Effectiveness of spironolactone for women with acne vulgaris (SAFA) in England and Wales: pragmatic, multicentre, phase 3, double blind, randomised controlled trial

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ABSTRACT

OBJECTIVE

To assess the effectiveness of oral spironolactone for acne vulgaris in adult women.

DESIGN

Pragmatic, multicentre, phase 3, double blind, randomised controlled trial.

SETTING

Primary and secondary healthcare, and advertising in the community and on social media in England and Wales.

PARTICIPANTS

Women (≥18 years) with facial acne for at least six months, judged to warrant oral antibiotics.

INTERVENTIONS

Participants were randomly assigned (1:1) to either 50 mg/day spironolactone or matched placebo until week six, increasing to 100 mg/day spironolactone or placebo until week 24. Participants could continue using topical treatment.

MAIN OUTCOME MEASURES

Primary outcome was Acne-Specific Quality of Life (Acne-QoL) symptom subscale score at week 12 (range 0-30, where higher scores reflect improved QoL). Secondary outcomes were Acne-QoL at week 24, participant self-assessed improvement; investigator's global assessment (IGA) for treatment success; and adverse reactions.

RESULTS

From 5 June 2019 to 31 August 2021, 1267 women were assessed for eligibility, 410 were randomly assigned to the intervention (n=201) or control group (n=209) and 342 were included in the primary analysis (n=176 in the intervention group and n=166 in the control group). Baseline mean age was 29.2 years (standard deviation 7.2), 28 (7%) of 389 were from ethnicities other than white, with 46% mild, 40% moderate, and 13% severe acne. Mean Acne-QoL symptom scores at baseline were 13.2 (standard deviation 4.9) and at week 12 were 19.2 (6.1) for spironolactone and 12.9 (4.5) and 17.8 (5.6) for placebo (difference favouring spironolactone 1.27 (95% confidence interval 0.07 to 2.46), adjusted for baseline variables). Scores at week 24 were 21.2 (5.9) for spironolactone and 17.4 (5.8) for placebo (difference 3.45 (95% confidence interval 2.16 to 4.75), adjusted). More participants in the spironolactone group reported acne improvement than in the placebo group: no significant difference was reported at week 12 (72% *v* 68%, odds ratio 1.16 (95% confidence interval 0.70 to 1.91)) but significant difference was noted at week 24 (82% *v* 63%, 2.72 (1.50 to 4.93)). Treatment success (IGA classified) at week 12 was 31 (19%) of 168 given spironolactone and nine (6%) of 160 given placebo (5.18 (2.18 to 12.28)). Adverse reactions were slightly more common in the spironolactone group with more headaches reported (20% *v* 12%; p=0.02). No serious adverse reactions were reported.

CONCLUSIONS

Spironolactone improved outcomes compared with placebo, with greater differences at week 24 than week 12. Spironolactone is a useful alternative to oral antibiotics for women with acne.

TRIAL REGISTRATION

ISRCTN12892056

WHAT IS ALREADY KNOWN ON THIS TOPIC

First line treatments for acne are fixed combination topical therapies, but many people receive second line treatments, including long courses of oral antibiotics, leading to antibiotic resistance

Spironolactone is used off license by dermatologists for acne in women because of its anti-androgenic properties

Evidence for the benefit of spironolactone in acne is not robust

WHAT THIS STUDY ADDS

Spironolactone improved acne on all outcomes: not all outcomes were significant at 12 weeks, but all were significant at 24 weeks

Spironolactone at doses of 50 mg and 100 mg were well tolerated with mild side effects similar to placebo

Spironolactone could provide a useful alternative to oral antibiotics for women with persistent acne where first line topical treatments have not worked

Introduction

Acne vulgaris (hereafter referred to as acne) is very common in adolescence and often persists into adulthood.[1] Negative social and psychological effects can be substantial[2 3] and many people with acne have frequent health service use.[4]

UK guidance recommends fixed combination topical preparations containing retinoids, benzoyl peroxide or antibiotics as a first line treatment for mild to moderate acne or, for moderate to severe acne, a fixed combination topical agent alone or together with oral lymecycline or doxycycline.[5] National Institute for Health and Care Excellence's guidance recommends that treatment regimens that include an antibiotic

(topical or oral) should not be continued for more than six months unless in exceptional circumstances (other guidelines limit oral antibiotic duration to three months).[5-8] Yet, doctors report barriers to discontinuing oral antibiotics once they have been started.[9]

A third of people who consult with acne receive long courses of oral antibiotics (28 days or more)[10] and acne accounts for most antibiotic exposure among people of 11-21 years in England.[11] Increasing prevalence of antibiotic resistance mean that alternatives to antibiotics are urgently needed.[12 13] Spironolactone could play a role in reducing antibiotic use in acne.[14]

Spironolactone, a potassium sparing diuretic, is widely used for indications such as hypertension and has been prescribed off-license for acne for many years because of its anti-androgenic properties. US and European guidelines suggest a role for spironolactone in the management of acne in women.[6 7] However, systematic reviews have highlighted a paucity of evidence from randomised controlled trials, with the largest trial to date including only 34 participants.[15 16]

The Spironolactone for Adult Female Acne (SAFA) trial aimed to evaluate whether spironolactone improves acne in women with persistent facial acne compared with placebo, in addition to use of standard topical care.

