



## Clinical trial results:

**Can simvastatin significantly reduce the amount of immunosuppressive medication required by patients with sight threatening uveitis? A phase IIb, single site, randomized, placebo controlled, double blinded trial.**

### Summary

EudraCT number	2014-003119-13
Trial protocol	GB
Global end of trial date	20 July 2018

### Results information

Result version number	v1 (current)
This version publication date	11 April 2019
First version publication date	11 April 2019

### Trial information

#### Trial identification

Sponsor protocol code	14/0172
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02252328
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	UCL
Sponsor organisation address	Joint Research Office, Gower Street , London , United Kingdom, WC1E 6BT
Public contact	Sue Lightman, UCL, +44 20 7566-2266, s.lightman@ucl.ac.uk
Scientific contact	Sue Lightman, UCL, +44 20 7566-2266, s.lightman@ucl.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	15 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 July 2018
Global end of trial reached?	Yes
Global end of trial date	20 July 2018
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To determine whether the mean reduction in prednisolone dosage achieved at 12 months is greater in the simvastatin group compared to the placebo treated group?

Protection of trial subjects:

Repeat clinical assessments and assessment of any adverse event. Monitoring of complete blood tests and blood chemistry including lipid and creatinine kinase levels.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2015
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	United Kingdom: 33
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	33
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The patient's recruitment process started in Sep 2015. Trial candidates were selected from the pool of patients under the care of one consultant (SL) at Moorfields Eye Hospital. Eligibility for the trial was assessed and patients were offered the trial. Participant's information sheet was given before subject's enrolment as per study protocol.

### Pre-assignment

Screening details:

A detailed medical history including current medications was performed. The information obtained were checked against the study inclusion and exclusion criteria. Finally, a consent form was obtained before subjects enrolment.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

We used an online software application (Sealed envelope) for randomising patients into the trial. A random code was generated after confirming that the patient does meet all the inclusion criteria and does not meet any exclusion criteria. During the trial subjects received double encapsulated IMPs.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Placebo drug

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

Dosage and administration details:

Placebo

<b>Arm title</b>	Simvastatin
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Arm description:

Simvastatin 80mg

Arm type	Active comparator
Investigational medicinal product name	Simvastatin 80mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Simvastatin 80mg

<b>Number of subjects in period 1</b>	Placebo	Simvastatin
Started	17	16
Completed	16	16
Not completed	1	0
Adverse event, serious fatal	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo drug	
Reporting group title	Simvastatin
Reporting group description:	
Simvastatin 80mg	

Reporting group values	Placebo	Simvastatin	Total
Number of subjects	17	16	33
Age categorical			
Units: Subjects			
Adults between 18 and 80 years old	17	16	33
Gender categorical			
Units: Subjects			
Female	11	10	21
Male	6	6	12

### Subject analysis sets

Subject analysis set title	Analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The primary outcome is prednisolone dose measured at 12 months. The main statistical analyses will estimate the difference in mean prednisolone dose between patients randomised to simvastatin and placebo by intention to treat at 12 months. Group difference estimates and corresponding confidence intervals will be reported. Initially, prednisolone dose at 12 months will be described for each treatment group using means and standard deviations. In addition, plots will be produced that show dosing over time (every 3 months) for each group and the percentage of patients whose dose is under 10mg (safe dose).

The outcome will be formally compared between treatment groups using a linear regression model (below) that adjusts for baseline dose. All modelling assumptions will be checked.

Reporting group values	Analysis		
Number of subjects	32		
Age categorical			
Units: Subjects			
Adults between 18 and 80 years old	32		
Gender categorical			
Units: Subjects			
Female	20		
Male	12		

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo drug	
Reporting group title	Simvastatin
Reporting group description:	
Simvastatin 80mg	
Subject analysis set title	Analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The primary outcome is prednisolone dose measured at 12 months. The main statistical analyses will estimate the difference in mean prednisolone dose between patients randomised to simvastatin and placebo by intention to treat at 12 months. Group difference estimates and corresponding confidence intervals will be reported. Initially, prednisolone dose at 12 months will be described for each treatment group using means and standard deviations. In addition, plots will be produced that show dosing over time (every 3 months) for each group and the percentage of patients whose dose is under 10mg (safe dose).

The outcome will be formally compared between treatment groups using a linear regression model (below) that adjusts for baseline dose. All modelling assumptions will be checked.

### Primary: Prednisolone dose at 1-year

End point title	Prednisolone dose at 1-year
End point description:	
The primary outcome is prednisolone dose measured at 12 months. The main statistical analyses will estimate the difference in mean prednisolone dose between patients randomised to simvastatin and placebo by intention to treat at 12 months. Group difference estimates and corresponding confidence intervals will be reported.	
Initially, prednisolone dose at 12 months will be described for each treatment group using means and standard deviations. In addition, plots will be produced that show dosing over time (every 3 months) for each group and the percentage of patients whose dose is under 10mg (safe dose).	
The outcome will be formally compared between treatment groups using a linear regression model that adjusts for baseline dose.	
End point type	Primary
End point timeframe:	
One year	

End point values	Placebo	Simvastatin	Analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	16 <sup>[1]</sup>	16	32	
Units: mg				
number (not applicable)	16	16	32	

Notes:

[1] - One subject did not complete primary endpoint due to fatal adverse event.

