



## Clinical trial results:

### **Spironolactone for Adult Female Acne: A pragmatic multicentre double-blind randomised superiority trial to investigate the clinical and cost-effectiveness of spironolactone for moderate or severe persistent acne in women**

#### **Summary**

EudraCT number	2018-003630-33
Trial protocol	GB
Global end of trial date	31 August 2021

#### **Results information**

Result version number	v1 (current)
This version publication date	11 April 2024
First version publication date	11 April 2024
Summary attachment (see zip file)	Adverse event (bmj-2022-074349.full_result.pdf)

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	SAFA study
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##### **Additional study identifiers**

ISRCTN number	ISRCTN12892056
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

##### **Sponsors**

Sponsor organisation name	University Hospital Southampton
Sponsor organisation address	University Rd, Southampton, United Kingdom, SO17 1BJ
Public contact	Southampton Clinical Trials Unit, University of Southampton, 44 02381205596, safa@soton.ac.uk
Scientific contact	Southampton Clinical Trials Unit, University of Southampton, 44 02381205596, safa@soton.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	31 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2021
Global end of trial reached?	Yes
Global end of trial date	31 August 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

This study will measure whether spironolactone plus standard care is better than placebo plus standard care for adult women (18 years or older) with persistent acne that would normally be treated with oral antibiotics.

This will be measured using a participant-reported acne-specific Quality of Life questionnaire (Acne-QoL) at 12 weeks.

Protection of trial subjects:

None

Background therapy:

Participants in both groups could continue to use their usual topical treatments throughout the trial but adherence to topical treatment was not promoted beyond usual care. Participants were asked not to change topical treatments between baseline and 12 weeks or take oral treatments for acne other than study medication; although, women who had been on oral contraception for more than three months could continue this medication. After 12 weeks, participants in both groups could receive usual care, such as oral antibiotics, hormonal treatments, or isotretinoin, if judged necessary by their usual clinical team.

Evidence for comparator: -

Actual start date of recruitment	01 February 2019
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: 410
Worldwide total number of subjects	410
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)	410
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited through primary care (search and mail-out or opportunistic recruitment), secondary care (opportunistic recruitment), and by advertising in the community and on social media.

### Pre-assignment

Screening details:

Baseline assessments were conducted in secondary care clinics to ensure standard clinical assessments because the IGA for acne was an inclusion criterion and an important secondary outcome. Baseline appointments also included a pregnancy test, blood test (to exclude renal impairment or raised serum potassium), participant photo.

### Period 1

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

Blinding implementation details:

Participants, recruiting staff, and investigators were masked to treatment allocation until participants were unmasked at 24 weeks.

### Arms

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

Arm description:

Intervention arm - 50 mg spironolactone one tablet daily for the first six weeks and then two tablets daily (totalling 100 mg at (or after) six weeks, providing the participant was tolerating side effects. Treatment continued for 24 weeks

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

Dosage and administration details:

50 mg spironolactone (one tablet daily) for the first six weeks and then two tablets daily (totalling 100 mg) at (or after) six weeks, providing the participant was tolerating side effects. Treatment continued for 24 weeks

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

Matched placebo (one tablet daily) for the first six weeks and then two tablets daily. Treatment continued for 24 weeks.

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

Dosage and administration details:

One tablet daily for the first six weeks and then two tablets daily. Treatment continued for 24 weeks.

<b>Number of subjects in period 1</b>	Spironolactone	Placebo
Started	201	209
Completed	181	176
Not completed	20	33
Wanted to be referred to a local dermatology	-	1
Started medication not permissible on study	-	3
did not attend their 12-week appointment	2	1
Site closed due to Covid	4	3
Participant believed study medication not working	1	1
No longer wants to take part in study	-	5
Pregnancy	3	1
Lost to follow-up	6	15
Withdrawn due to breast cancer	-	1
Unacceptable side effects	2	2
no improvement in skin condition	1	-
Prefers not to say why	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Spironolactone
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Reporting group description:

Intervention arm - 50 mg spironolactone one tablet daily for the first six weeks and then two tablets daily (totalling 100 mg at (or after) six weeks, providing the participant was tolerating side effects. Treatment continued for 24 weeks

Reporting group title	Placebo
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Reporting group description:

Matched placebo (one tablet daily) for the first six weeks and then two tablets daily. Treatment continued for 24 weeks.