Methods

SAFA is a pragmatic, multicentre, double blind, randomised trial with two (1:1) parallel treatment arms: spironolactone compared with placebo. A pragmatic trial design was chosen to test the intervention in a real-life context. This design included a participant reported outcome measure and allowed concomitant use of topical treatments. The trial protocol paper has been published.[17] We revised the target sample size (details later) and made amendments to allow retention of research participants during the covid-19 pandemic through flexible trial procedures, particularly through remote follow-up.

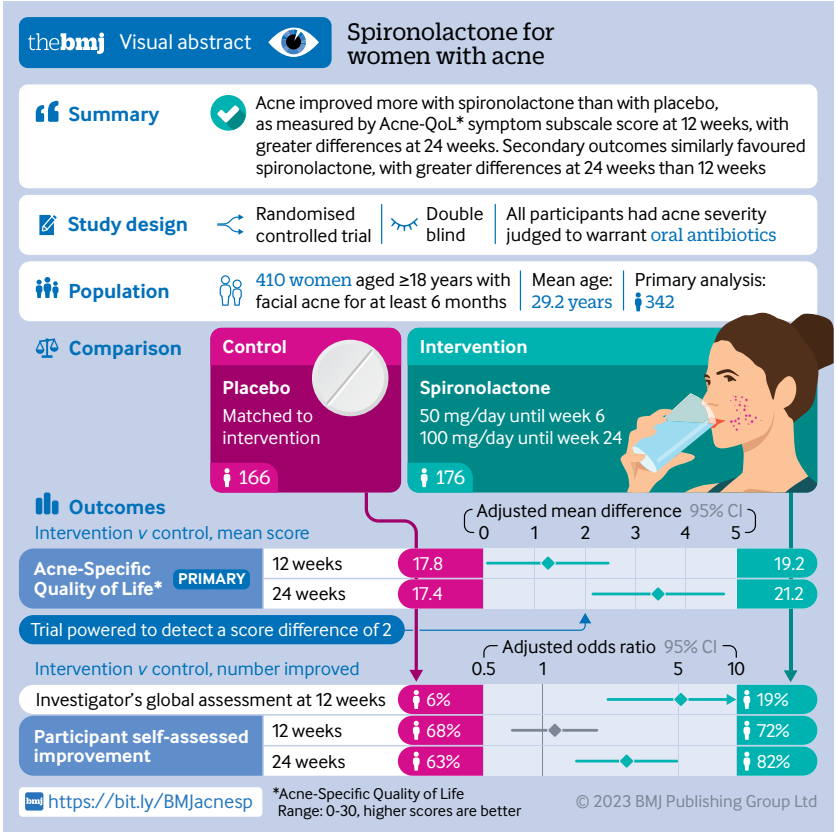
Participants

Participants were eligible for inclusion if they were women aged 18 years or over with facial acne for at least six months; had acne of sufficient severity to warrant treatment with oral antibiotics, as judged by the trial clinician; and had an investigator's global assessment (IGA) of least 2 (mild or worse). Women at risk of pregnancy had to be willing to use their usual hormonal or barrier method of contraception for the first six months of the trial and for at least four weeks afterwards. Participants had to be willing to partake and give written informed consent and had sufficient English to self-complete the Acne-Specific Quality of Life (Acne-QoL) questionnaire. We excluded potential participants if they: had a score from the IGA acne of 0-1 (clear or almost clear); had ever taken spironolactone; had taken oral isotretinoin within the past six months; had taken oral antibiotics (longer than one week) for acne within the previous month; started, stopped, or changed hormonal contraception, co-cyprindiol, or other hormonal treatment within the past three months, or were planning to start, stop, or change within the next three months; were intending to become pregnant in the next six months; were spironolactone contraindicated (eg, taking potassium sparing diuretic, angiotensin converting enzyme inhibitors, angiotensin II receptor blocker or hereditary problems of galactose intolerance); had an estimated glomerular filtration rate of less than 60 mL/min per 1.73 m^2; or had serum potassium concentrations above the upper limit of laboratory reference range.

Setting

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. 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 (to aid subsequent recall about acne changes), and contraceptive counselling. A research nurse or dermatologist, or both, conducted the baseline visit.

Participants were followed up face-to-face (or by video call or telephone due to the covid-19 pandemic) in secondary care at six weeks and 12 weeks, with a



primary outcome assessment at 12 weeks, and longer term follow-up by questionnaires at 24 weeks and up to 52 weeks.

Intervention and comparator

Trial participants were randomly assigned to receive either 50 mg spironolactone or matched placebo (one tablet daily) for the first six weeks and then two tablets daily (totalling 100 mg spironolactone or matched placebo) at (or after) six weeks, providing the participant was tolerating side effects. Treatment continued for 24 weeks in both groups.

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.

In both groups, spironolactone or placebo was stopped at 24 weeks, participants were informed of their treatment allocation and entered an unblinded follow-up period for up to 52 weeks. After 24 weeks, participants could seek any treatment from their usual clinical team, including spironolactone if they wished.