<b>Attachments (see zip file)</b>	Mean reduction in prednisolone dose at 52 weeks/Screenshot
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## Statistical analyses

<b>Statistical analysis title</b>	Prednisolone dose at 1 year
Comparison groups	Placebo v Simvastatin v Analysis
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.54 [2]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	3.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.15
upper limit	15.38
Variability estimate	Standard deviation

Notes:

[2] - The regression analysis adjusted for baseline dose suggests no significant difference at 12 months, i.e. patients in simvastatin group have higher prednisolone dose, and the mean difference is 3.62mg (95% CI: -8.15 to 15.38) with a p-value of 0.54

## Secondary: Reduction in immunosuppressive agents at 24 months

End point title	Reduction in immunosuppressive agents at 24 months
End point description:	
This will be analysed using a chi-squared test	
End point type	Secondary
End point timeframe:	
Two years	

End point values	Placebo	Simvastatin	Analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	3	2	21	
Units: numbers				
Reduction in second-line immunosuppressive agent	3	2	5	

## Statistical analyses

<b>Statistical analysis title</b>	Reduction in second-line immunosuppressive agent
Statistical analysis description:	
The total number of patients included in the analysis is 12, with 6 from each of the treatment arms. chi-square test suggests a test statistic of 0.34 with a p-value of 0.56.	
Comparison groups	Simvastatin v Placebo v Analysis

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.56 <sup>[3]</sup>
Method	Chi-squared
Parameter estimate	NA
Confidence interval	
level	95 %
sides	2-sided

Notes:

[3] - The reduction in second-line immunosuppressive agent does not differ significantly between the two groups at 5% level.

### Secondary: Number of patients with disease relapses at 24 months

End point title	Number of patients with disease relapses at 24 months
End point description:	
Disease relapses at 24 months	
The number of patients who had disease relapses at 24 months is shown below. The number of patients included in the analysis are 10 and 11 for placebo and simvastatin group, respectively. The proportion of patients who had disease relapses at 24 months is higher (45.5%) compared to that in the placebo group (10%).	
will be analysed using a chi-squared test.	
End point type	Secondary
End point timeframe:	
Two years	

End point values	Placebo	Simvastatin	Analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1	5	21	
Units: numbers				
Number of disease relapse	1	5	6	

### Statistical analyses

<b>Statistical analysis title</b>	Number of patients with disease relapse at 2 years
Statistical analysis description:	
e proportion of patients who had disease relapse by 24 months was higher in the simvastatin group (45.5%) compared to that in the placebo group (10%).	
Comparison groups	Placebo v Simvastatin
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[4]</sup>
P-value	= 0.072 <sup>[5]</sup>
Method	Chi-squared
Parameter estimate	Na

Confidence interval	
level	95 %
sides	2-sided

Notes:

[4] - The chi-square test suggests that there is weak evidence of a difference between the two groups in disease relapses

[5] - The chi-square test suggests a test statistics of 3.23 with a P-value of 0.072, therefore, the disease relapse rate does not differ significantly at 5% level.

### Secondary: Mean reduction in prednisolone dose at two years

End point title	Mean reduction in prednisolone dose at two years
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End point description:

Prednisolone dose at 24 months

The number of patients included in the secondary analysis is 11 and 10 for simvastatin and placebo group, respectively. The results from the regression analysis suggest that there is little difference in mean prednisolone dose between the groups at 24 months (difference: -0.3 (Simvastatin.-Placebo.) 95% CI: -4.7 to 4.0, P = 0.87).

End point type	Secondary
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End point timeframe:

Two years

End point values	Placebo	Simvastatin	Analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	17	16	21 <sup>[6]</sup>	
Units: mg				
arithmetic mean (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)	-0.34 (-4.71 to 4.03)	

Notes:

[6] - 10 in placebo and 11 in simvastatin

### Statistical analyses

Statistical analysis title	Prednisolone dose at 2 years
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Statistical analysis description:

Prednisolone dose at 24 months

The number of patients included in the secondary analysis is 11 and 10 for simvastatin and placebo group, respectively. The results from the regression analysis suggest that there is little difference in mean prednisolone dose between the groups at 24 months (difference: -0.3 (Simvastatin.-Placebo.) 95% CI: -4.7 to 4.0, P = 0.87).

Comparison groups	Simvastatin v Placebo v Analysis
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.87
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.71
upper limit	4.03
Variability estimate	Standard deviation
Dispersion value	0

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### Secondary: Cholesterol at 24 months

End point title	Cholesterol at 24 months
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End point description:

End point type	Secondary
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End point timeframe:

Two years

End point values	Placebo	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: mmol/L				
arithmetic mean (standard deviation)	9.92 (± 13.17)	4.56 (± 1.48)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Jan 2016 to July 2018

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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### Reporting groups

Reporting group title	Simvastatin
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

<b>Serious adverse events</b>	Simvastatin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 16 (12.50%)	3 / 17 (17.65%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Surgical and medical procedures			
Surgical procedures			
subjects affected / exposed	2 / 16 (12.50%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory, thoracic and mediastinal disorders			
Death			Additional description: Severe Sickle cell crises led to respiratory and renal failure which ended in death of that patient
subjects affected / exposed	0 / 16 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

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

<b>Non-serious adverse events</b>	Simvastatin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	17 / 17 (100.00%)	
General disorders and administration site conditions			
General symptom			
subjects affected / exposed	16 / 16 (100.00%)	17 / 17 (100.00%)	
occurrences (all)	16	17	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported