising from 140 participants. Of these 493 reports, 481 (97.6%) included the location of the muscle symptoms.

Subject analysis set title	Secondary outcome - adherence
Subject analysis set type	Full analysis

Subject analysis set description:

Adherence to study medication was self-reported and verified by a drug accountability count of returned treatment packs containing the trial medication.

Primary: Mean difference in self-reported muscle symptoms on a visual analogue scale

End point title	Mean difference in self-reported muscle symptoms on a visual analogue scale

End point description:

The primary outcome is self-reported ‘muscle symptoms’, defined as pain, weakness, tenderness, stiffness or cramp to the body of any intensity, recorded where the participant believes they are associated with the study medication; these are the symptoms most commonly reported by patients and are often the reasons for discontinuation. The primary outcome will be assessed by the mean difference in VAS scores (range 0 to 100) between treatment periods with the trial treatment and treatment periods with placebo, estimated via a linear mixed model.

End point type	Primary

End point timeframe:

The primary outcome was measured each day with a validated visual analogue scale (0-10, score 0=no

symptoms, 5=moderate symptoms, and 10=worst possible symptoms) for the last seven days of each two month treatment period for 1 year.

End point values	Primary outcome analysis - statin periods	Primary outcome analysis - placebo periods		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151	151		
Units: n/a				
arithmetic mean (standard deviation)	1.68 (± 2.57)	1.85 (± 2.74)		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

The primary analysis was a linear mixed model for visual analogue scale muscle symptom scores with random effects for participant and treatment. The analysis accounted for correlation between the seven daily measurements by modelling the residual errors with a first order autoregressive error structure within each treatment period, and non-normality of the symptom scores by robust standard errors. For the primary outcome, 95% confidence intervals are presented with a two sided P value.

Comparison groups	Primary outcome analysis - placebo periods v Primary outcome analysis - statin periods
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.14

Secondary: Whether patients found their own trial result helpful in making the decision about future statin use

End point title	Whether patients found their own trial result helpful in making the decision about future statin use

End point description:

End point type	Secondary

End point timeframe:

Collected three months after the end of the participant's final treatment period

End point values	N-of-1 trial			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: Participants				
Yes	99			
No	14			

Statistical analyses

No statistical analyses for this end point

Secondary: Whether the participant had, or intended to, restart treatment with statins

End point title	Whether the participant had, or intended to, restart treatment with statins

End point description:

End point type	Secondary

End point timeframe:

Collected three months after the end of the participant's final treatment period

Statistical analyses

No statistical analyses for this end point

Secondary: Location of reported muscle symptoms

End point title	Location of reported muscle symptoms

End point description:

End point type	Secondary

End point timeframe:

Collected on the last day of each two month treatment period for the entire two month period.

End point values	Secondary outcome - location of muscle symptoms			
Subject group type	Subject analysis set			
Number of subjects analysed	140[1]			
Units: Reports				
Head and Neck	18			
Lower limbs	312			
Trunk	73			
Upper limbs	78			

Notes:

[1] - 140 participants reported 481 locations of muscle symptoms

Statistical analyses

No statistical analyses for this end point

Secondary: Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to 100) for General activity

End point title	Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to 100) for General activity

End point description:

End point type	Secondary

End point timeframe:

Collected on the last day of each two month treatment period.

End point values	Secondary outcome analysis - statin compared to placebo period			
Subject group type	Subject analysis set			
Number of subjects analysed	152			
Units: VAS units				
number (confidence interval 99%)	0.09 (-0.25 to 0.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to 100) for Mood

End point title	Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to 100) for Mood

End point description:

End point type	Secondary

End point timeframe:

Collected on the last day of each two month treatment period.

End point values	Secondary outcome analysis - statin compared to placebo period			
Subject group type	Subject analysis set			
Number of subjects analysed	152			
Units: VAS units				
number (confidence interval 99%)	0.26 (-0.04 to 0.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to 100) for Walking ability

End point title	Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to 100) for Walking ability

End point description:

End point type	Secondary

End point timeframe:

Collected on the last day of each two month treatment period.

End point values	Secondary outcome analysis - statin compared to placebo period			
Subject group type	Subject analysis set			
Number of subjects analysed	152			
Units: VAS unites				
number (confidence interval 99%)	0.11 (-0.22 to 0.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to 100) for Normal work (includes both work outside the home and housework)

End point title	Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to 100) for Normal work (includes both work outside the home and housework)

End point description:

End point type	Secondary

End point timeframe:

Collected on the last day of each two month treatment period.

