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APPENDIX

Table S1 – Participant recruitment centres[1]

Characteristic	Spironolactone (n=201)	Placebo (n=209)	Total (n= 410)
Centre – n (%)[2]			
Bristol Royal Infirmary	34 (16.9%)	36 (17.2%)	70 (17.1%)
Epsom Hospital	7 (3.5%)	8 (3.8%)	15 (3.7%)
Harrogate District Hospital	43 (21.4%)	46 (22.0%)	89 (21.7%)
Nottingham University Hospitals NHS Trust – Queen's Medical Centre Campus	14 (7.0%)	14 (6.7%)	28 (6.8%)
Poole General Hospital	26 (12.9%)	26 (12.4%)	52 (12.7%)
Queen Elizabeth Hospital (Birmingham)	23 (11.4%)	25 (12.0%)	48 (11.7%)
Singleton Hospital (Swansea)	3 (1.5%)	4 (1.9%)	7 (1.7%)
St Mary's General Hospital (Portsmouth)	42 (20.9%)	42 (20.1%)	84 (20.5%)
St Mary's Hospital (HQ) (London)	6 (3.0%)	5 (2.4%)	11 (2.7%)
University Hospital of Wales (Cardiff)	3 (1.5%)	3 (1.4%)	6 (1.5%)

[1] The numbers in this table relate to those with a baseline characteristics form available.

[2] These statistics are calculated using the number of participants with non-missing information available.

[3] This percentage is calculated as the number of participants with this information missing divided by those with the information available.

Table S2 – Baseline treatment use[1]

Characteristic	Spironolactone (n=201)	Placebo (n=209)	Total (n=410)
Have you used, or are you currently using, topical treatments (creams/lotions/gels) for your acne?- n (%)[2]			
Yes	169 (84.9%)	171 (82.2%)	340 (83.5%)
No	30 (15.1%)	37 (17.8%)	67 (16.5%)
Missing – n (%)[4]	2 (1.0%)	1 (0.5%)	3 (0.7%)
If Yes[3]:			
Benzoyl peroxide	22/165 (13.3%)	30/168 (17.9%)	52/333 (15.6%)
Azelaic acid	10/165 (6.1%)	15/167 (9.0%)	25/332 (7.5%)
Topical adapalene	22/167 (13.2%)	21/167 (12.6%)	43/334 (12.9%)
Nicotinamide	9/165 (5.5%)	3/167 (1.8%)	12/332 (3.6%)
Antibiotic	8/167 (4.8%)	6/167 (3.6%)	14/334 (4.2%)
Combination	28/167 (16.8%)	21/168 (12.5%)	49/335 (14.6%)
Other	20/137 (14.6%)	25/148 (16.9%)	45/285 (15.8%)
Not sure	7/134 (5.2%)	7/147 (4.8%)	14/281 (5.0%)
If topical treatments have been prescribed, how often are they used?[2]			
Not at all	17 (8.5%)	32 (15.3%)	49 (12.0%)
Less than once a day	16 (8.0%)	19 (9.1%)	35 (8.6%)
Once a day	62 (31.0%)	58 (27.8%)	120 (29.3%)
Twice a day	25 (12.5%)	20 (9.6%)	45 (11.0%)
More than twice a day	1 (0.5%)	2 (1.0%)	3 (0.7%)
Not been prescribed topical treatments	64 (32.0%)	64 (30.6%)	128 (31.3%)
Not answered	16 (8.0%)	14 (6.7%)	30 (7.3%)

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Characteristic	Spironolactone (n=201)	Placebo (n=209)	Total (n=410)
Is the participant currently using any hormonal treatment – n (%)[2]			
Yes	81 (40.3%)	91 (43.5%)	172 (42.0%)
No	120 (59.7%)	118 (56.5%)	238 (58.1%)
If 'Yes', please state which hormonal treatment[5]			
Combined oral contraception[6]	27 (33.3%)	22 (24.2%)	49 (28.5%)
Progesterone only pill or other progesterone only contraception[7]	54 (66.7%)	69 (75.8%)	123 (71.5%)

[1] The numbers in this table relate to those with acne medication available.

[2] These statistics or percentages are calculated using the number of participants with non-missing information available.

[3] These percentages are calculated using the number of participants who are currently using topical treatments or currently using topical treatments and have also been using them in the past divided by those with non-missing information.

[4] This percentage is calculated as the number of participants with this information missing divided by those with acne medication information/contraception information available.

[5]These statistics or percentages are calculated using the number of participants who answered yes to using hormonal treatment.

[6] Participants taking co-cyprindiol are included in 'combined oral contraception'. There were 5 participants who reported taking co-cyprindiol, 3 in the spironolactone group and 2 in the placebo group.

[7]Other progesterone only contraception includes: contraceptive implant, IUCS or contraceptive injection

Table S3 Baseline assessments of acne[1]

Characteristic	Spironolactone (n=201)	Placebo (n=209)	Total (n=410)
How would you describe the acne on your face at the moment? – n (%)[2]			
Clear	0 (0.0%)	0 (0.0%)	0 (0.0%)
Almost clear	3 (1.5%)	1 (0.5%)	4 (1.0%)
Mild severity	37 (18.4%)	49 (23.4%)	86 (21.0%)
Moderate severity	115 (57.2%)	101 (48.3%)	216 (52.7%)
Severe	44 (21.9%)	58 (27.8%)	102 (24.9%)
Not answered	2 (1.0%)	0 (0.0%)	2 (0.5%)
Using the IGA scale for acne, how would you describe the participant's facial acne – n (%)[2]			
Clear	0 (0.0%)	0 (0.0%)	0 (0.0%)
Almost clear	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mild severity	92 (45.8%)	98 (46.9%)	190 (46.3%)
Moderate severity	84 (41.8%)	82 (39.2%)	166 (40.5%)
Severe	25 (12.4%)	29 (13.9%)	54 (13.2%)

[1] The numbers in this table relate to those with a baseline self-assessment available.

[2] These statistics or percentages are calculated using the number of participants with non-missing information available.

[3] This percentage is calculated as the number of participants with this information missing divided by those with the baseline self-assessment/IGA/contraception information available.

Table S4 Secondary outcomes – other Acne-QoL subscales and total Acne-QoL score at 12 and 24 weeks

Outcome	n	Mean score spironolactone (N=201)	n	Mean score placebo (N=209)	Unadjusted mean difference in score (95% CI)	Adjusted* mean difference in score (95% CI)
Acne-QoL role-social subscale score at 12 weeks (mean, SD)	176	18.7 (6.1)	165	17.0 (6.7)	1.88 (0.64 to 3.13)	**1.99 (0.70 to 3.28)**
Acne-QoL role-emotional subscale score at 12 weeks (mean, SD)	175	20.2 (7.8)	166	17.5 (8.1)	2.66 (1.08 to 4.25)	**2.75 (1.11 to 4.39)**
Acne-QoL self-perception subscale score at 12 weeks (mean, SD)	175	19.2 (8.5)	166	16.9 (8.2)	2.21 (0.55 to 3.86)	**2.10 (0.39 to 3.82)**
Acne-QoL total score at 12 weeks (mean, SD)	176	77.0 (26.5)	166	69.0 (26.2)	8.18 (2.98 to 13.38)	**8.03 (2.68 to 13.37)**
Acne-QoL role-social subscale score at 24 weeks (mean, SD)	163	19.6 (5.6)	136	16.7 (6.8)	3.03 (1.78 to 4.28)	**3.06 (1.77 to 4.35)**

Acne-QoL role-emotional subscale score at 24 weeks (mean, SD)	164	21.1 (7.3)	137	16.5 (8.2)	4.50 (2.81 to 6.18)	**4.35 (2.64 to 6.05)**
Acne-QoL self-perception subscale score at 24 weeks (mean, SD)	164	21.3 (7.7)	137	16.3 (8.7)	4.98 (3.23 to 6.74)	**4.77 (2.97 to 6.56)**
Acne-QoL total score at 24 weeks (mean, SD)	164	83.0 (25.0)	137	66.7 (27.5)	16.25 (10.66 to 21.84)	**15.73 (10.04 to 21.42)**

*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 PCOS status.