Outcomes

The primary outcome was comparison of the mean Acne-QoL symptom subscale score between groups at 12 weeks, 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-

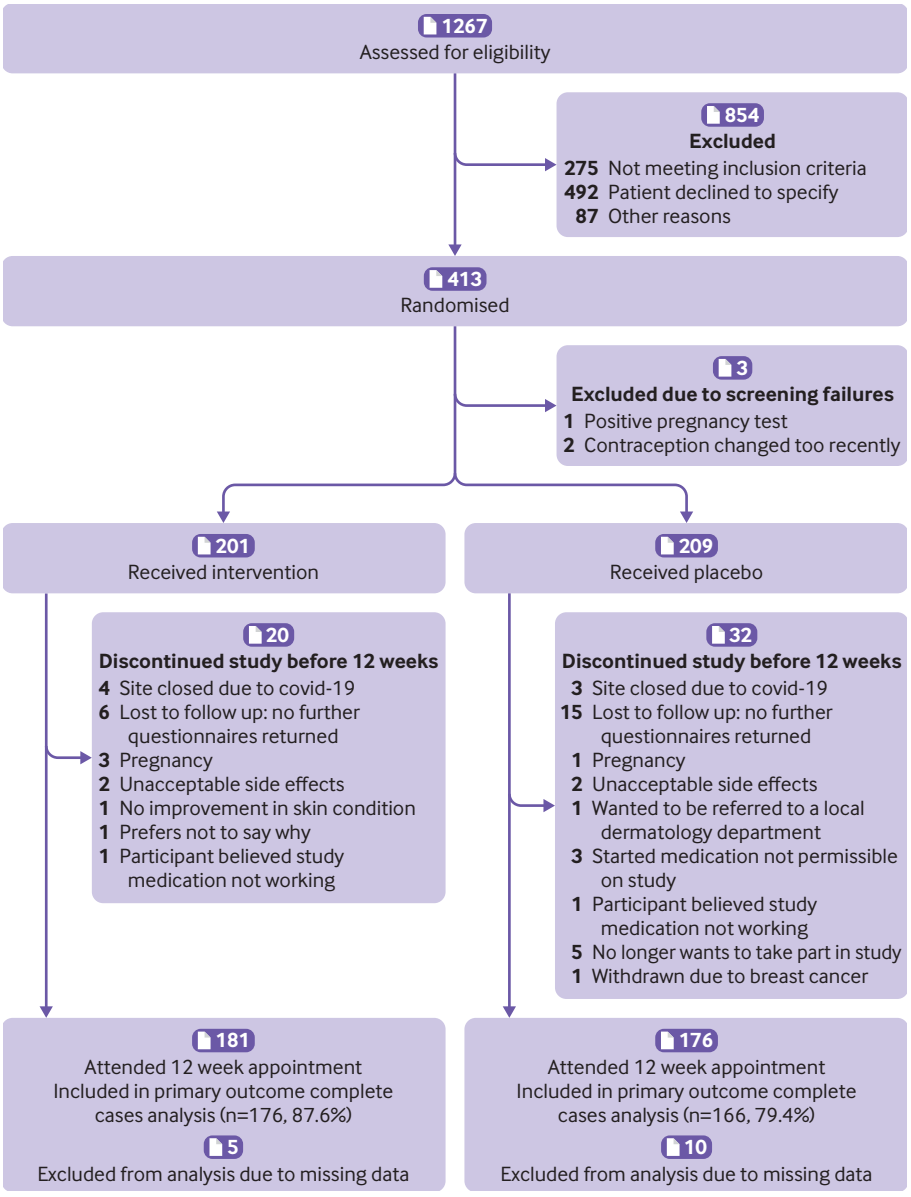


Fig 1 | Recruitment to SAFA trial

Table 1 | Participant characteristics at baseline

Characteristic	Spironolactone (n=201)	Placebo (n=209)	Total (n=410)
Age, years (mean, SD)	29.6 (7.4)	28.7 (7.0)	29.2 (7.2)
Ethnic group*:			
White	158 (84)	170 (85)	328 (84)
Asian	5 (3)	4 (2)	9 (2)
Black	4 (2)	2 (1)	6 (2)
Mixed	6 (3)	3 (2)	9 (2)
Other	1 (1)	3 (2)	4 (1)
Prefer not to answer	14 (8)	19 (10)	33 (9)
Missing data	13 (7)	8 (4)	21 (5)
Body mass index (mean, SD)	25.7 (5.3)	26.5 (5.9)	26.1 (5.6)
Where the participant heard about the trial:			
Community advertising	12 (6)	15 (7)	27 (7)
General Practitioner	35 (17)	29 (14)	64 (16)
Online search	6 (3)	10 (5)	16 (4)
Secondary care	38 (19)	43 (21)	81 (20)
Social media advertising	98 (49)	97 (46)	195 (48)
Word of mouth	12 (6)	15 (7)	27 (7)
Polycystic ovary syndrome diagnosis or suspected*†:	30 (15)	47 (23)	77 (19)
Missing data	6 (3)	7 (3)	13 (3)
IGA 3 or more	109 (54)	111 (53)	220 (54)
Length of current episode of acne:			
<6 months	0 (0)	0 (0)	0 (0)
6 months to 2 years	48 (24)	56 (27)	104 (25)
2-5 years	44 (22)	49 (23)	93 (23)
>5 years	109 (54)	104 (50)	213 (52)
Not answered	0 (0)	0 (0)	0 (0)
Age acne started, years (mean, SD)	16.1 (5.4)	16.7 (5.8)	16.4 (5.6)
Acne-QoL symptom subscale score (mean, SD)	13.2 (4.9)	12.9 (4.5)	13.0 (4.7)
Participant's global assessment of current acne:			
Clear	0 (0)	0 (0)	0 (0)
Almost clear	3 (1)	1 (0.5)	4 (1)
Mild severity	37 (18)	49 (23)	86 (21)
Moderate severity	115 (57)	101 (48)	216 (53)
Severe	44 (22)	58 (28)	102 (25)
Not answered	2 (1)	0 (0)	2 (1)
Clinician reported (IGA scale) severity of current acne:			
Clear	0 (0)	0 (0)	0 (0)
Almost clear	0 (0)	0 (0)	0 (0)
Mild severity	92 (46)	98 (47)	190 (46)
Moderate severity	84 (42)	82 (39)	166 (40)
Severe	25 (12)	29 (14)	54 (13)