End point values	Secondary outcome analysis - statin compared to placebo period			
Subject group type	Subject analysis set			
Number of subjects analysed	152			
Units: VAS units				
number (confidence interval 99%)	0.15 (-0.17 to 0.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to 100) for Relations with other people

End point title	Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to 100) for Relations with other people

End point description:

End point type	Secondary

End point timeframe:

Collected on the last day of each two month treatment period.

End point values	Secondary outcome analysis - statin compared to placebo period			
Subject group type	Subject analysis set			
Number of subjects analysed	152			
Units: VAS units				
number (confidence interval 99%)	0.15 (-0.09 to 0.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to 100) for Sleep

End point title	Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to 100) for Sleep

End point description:

End point type	Secondary

End point timeframe:

Collected on the last day of each two month treatment period.

End point values	Secondary outcome analysis - statin compared to placebo period			
Subject group type	Subject analysis set			
Number of subjects analysed	152			
Units: VAS units				
number (confidence interval 99%)	-0.02 (-0.32 to 0.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to 100) for Enjoyment of life

End point title	Among patients reporting muscle symptoms, the difference in mean VAS scores (range 0 to 100) for Enjoyment of life

End point description:

End point type	Secondary

End point timeframe:

Collected on the last day of each two month treatment period.

End point values	Secondary outcome analysis - statin compared to placebo period			
Subject group type	Subject analysis set			
Number of subjects analysed	152			
Units: VAS units				
number (confidence interval 99%)	0.13 (-0.22 to 0.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence to medication

End point title	Adherence to medication

End point description:

End point type	Secondary

End point timeframe:

Collected on the last day of each two month treatment period.

End point values	Secondary outcome - adherence			
Subject group type	Subject analysis set			
Number of subjects analysed	200			
Units: Participants	200			

Attachments (see zip file)	Adherence to study medication/Adherence to study medication.

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of statins on the occurrence of muscle symptoms overall

End point title	Effect of statins on the occurrence of muscle symptoms overall

End point description:

The proportion of patients with muscle symptoms during each two-month period comparing periods of statin treatment with placebo.

End point type	Secondary

End point timeframe:

Collected on the last day of each two month treatment period.

End point values	Secondary outcome analysis - statin compared to placebo period			
Subject group type	Subject analysis set			
Number of subjects analysed	152			
Units: Odds ratio				
number (confidence interval 99%)	1.11 (0.62 to 1.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of statins on muscle symptoms that could not be attributed to a cause other than the intervention

End point title	Effect of statins on muscle symptoms that could not be attributed to a cause other than the intervention

End point description:

The proportion of patients with muscle symptoms during each two-month period who report that they believe their symptoms were caused by the study medication, comparing periods of statin treatment with placebo.

End point type	Secondary

End point timeframe:

Collected on the last day of each two month treatment period.

End point values	Secondary outcome analysis - statin compared to placebo period			
Subject group type	Subject analysis set			
Number of subjects analysed	152			
Units: Odds ratio				
number (confidence interval 99%)	1.22 (0.77 to 1.94)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From time of recruitment until completion of trial at end of final treatment period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	N-of-1 trial

Reporting group description:

All participants were randomly assigned one of 8 sequences of alternating statin or placebo treatment as an N-of-1 trial.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: On the basis that patients: (1) have had prior exposure the trial treatment, (2) the trial treatment is clinically indicated for their medical condition, and (3) the known safety profile of the trial treatment, adverse event reporting was limited to Serious Adverse Events. This approach received regulatory and ethical approval.

Serious adverse events	N-of-1 trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 200 (6.00%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Investigations			
Electrocardiogram T wave inversion	Additional description: Patient admitted 06/08/17 with epigastric pain sudden onset and lateral inferior TWI		
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Haematoma	Additional description: Large haematoma and nerve compression to right upper arm		
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Lacunar infarction			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cyst			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	N-of-1 trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 200 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2016	Added a blood test to be completed prior to consenting patients. The blood test results must be within 3 months of the screening visit. The StatinWISE team will now record the CK and ALT results from this blood test to ensure the patient is eligible. Additional exclusion criterion to reference the contra-indications listed in the SmPC for atorvastatin 20mg. Additional sites have been added
19 December 2016	Addition of all English CCGs as recruiting sites in the study.
23 May 2017	Revised Patient Information Leaflet GP surgery poster & waiting room screen display text Documents pertaining to recruitment via general advertising.
14 July 2017	The amendment is to seek approval for the materials to be used to support our recruitment plan through general advertising.
04 April 2018	The amendment is for the review and approval for the following documents that is part of our already approved process of providing each patient with their study data at the end of their participation, including revealing their treatment allocation for each treatment period and their study 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.

n/a

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33627334