Table S5 Secondary outcomes – oral acne treatments used by participants at 24 and up to 52 weeks

Characteristic	Spironolactone (n=201)	Placebo (n=209)	Total (n=410)
At 24 weeks			
Are you using oral antibiotic?			
N	168	146	314
Yes	4 (2.4%)	6 (4.1%)	10 (3.2%)
Are you using oral isotretinoin?			
N	168	146	314
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)
At 52 weeks			
Are you using oral antibiotic?			
N	103	89	192
Yes	6 (5.8%)	12 (13.5%)	18 (9.4%)
Are you using spironolactone?			
N	103	89	192
Yes	36 (35.0%)	25 (28.1%)	61 (31.8%)
Are you using oral isotretinoin?			
N	103	89	192
Yes	2 (1.9%)	6 (6.7%)	8 (4.2%)

Characteristic	Spironolactone (n=201)	Placebo (n=209)	Total (n=410)

* Data represents responses to questionnaire asking whether they were taking medication by mouth (yes/no/not answered). If they answered yes, they then had the option of ticking "yes" to a specific medication or leave it not answered.

Table S6 Subgroup analyses

Subgroup	n	Mean score spironolactone (N=201)	n	Mean score placebo (N=209)	Adjusted* mean difference in score (95% CI)	p-value of the interaction term in the adjusted* model
PCOS status						
With PCOS or suspected PCOS	26	17.4 (6.0)	35	17.3 (5.2)	1.37 (-1.40 to 4.14)	REF
Without PCOS or suspected PCOS	144	19.4 (6.2)	124	17.7 (5.8)	**1.46 (0.12 to 2.80)****	0.642
Age group						
Below 25 years	44	16.9 (5.8)	46	18.7 (5.6)	-0.87 (-3.67 to 1.92)	REF
25 years and above	132	20.0 (6.0)	120	17.4 (5.6)	**2.42 (1.00 to 3.84)**	0.005
BMI						
BMI ≤ 25	99	19.8 (5.7)	82	17.7 (5.2)	1.89 (0.32 to 3.46)	REF
BMI >25	77	18.4 (6.6)	84	17.8 (6.0)	0.34 (-1.56 to 2.24)	0.244
IGA						
IGA < 3	79	20.4 (5.8)	80	18.2 (5.8)	1.63 (-0.10 to 3.35)	REF
IGA ≥ 3	97	18.3 (6.2)	86	17.4 (5.4)	1.35 (-0.33 to 3.03)	0.877
Hormonal contraception						
Not taking	102	18.8 (6.1)	90	17.5 (5.7)	1.79 (0.12 to 3.46)	REF
Combined oral contraceptive	27	21.1 (6.7)	18	19.2 (6.1)	2.70 (-1.77 to 7.17)	0.560
Progesterone only pill or other progesterone only contraception	47	18.9 (5.8)	58	17.7 (5.3)	1.03 (-0.83 to 2.90)	0.705
Topical treatment at Baseline						
Not using	24	18.8 (5.8)	27	17.2 (6.7)	1.91 (-1.82 to 5.65)	REF
Using	150	19.2 (6.1)	138	17.9 (5.4)	1.22 (-0.09 to 2.53)	0.566
COVID						
Pre-COVID	35	20.1 (6.3)	32	17.7 (4.7)	N/A	N/A
Post-COVID	141	19.0 (6.1)	134	17.8 (5.8)	N/A	N/A
Ethnicity						
White	143	19.6 (6.1)	149	17.4 (5.6)	N/A	N/A
Non-White	15	16.1 (5.6)	7	19.9 (5.3)	N/A	N/A

Statistically significant differences indicated **in bold**

*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 PCOS status.

**When an interaction term for PCOS was included in the adjusted model, the interaction term was found to be insignificant (p-value = 0.642), therefore no strong conclusions should be made concerning the effect of spironolactone by PCOS status