Data are number (percentage), unless otherwise mentioned. IGA=investigator's global assessment; SD=standard deviation; QoL=quality of life.
*These statistics or percentages are calculated using the number of participants with non-missing information available.
†19 (63%) of 30 participants in the spironolactone group and 22 (47%) of 47 in the placebo group did not report having a diagnosis of polycystic ovary syndrome but were classified as having suspected polycystic ovary syndrome according to the Rotterdam criteria.

emotional, and acne symptoms): each subscale has a range of 0-30, in which higher scores reflect improved quality of life.[18 19]

Effectiveness of acne treatments is usually judged clinically at 8-12 weeks so we chose 12 weeks for our primary outcome. Results from a survey that was done before the trial (see protocol paper[17]) suggested that people with persistent acne might not be willing to be in the placebo group for longer than 12 weeks, which supported use of this time point. However, blinded treatment continued to 24 weeks to assess medium term outcomes with further unblinded follow-up beyond this.

Secondary outcomes included: Acne-QoL symptom subscale score at weeks 6, 24, and up to 52; other subscales of Acne-QoL (self-perception, role-emotional, and role-social) and total score at weeks 6, 12, 24, and up to 52; participant self-assessed overall improvement on a six point Likert scale (with baseline photo to aid recall) at weeks 6, 12, 24, and up to 52;[20] Change in IGA score from baseline to week 12;[21] participant's global assessment (five point scale same as IGA but in plain English) change from baseline at weeks 6, 12, 24, and up to 52; participant satisfaction with trial treatment asked before treatment allocation is revealed at 24 weeks ("do you think the tablets you received in this trial have helped your skin?," measured on a scale of 0 ("not at all") to 5 ("a lot") with higher scores indicating increased satisfaction with treatment); health-related quality of life (measured by use of EQ-5D-5L)[22] at weeks 6, 12, 24, and up to 52 weeks; adverse reactions of special interest asked at weeks 6, 12, 24, and up to 52 weeks; use of oral acne treatment during follow-up (eg, antibiotics and isotretinoin). We also measured resource use (ie, medication, health service use, and costs related to acne incurred by participant), which will be reported separately.

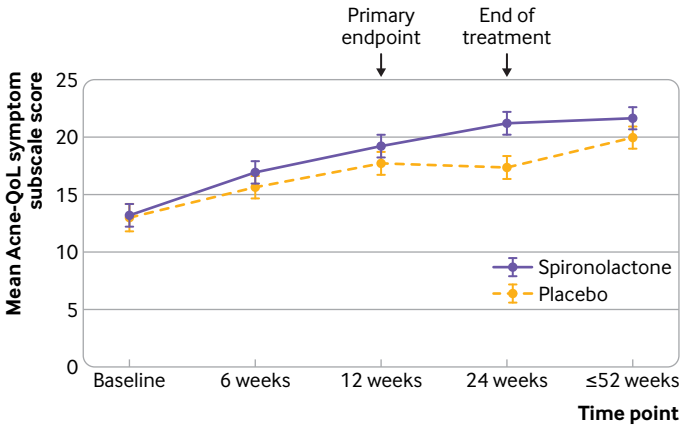


Fig 2 | Mean Acne-QoL symptom subscale score by time point for each treatment group. QoL=quality of life

Sample size

Based on a comparison of Acne-QoL symptom subscale scores between two groups at 12 weeks, at a power of 90%, α of 0.05, and seeking a difference of two points between groups (effect size 0.35 with a 1:1 treatment allocation ratio),[23] a total target sample size of 346 participants was initially estimated, or 434 participants allowing for 20% loss to follow-up. During the trial, the target sample size was reduced to allow for correlation between baseline and follow-up measures. Allowing for a correlation with baseline of 0.293 and a deflation factor of $1-\rho^2$,[24] the revised target sample size was 398 participants, 199 per arm (including 20% loss to follow up).

Randomisation and masking

Participants were randomly assigned in a 1:1 ratio to either spironolactone or matched placebo, by use of an independent web-based system (TENELEA) and varying blocks of size two and four, stratified by recruitment centre and baseline severity (IGA of less than 3 *v* 3 or 4). The allocation sequence was generated by the system.