Reporting group values	Spironolactone	Placebo	Total
Number of subjects	201	209	410
Age categorical			
Units: Subjects			
Adults (18-64 years)	201	209	410
Age continuous			
Units: years			
arithmetic mean	29.4	28.7	
standard deviation	± 7.4	± 7.0	-
Gender categorical			
Units: Subjects			
Female	201	209	410
Male	0	0	0
Length of current episode of acne			
Units: Subjects			
Less than 6 month	0	0	0
6 months to 2 years	48	56	104
2-5 years	44	49	93
More than 5 years	109	104	213
Not answered	0	0	0
Participant's global assessment of current acne			
Units: Subjects			
Clear	0	0	0
Almost clear	3	1	4
Mild severity	37	49	86
Moderate severity	115	101	216
Severe	44	58	102
Not answered	2	0	2
Clinician reported (IGA scale) severity of current acne			
Units: Subjects			
Clear	0	0	0
Almost clear	0	0	0
Mild severity	92	98	190
Moderate severity	84	82	166
Severe	25	29	54

Age acne started			
Units: years			
arithmetic mean	16.1	16.7	
standard deviation	± 5.4	± 5.8	-
Acne-QoL symptom subscale score			
Units: number			
arithmetic mean	13.2	12.9	
standard deviation	± 4.9	± 4.5	-

## End points

### End points reporting groups

Reporting group title	Spironolactone
Reporting group description: Intervention arm - 50 mg spironolactone one tablet daily for the first six weeks and then two tablets daily (totalling 100 mg at (or after) six weeks, providing the participant was tolerating side effects. Treatment continued for 24 weeks	
Reporting group title	Placebo
Reporting group description: Matched placebo (one tablet daily) for the first six weeks and then two tablets daily. Treatment continued for 24 weeks.	

### Primary: Acne-QoL symptom subscale score at 6 weeks

End point title	Acne-QoL symptom subscale score at 6 weeks <sup>[1]</sup>
End point description: The primary outcome was comparison of the mean Acne-QoL symptom subscale score between groups, adjusted for baseline variables. The Acne-QoL contains 19 questions with seven response categories, each referring to the past week, reported in four domains (self-perception, role-social, role-emotional, and acne symptoms): each subscale has a range of 0-30, in which higher scores reflect improved quality of life.	
End point type	Primary
End point timeframe: 6 weeks	

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: Week 6 data are not presented as participants were not yet on full dose of spironolactone.

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176 <sup>[2]</sup>	179 <sup>[3]</sup>		
Units: number				
arithmetic mean (standard deviation)	17 (± 6)	15.6 (± 6)		

Notes:

[2] - Participants who did not finish the treatment or had a missing data excluded from the analyses

[3] - Participants who did not finish the treatment or had a missing data excluded from the analyses

### Statistical analyses

No statistical analyses for this end point

### Primary: Acne-QoL symptom subscale score at 12 weeks

End point title	Acne-QoL symptom subscale score at 12 weeks
End point description:	
End point type	Primary
End point timeframe: 12 weeks	



<b>End point values</b>	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176 <sup>[4]</sup>	166 <sup>[5]</sup>		
Units: Number				
arithmetic mean (standard deviation)	19.2 (± 6)	17.8 (± 6)		

Notes:

[4] - Participants who did not finish the treatment or had a missing data excluded from the analyses

[5] - Participants who did not finish the treatment or had a missing data excluded from the analyses

## Statistical analyses

<b>Statistical analysis title</b>	Mean differences Adjusted
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Linear
Parameter estimate	Adjusted Mean differences
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	2.46

<b>Statistical analysis title</b>	Mean differences Unadjusted
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Linear
Parameter estimate	Unadjusted mean difference
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.67

<b>Statistical analysis title</b>	Mean differences Adjusted (100 imputations)
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Statistical analysis description:

100 imputations - Adjusted for stratification factors (site and baseline severity (IGA <3 versus 3 or more)), baseline Acne-QoL symptom subscale score, topical treatment use (yes/no to using any topical

treatment), hormonal treatment, age, and polycystic ovary syndrome status.

Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Linear
Parameter estimate	Adjusted mean difference
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	2.48

### Primary: Acne-QoL symptom subscale score at 24 weeks

End point title	Acne-QoL symptom subscale score at 24 weeks
End point description:	
End point type	Primary
End point timeframe:	
24 weeks	

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163 <sup>[6]</sup>	136 <sup>[7]</sup>		
Units: Number				
arithmetic mean (standard deviation)	21.2 (± 6)	17.4 (± 6)		

Notes:

[6] - Participants who did not finish the treatment or had a missing data excluded from the analyses

[7] - Participants who did not finish the treatment or had a missing data excluded from the analyses

### Statistical analyses

<b>Statistical analysis title</b>	Mean differences Adjusted
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted mean differences
Point estimate	3.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.16
upper limit	4.75

<b>Statistical analysis title</b>	Mean differences Unadjusted
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Unadjusted mean difference
Point estimate	3.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	5.03

### Primary: Acne-QoL symptom subscale score at 52 weeks

End point title	Acne-QoL symptom subscale score at 52 weeks <sup>[8]</sup>
End point description:	
End point type	Primary
End point timeframe:	
52 weeks	

Notes:

[8] - 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: Week 52 data not presented as participants were unmasked at 24 weeks and both groups could seek any treatments after that point, including spironolactone.

<b>End point values</b>	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95 <sup>[9]</sup>	81 <sup>[10]</sup>		
Units: Number				
arithmetic mean (standard deviation)	21.7 (± 6)	20 (± 6)		

Notes:

[9] - Participants who did not finish the treatment or had a missing data excluded from the analyses

[10] - Participants who did not finish the treatment or had a missing data excluded from the analyses

### Statistical analyses

No statistical analyses for this end point

### Secondary: Self-assessed overall improvement score of 3-6 at 12 weeks

End point title	Self-assessed overall improvement score of 3-6 at 12 weeks
End point description:	
Data are number of participants/total number (percentage)	
End point type	Secondary
End point timeframe:	
12 weeks	

<b>End point values</b>	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169 <sup>[11]</sup>	159 <sup>[12]</sup>		
Units: Percentage	72	68		

Notes:

[11] - Participants who did not finish the treatment or had a missing data excluded from the analyses

[12] - Participants who did not finish the treatment or had a missing data excluded from the analyses

## Statistical analyses

<b>Statistical analysis title</b>	Unadjusted odds ratio at 12 weeks
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.96

<b>Statistical analysis title</b>	Adjusted* odds ratio at 12 weeks
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Statistical analysis description:

\*Adjusted for stratification factors (site and baseline severity (IGA <3 versus 3 or more)), baseline Acne-QoL symptom subscale score, topical treatment use (yes/no to using any topical treatment), hormonal treatment, age, and polycystic ovary syndrome status.

Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.91

## Secondary: Self-assessed overall improvement score of 3-6 at 24 weeks

End point title	Self-assessed overall improvement score of 3-6 at 24 weeks
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End point description:

End point type	Secondary
End point timeframe:	
24 weeks	

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160 <sup>[13]</sup>	128 <sup>[14]</sup>		
Units: Percentage	82	63		

Notes:

[13] - Participants who did not finish the treatment or had a missing data excluded from the analyses

[14] - Participants who did not finish the treatment or had a missing data excluded from the analyses

### Statistical analyses

Statistical analysis title	Unadjusted odds ratio at 24 weeks
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	2.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.53
upper limit	4.5

Statistical analysis title	Adjusted* odds ratio at 24 weeks
Statistical analysis description:	
*Adjusted for stratification factors (site and baseline severity (IGA <3 versus 3 or more)), baseline Acne-QoL symptom subscale score, topical treatment use (yes/no to using any topical treatment), hormonal treatment, age, and polycystic ovary syndrome status	
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	2.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	4.93

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**Secondary: Satisfaction with trial treatment, score 3-5 at 24 weeks**

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End point title	Satisfaction with trial treatment, score 3-5 at 24 weeks
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End point description:

End point type	Secondary
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End point timeframe:

24 weeks

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End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143 <sup>[15]</sup>	123 <sup>[16]</sup>		
Units: Percentage	71	43		

Notes:

[15] - Participants who did not finish the treatment or had a missing data excluded from the analyses

[16] - Participants who did not finish the treatment or had a missing data excluded from the analyses

**Statistical analyses**

Statistical analysis title	Unadjusted odds ratio at 24 weeks
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	3.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.91
upper limit	5.27

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<b>Statistical analysis title</b>	Adjusted odds ratio at 24 weeks
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Statistical analysis description:

\*Adjusted for stratification factors (site and baseline severity (IGA <3 versus 3 or more)), baseline Acne-QoL symptom subscale score, topical treatment use (yes/no to using any topical treatment), hormonal treatment, age, and polycystic ovary syndrome status.