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

Statistical methods

The modified intention-to-treat population consisted of all participants who have been randomly assigned to a treatment arm, regardless of compliance, and had complete data for the outcome and time point being analysed. All analyses were conducted in the modified intention-to-treat population. The frequency and pattern of missing data were examined, and a sensitivity analysis for the primary outcome was carried out by use of multiple imputation by chained equations, including all outcomes and covariates used in the final analysis. 100 imputed datasets were generated.

For the primary analyses, descriptive statistics were used to characterise recruited participants and assess baseline comparability between groups. For the primary outcome, a linear regression model was used to analyse Acne-QoL symptom subscale at week 12, adjusting for baseline variables (ie, "stratification factors, baseline Acne-QoL symptom subscale score, topical treatment use, hormonal treatment use, age, and polycystic ovary syndrome status). A 95% confidence interval for the least squares mean difference between groups in Acne-QoL symptom subscale at 12 weeks was calculated. We used the same analysis methods to summarise Acne-QoL symptom subscale at other time points (weeks 6, 24, and up to 52 after baseline) and for the other Acne-QoL subscales (self-perception, role-emotional, and role-social) and total score.

The IGA and participant's global assessment at weeks 6, 12, and 24 were dichotomised as a success or not a success as recommended by the US Food and Drug Administration[21] (with success for IGA and participant's global assessment defined as clear or almost clear (grade 0 or 1) and at least a two grade improvement from baseline, representing a clinically meaningful outcome). Participants' comparison with their baseline photo at weeks 6, 12, and 24 was dichotomised as a success (slight improvement; moderate improvement; excellent improvement or completely cleared) or not a success (no improvement or worse). Participants' satisfaction with trial treatment (0-5, with 0 "not at all" and 5 "a lot") was also dichotomised (0 to 2 *v* 3 to 5). Dichotomised outcomes were compared by group using logistic regression, adjusting for the same baseline variables as the primary analysis.

Polycystic ovary syndrome status was based on participants' self-report of a diagnosis plus investigator determined suspected polycystic ovary syndrome based on the Rotterdam criteria,[25] which define suspected polycystic ovary syndrome as having oligo/anovulation (missed or infrequent periods) in addition

Table 2 | Primary outcome: Acne-QoL symptom subscale score

	Spironolactone (n=201)		Placebo (n=209)		Mean difference		
Time	Participants	Mean score	Participants	Mean score	Unadjusted*	Adjusted*	Adjusted† (100 imputations)
Week 6	176	17.0 (6)	179	15.6 (6)	NA	NA	NA
Week 12	176	19.2 (6)	166	17.8 (6)	1.48 (0.30 to 2.67)	1.27 (0.07 to 2.46)	1.26 (0.04 to 2.48)
Week 24	163	21.2 (6)	136	17.4 (6)	3.77 (2.50 to 5.03)	3.45 (2.16 to 4.75)	NA
Week 52	95	21.7 (6)	81	20.0 (6)	NA	NA	NA

Data are number, mean (standard deviation), or mean difference (95% CI). CI=confidence interval; IGA=investigator's global assessment; NA=not applicable; QoL=quality of life.
*Week 6 data are not presented as participants were not yet on full dose of spironolactone. Week 52 data not presented as participants were unmasked at 24 weeks and both groups could seek any treatments after that point, including spironolactone.
†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.

Table 3 | Secondary outcomes

Outcome	Spironolactone (%)	Placebo (%)	Unadjusted odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
Self-assessed overall improvement score of 3-6:				
12 weeks	122/169 (72)	108/159 (68)	1.23 (0.76 to 1.96)	1.16 (0.70 to 1.91)
24 weeks	131/160 (82)	81/128 (63)	2.62 (1.53 to 4.50)	2.72 (1.50 to 4.93)†
Satisfaction with trial treatment, score 3-5:				
24 weeks	101/143 (71)	53/123 (43)	3.18 (1.91 to 5.27)	3.12 (1.80 to 5.41)†
PGA success score:				
12 weeks	36/176 (21)	20/166 (12)	1.91 (1.05 to 3.45)	1.69 (0.89 to 3.19)
24 weeks	53/164 (32)	15/136 (11)	3.93 (2.09 to 7.37)	3.76 (1.95 to 7.28)†
IGA success score:				
12 weeks	31/168 (19)	9/160 (6)	3.78 (1.73 to 8.27)	5.18 (2.18 to 12.28)†

Data are number of participants/total number (percentage), unless otherwise specified. CI=confidence interval; IGA=investigator's global assessment; PGA=participant's global assessment; QoL=quality of life.
*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.
†Statistically significant differences indicated.

to hyperandrogenism (excess facial and body hair or female pattern baldness) or polycystic ovaries on ultrasound. No ultrasounds were done in this study so participants were assigned as suspected polycystic ovary syndrome if they had the other criteria to qualify as having suspected polycystic ovary syndrome (missed or infrequent periods and excess hair or female pattern baldness).

Prespecified subgroup analyses explored treatment effect by polycystic ovary syndrome status, age (<25 years *v* ≥25 years), by higher and lower baseline IGA scores, use of hormonal co-treatments (yes/no), and use of topical co-treatments (yes/no). Descriptive statistics were used to describe differences in mean Acne-QoL symptom subscale score before the covid-19 pandemic and after and among different self-reported ethnic groups.

We used a complier average causal effect (known as CACE) analysis to compare compliant participants (ie, those who reported that they took their study medication) in the intervention group with those in the control group. Compliance was defined as reporting taking at least 80% of the study medication over the 12-24 week period (because data were scarce at 12 weeks). To explore the sensitivity of this analysis to the definition of compliance, we also completed two further sensitivity analyses defining compliance as taking 100% of the trial medication and 50% of the trial medication. Compliance was presented by frequencies and percentages and compared by groups with a single equation instrumental variables regression model adjusting for baseline variables.

Adverse reactions of special interest and serious adverse events were summarised by group with frequencies and percentages and compared with Pearson's χ^2 tests.

The same analysis methods were applied to the outcomes collected at up to 52 weeks; however, the interpretation of these results was assessed with caution because participants were no longer masked to treatment use and could have started a different acne treatment.

We used Stata or SAS for all analyses. No interim analyses were planned or conducted.

Patient and public involvement

A James Lind Alliance Priority Setting Partnership on acne prioritised the research question about how to manage acne in women who might or might not have underlying hormonal abnormalities.[26] This could have led to the funding call on this topic.

We gained feedback on key questions relating to research design from a virtual, acne specific, patient panel, as well as a patient survey carried out with the support of the UK Dermatology Clinical Trials Network. Findings suggested that participants would find abstaining from using topical treatments difficult and that asking participants to take a placebo for one year would be a barrier to recruitment. These findings strongly influenced our design decisions around use of topical treatments in the trial and choice of primary outcome at 12 weeks with unmasking at 24 weeks.

Two public contributors (IS and KT) with experience of acne were members of the trial management group and influenced design decisions. For instance, they highlighted that the originally planned upper age limit of 50 years was arbitrary, which was then abandoned, and they also contributed to our choice of primary and secondary outcomes. They also ensured that trial procedures were feasible for participants and that trial materials were readable and included all relevant information that participants would want. Although no specific charities are available to liaise with in the field of acne, public contributors will be involved in sharing the results and have suggested routes to dissemination.

Results

Participant characteristics

We recruited participants from 5 June 2019 to 31 August 2021 with an enforced pause from 23 March 2020 to 11 June 2020 due to the covid-19 pandemic. A total of 1267 women were assessed for eligibility, 413 were randomly assigned from 10 centres in England and Wales (supplementary table S1). Three

Table 4 | Menstrual bleeding information and adverse reactions of special interest collected by participant questionnaire from consent up to 24 weeks

Characteristic	Spironolactone (n=201)	Placebo (n=209)	Total (n=410)	p value
Irregular menstrual bleeding in the 12-24 week period*:				
Yes	57 (32)	61 (35)	118 (33)	—
No/do not have periods	123 (68)	112 (65)	235 (67)	0.47
Missing†	21 (11)	36 (17)	57 (14)	—
At least one adverse reaction:	128 (64)	107 (51)	235 (57)	0.01
Summary of adverse reactions‡:				
Abdominal pain	9 (5)	10 (5)	19 (5)	0.88
Breast enlargement	31 (15)	25 (12)	56 (14)	0.31
Diarrhoea	7 (4)	11 (5)	18 (4)	0.38
Dizziness/vertigo/light headedness	38 (19)	26 (12)	64 (16)	0.07
Drowsiness/sleepiness	14 (7)	18 (9)	32 (8)	0.53
Fatigue/tiredness	23 (11)	29 (14)	52 (13)	0.46
Headache	41 (20)	25 (12)	66 (16)	0.02
Indigestion/heartburn/dyspepsia	23 (11)	17 (8)	40 (10)	0.26
Nausea/feeling sick	21 (11)	16 (8)	37 (10)	0.32
Polyuria (passing much more urine than usual)	62 (31)	52 (25)	114 (28)	0.18
Reduced libido	15 (8)	11 (5)	26 (6)	0.36
Tenderness of the breasts	40 (20)	37 (18)	77 (19)	0.57
Tingling	6 (3)	10 (5)	16 (4)	0.35
Vomiting/being sick	4 (2)	1 (1)	5 (1)	0.16
Weight gain	13 (7)	17 (8)	30 (7)	0.52
Other	34 (17)	22 (11)	56 (14)	0.06

Data are number of participants (percentage), unless otherwise specified and p values are from Pearson's x^2 test.
*Calculated using the no. of participants with non-missing information available.
†Calculated as the no. of participants with this information missing (ie, did not provide period information at any of the time points) divided by those with period information available.
‡Calculated using the no. of participants in the spironolactone/placebo group.

participants were removed from analyses after being randomly assigned because two had recently changed contraception and one had a pregnancy test that was incorrectly done after randomisation. This change led to 201 women being assigned the intervention and 209 being assigned placebo. The primary outcome data were provided for 176 (88%) of 201 participants in the intervention group and 166 (79%) of 209 in the control group (fig 1). Participant characteristics were well balanced at baseline (table 1).