Comparison groups	Spironolactone v Placebo
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Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	3.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	5.41

### Secondary: PGA success core at 24 weeks

End point title	PGA success core at 24 weeks
End point description:	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164 <sup>[17]</sup>	136 <sup>[18]</sup>		
Units: Percentage	32	11		

Notes:

[17] - Participants who did not finish the treatment or had a missing data excluded from the analyses

[18] - Participants who did not finish the treatment or had a missing data excluded from the analyses

### Statistical analyses

<b>Statistical analysis title</b>	Unadjusted odds ratio at 24 weeks
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	3.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.09
upper limit	7.37

<b>Statistical analysis title</b>	Adjusted odds ratio at 24 weeks
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**Statistical analysis description:**

Adjusted for stratification factors (site and baseline severity (IGA <3 versus 3 or more)), baseline Acne-QoL symptom subscale score, topical treatment use (yes/no to using any topical treatment), hormonal treatment, age, and polycystic ovary syndrome status.

Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	3.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.95
upper limit	7.28

**Secondary: IGA success score at 12 weeks**

End point title	IGA success score at 12 weeks
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168 <sup>[19]</sup>	160 <sup>[20]</sup>		
Units: Percentage	19	6		

Notes:

[19] - Participants who did not finish the treatment or had a missing data excluded from the analyses

[20] - Participants who did not finish the treatment or had a missing data excluded from the analyses

**Statistical analyses**

<b>Statistical analysis title</b>	Unadjusted odds ratio at 12 weeks
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	3.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.73
upper limit	8.27



<b>Statistical analysis title</b>	Adjusted odds ratio at 12 weeks
Comparison groups	Placebo v Spironolactone
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	5.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.18
upper limit	12.28

### Secondary: PGA success core at 12 weeks

End point title	PGA success core at 12 weeks
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

<b>End point values</b>	Spironolactone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	166		
Units: Percentage	21	12		

### Statistical analyses

<b>Statistical analysis title</b>	Unadjusted odds ratio at 12 weeks
Comparison groups	Spironolactone v Placebo
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	3.45

<b>Statistical analysis title</b>	Adjusted odds ratio at 12 weeks
Comparison groups	Placebo v Spironolactone
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	3.19

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

52 weeks

Assessment type	Non-systematic
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### Dictionary used

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Dictionary name	Acne-QoL symptom sub
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Dictionary version	1
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Frequency threshold for reporting non-serious adverse events: 0 %

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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: The adverse reaction does not have SOC terms or seriousness, just symptom and severity information.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2019	Exclusion of women who have 'ever taken spironolactone' due to unknown effect duration of spironolactone Use of social media advertising campaign as recruitment avenue
03 December 2019	Updated social media advertising campaign process Blood test results clarified as stopping criteria rather than eligibility criteria Clarification of oral antibiotic use to treat infections unrelated to acne Addition of two more CRNs as Participant Identification Centres
15 June 2020	Addition of hospital Trusts as trial sites and CRNs local to new hospital Trusts Addition of hospital Trusts as secondary care Participant Identification Centres GP Invite Card • Summary sheet for mail-out pack Revised 52-week follow-up documents: protocol, unblinding letter, PIS, ICF, Follow-up questionnaire
06 April 2021	Reduction of sample size to 398 participants Update to pregnancy reporting process wording in protocol Option of patients to send photos their acne to site team for assessment at follow-up appointments Updated process in protocol on sharing consent forms and follow-up questionnaires with Southampton CTU to facilitate follow-up during pandemic
02 August 2021	Addition of optional qualitative interviews participants taking part in the main trial Updated existing trial documents with qualitative interview sub-trial information New trial documents for qualitative interview sub-trial: Qualitative interview PIS, Qualitative interview ICF, Qualitative interview guide and invitation letter. Collection of ethnicity in retrospect using ethnicity group reply slip

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/37192767>