Of 410 participants, almost half were recruited through social media advertising, followed by through secondary care, primary care, community advertising, word of mouth, and participants' online search (table 1).

At baseline, 340 (84%) of 407 participants reported that they were using or had used topical treatments and 172 (42%) of 410 were using hormonal treatments. Percentages of participants using topical treatment and hormonal treatment at baseline were similar in both groups (table S2).

At baseline, 406 (99%) of IGA were carried out face-to-face with the three completed by photo and one by video consultation. Of 410 women assessed at baseline 190 (46%) had mild acne, 166 (40%) had moderate acne, and 54 (13%) had severe acne. At 12 weeks, 192 (59%) of 327 were carried out face to face (97 (58%) of 168 in spironolactone group and 95 (60%) of 159 in placebo group), with 102 (31%) of 327 assessed by photo and 33 (10%) of 327 by video consultation. Assessments of baseline acne severity are shown in table 1.

Most women (364 (98%) of 410) increased to two tablets per day at their six week visit. The proportion of women on two tablets per day between six and 12 weeks was 343 (96%) of 358 and between 12 weeks and 24 weeks was 282 (90%) of 314, with similar percentages for both groups.

Primary outcome

Acne-QoL symptom subscale scores improved in both groups, with higher scores in the spironolactone group, indicating greater improvement (fig 2 and table 2). At 12 weeks, the mean Acne-QoL symptom subscale score was 19.2 (standard deviation 6.1) in the spironolactone group and 17.8 (5.6) in the placebo group, giving a mean difference of 1.27 (95% confidence interval 0.07 to 2.46) after adjusting for baseline variables. This difference is small but represents a statistically significant greater improvement in the spironolactone group. The sensitivity analysis on multiply imputed data gave similar results and inferences (table 2).

At 24 weeks, the spironolactone group had larger improvements in the Acne-QoL symptom subscale compared with the placebo group (table 2): mean difference between groups in the adjusted analysis was 3.45 (2.16 to 4.75), which represents a statistically significant greater improvement in the spironolactone group.

Secondary outcomes

Participants in the spironolactone group were more likely to report overall acne improvement from baseline photo than those in the placebo group (table 3). Although this difference was not statistically significant at 12 weeks, the odds ratio was larger and statistically significant at 24 weeks (table 3). Post hoc analyses showed that this result equated to a number

needed to treat of 5 (95% confidence interval 3 to 12) at 24 weeks.

Using the IGA score, clinicians were significantly more likely to consider treatment as successful for participants in the spironolactone group at 12 weeks (table 3). The IGA was not measured at 24 weeks because no face-to-face assessments were done at this point. The adjusted odds ratio from the participant's global assessment score at 12 weeks was not statistically significant, but was statistically significant at 24 weeks in favour of the spironolactone group (table 3).

Before unblinding at 24 weeks, a significantly higher proportion of people receiving spironolactone felt satisfied that their skin had been helped compared with those receiving placebo (table 3; number needed to treat of 4 (95% confidence interval 3 to 6)).

The results for all the other Acne-QoL subscales and for total Acne-QoL score at 12 and 24 weeks were also statistically significant in favour of the spironolactone group (appendix table S4).

Although numbers are small, up to 52 weeks, fewer women in the spironolactone group than in the placebo group reported that they were taking oral antibiotics (six (6%) of 103 *v* 12 (14%) of 89) or isotretinoin (two (2%) of 103 *v* six (7%) of 89) (appendix table S5). At the time of the final follow-up questionnaire (up to 52 weeks), women in both groups reported continuing or commencing spironolactone: 36 (35%) of 103 women in the intervention group and 25 (28%) of 89 in the control group reported that they were taking this medication.

Subgroup analyses

Prespecified subgroup analyses show that the only statistically significant interaction term was for age (categorised as <25 years and ≥25 years), suggesting that spironolactone is a more effective treatment for acne among women 25 years and older. However, the number of women in the trial younger than 25 years was small (n=44) and, therefore, conclusions are not definitive. Subgroup analyses show that participants allocated to spironolactone showed similar benefit in acne outcomes on other key characteristics, regardless of baseline acne severity (IGA), body mass index, polycystic ovary syndrome status, ethnic group, topical treatment use, or hormonal treatment use (appendix table S6).

Treatment adherence

At 24 weeks, 195 (74%) of 264 women reported taking at least 80% of study medication. The results from the complier-average causal effect analysis on self-reported treatment adherence showed that treatment effect was greater among women who met this adherence threshold (adjusted mean difference in Acne-QoL symptom subscale 5.13 (95% confidence interval 3.17 to 7.08). Treatment adherence could be assessed only over the period from 12 weeks to 24 weeks because data collection before this time point was poorly reported, in part due to the covid-19 pandemic, because pill count at six weeks and 12 weeks was initially planned but often not possible.

For all thresholds of compliance (50%, 80%, and 100%), the proportion of participants meeting compliance were similar in both spironolactone and placebo groups, suggesting that spironolactone was well tolerated (table S7).

Adverse reactions and events

Adverse reactions of special interest were included in the participant questionnaire (table 4). Most adverse reactions were mild, but overall adverse reactions were slightly more common among women on spironolactone compared with placebo (128 (64%) of 201 *v* 107 (51%) of 209), mainly driven by differences in numbers who had headaches and dizziness. We did not identify any serious adverse reactions related to study medication.

Discussion

We found that women reported greater improvements in acne when taking spironolactone than placebo, as measured by the Acne-QoL symptom subscale score at 12 weeks, with more substantial differences at 24 weeks. Secondary outcomes similarly favoured spironolactone, showing greater differences at 24 weeks than 12 weeks. The only difference not statistically significant was that participants' report of overall acne improvement at 12 weeks but at 24 weeks the difference was substantial and statistically significant. The number needed to treat for participants to report that their acne had improved was five at 24 weeks. The number needed to treat that is based on a participant report of overall improvement is likely to be easier to convey to patients than the number needed to treat based on scores or scales.

Adverse reactions to study medications were commonly reported in both groups; more frequent headaches in the intervention group over the placebo group was the only significant difference between groups. Our trial design included starting all participants on 50 mg spironolactone or matched placebo (one tablet daily) and increasing to two tablets daily at six weeks if tolerated. More than 95% of participants in both groups tolerated the treatment and increased their dosage after six weeks. Treatment adherence was similar in both groups, further supporting the suggestion that spironolactone was well tolerated on this dosing regimen.

Strengths and limitations

To our knowledge, the Spironolactone for Adult Female Acne (SAFA) trial is the largest randomised trial to date evaluating the effectiveness of spironolactone in the treatment of acne. We designed a pragmatic trial to inform real world decision making for women with acne and to reflect the potential role of spironolactone in the clinical pathway. As such, we allowed participants in both groups to continue to use their usual topical treatments for acne alongside study medication.

At the start of this trial, few outcome measures that were participant reported were validated for acne, therefore, we chose the Acne-QoL symptoms subscale as the primary outcome, although more recent measures

might have advantages.[27] Results from an exploration of the minimum clinically important difference for the Acne-QoL showed no firm conclusions and further research was suggested.[23] We based our sample size calculation on seeking to detect a difference of two points at week 12 between groups and, although all of the results were statistically significant, the week 12 symptoms subscale score (primary outcome) point estimate of 1.27 does not exceed the two point target, although the 95% confidence interval of 0.07 to 2.46 does include this value. At week 24, the difference of 3.45 clearly exceeds this target (95% confidence interval 2.16 to 4.75). Furthermore, the strength of evidence from the secondary outcomes points towards spironolactone as an effective treatment for women with acne.

Adaptions during the covid-19 pandemic were crucial to completing the trial but led to limitations, including remote follow-up visits (via phone or video call), limited collection of investigator assessed acne severity, and reduced availability of data for treatment adherence. Many participants were not seen face-to-face at 12 weeks; therefore, we based the analysis on self-report over the period from 12 weeks to 24 weeks (rather than pill count at 12 weeks as originally planned) as a useful secondary analysis and the best estimate of treatment adherence available. A slightly lower rate of follow up in the placebo group (79% *v* 88%) seems unlikely to have artificially inflated treatment effect because this would only occur if women in the placebo group who had noted more improvement had not returned questionnaires.

Comparison with other studies

The similarity in reporting of side effects between groups in this trial is reassuring because previous research suggests that side effects are common, particularly menstrual irregularities, but this might be a feature of higher doses of spironolactone.[15] In this trial, women were started on 50 mg daily of spironolactone, which increased to 100 mg daily at or after six weeks if tolerated. We found that more than 95% of women did increase their dose to 100 mg. We might have seen greater effect of spironolactone at 12 weeks if participants had commenced on 100 mg. Starting at this dose, and then down titrating only if side effects develop, might lead to more rapid improvement in acne symptoms.

Implications for future research

Two ongoing trials of spironolactone in acne both chose a higher starting dose of spironolactone (100 mg and 150 mg) and the data for tolerability, adherence, and adverse effects will be interesting in these trials.[28 29] Outcomes of these might also provide opportunities for meta-analysis and greater power to examine effects within subgroups, particularly age, body mass index, and ethnicity.

Implications for health care

Although spironolactone has been used widely in the community to treat hypertension and some related disorders, the medication is not licensed for the management of acne and some clinicians might be reticent to prescribe it off license in this context. The findings from this trial show the effectiveness, safety, and tolerability of spironolactone in women with acne. Adopting a combined approach using oral spironolactone and topical agents has the potential to reduce the long term prescribing of oral antibiotics and therefore to reduce the likelihood of emerging bacterial resistance. Treatment courses of spironolactone over three months are likely of greater benefit than shorter treatment duration.

Participants were given contraceptive advice at each visit and a pregnancy test was carried out at baseline, yet despite this measure, seven pregnancies were reported in the trial. Although spironolactone is cautioned against in pregnancy, the effects are probably less teratogenic than oral tetracyclines,[30] which are commonly used for acne in young women, so in usual practice, spironolactone would be treated with no special restriction beyond contraceptive counselling. Consensus is growing that, although baseline checks of renal function and potassium levels is advisable before starting patients on spironolactone, ongoing monitoring is unnecessary for most young women.[6 15]

Overall, spironolactone provides a safe and effective alternative to oral antibiotics for adult women with persistent acne.

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The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned and registered have been explained.

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Web appendix: Online appendix