Southampton Clinical Trials Unit

Statistical Analysis Plan

Short trial name:	SAFA
Full trial name:	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.
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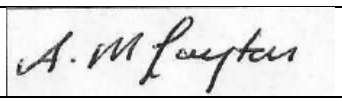
Co-chief Investigator	Alison Layton		01 February 2022
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SAP revision history

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0.1	First draft	Natalia Permyakova	27-Jul-2021

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List of Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DMEC	Data Monitoring and Ethics Committee
EQ-5D-5L	EuroQol Five Dimensions Five Level
GCP	Good Clinical Practice
HEAP	Health Economics Analysis Plan
IGA	Investigator's Global Assessment
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
NCI	National Cancer Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PCOS	Polycystic Ovary Syndrome
PI	Principal Investigator
PPI	Patient and Public Involvement
QoL	Quality of Life
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SCTU	Southampton Clinical Trials Unit
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UoS	University of Southampton

Keywords

Spironolactone
Adult female acne
Topical therapy
Dermatology

1 Introduction

1.1 Purpose of SAP

This statistical analysis plan (SAP) describes in detail the methods that will be used to analyse the data collected as part of the SAFA trial. This will form the basis of the final trial publication. The final analysis will follow the SAP to ensure that the analyses are conducted in a scientifically valid manner and to avoid post hoc decisions which may affect the interpretation of the statistical analysis. Any deviations from the SAP will be detailed in the final report.

This SAP supports the published study protocol (http://dx.doi.org/10.1136/bmjopen-2021-053876).[1]

1.2 Trial Personnel

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1.3 Trial synopsis

Acne vulgaris (from here on referred to as acne) is a very common condition that typically starts in adolescence. Some degree of acne affects almost all people aged 15 to 17 years and is moderate or severe in about 15 to 20%, often persisting to adulthood. Acne can have a negative impact on quality of life, with increased risk of depression and suicide.

First line treatment for moderate acne is fixed dose combination topical preparations, but side-effects and non-adherence are common. Patients often seek second-line therapies, such as oral antibiotics, co-cyprindiol, combined oral contraceptives or, in severe acne, oral isotretinoin.

A third of people who consult with acne are prescribed long courses of oral antibiotics. Rising rates of antibiotic resistance suggest an urgent need for evidence to support alternatives, particularly as the combined oral contraceptive pill and co-cyprindiol are not suitable for all female patients.

Spironolactone is a potassium-sparing diuretic that is widely used in the UK for indications including hypertension. It has been used off-license in acne affecting females for over 30 years due to its antiandrogenic properties, although there is little evidence of its benefit. If shown to be effective, spironolactone could reduce the use of antibiotics for acne, be cost-effective and would be more suitable for long-term use than other second line treatments in female patients.

The objective of this pragmatic multicentre double-blind randomised superiority trial is to determine the clinical and cost effectiveness of spironolactone compared with placebo, in addition to standard care, in the treatment of moderate or severe persistent facial acne in adult women

1.4 Definition of endpoints

Study outcomes are described in Section 3.1 of the SAFA Protocol.

1.4.1 Definition of primary endpoint

The primary outcome is the Acne-QoL[2,3] symptom subscale score at 12 weeks.

1.4.2 Definition of secondary endpoints

- Acne-QoL symptom subscale score at end of treatment (24 weeks)
- Acne-QoL other subscales (self-perception, role-emotional and role-social), and total score, at 12 and 24 weeks
- Participant self-assessed overall improvement at 12 and 24 weeks recorded on a 6-point Likert scale with photographs taken at the baseline visit to aid recall, as was carried out in the previous HTA-funded trial in acne[4]
- Investigator's Global Assessment (IGA) at 12 weeks
- Participant's Global Assessment at 12 and 24 weeks
- Participant satisfaction with study treatment (asked prior to revealing treatment allocation at 24 weeks)
- Health-related quality of life using EQ-5D-5L at 6, 12 and 24 weeks (to be described separately in the HEAP)
- Cost-effectiveness over 24 weeks (to be described separately in the HEAP)

1.4.3 Definition of tertiary endpoints

- Acne-QoL symptom subscale score at 6 weeks and at up to 52 weeks
- Acne-QoL other subscales (self-perception, role-emotional and role-social), and total score, at 6 weeks and up to 52 weeks
- Participant self-assessed overall improvement at 6 weeks and up to 52 weeks recorded on a 6-point Likert scale
- Participant's Global Assessment at 6 weeks and up to 52 weeks
- ARs of special interest
- Use of other oral acne treatment (e.g. antibiotics, isotretinoin) (participant report)
- Health-related quality of life using EQ-5D-5L at up to 52 weeks (to be described separately in the HEAP)
- Cost and cost-effectiveness at 24 weeks (participant report) (to be described separately in the HEAP)

1.5 Analysis principles

All analyses will be reported according to CONSORT 2010 and Southampton Clinical Trials Unit (SCTU) standard operating procedure (SOP) on planning, implementing and reporting statistical analyses (CTU/SOP/5058).

2 Design considerations

2.1 Description of trial design

A multicentre double-blind randomised superiority trial to investigate the clinical and cost-effectiveness of spironolactone in the treatment of moderate or severe persistent facial acne in adult women compared to placebo, in addition to standard treatment.

2.2 Trial power and sample size

The trial requires a total sample size (including allowing for 20% loss to follow up) of 398 participants. This allows 90% power to detect a difference of 2 points on the Acne-QoL subscale at 12 weeks (s.d. 5.8, effect size 0.35) between treatment and usual care groups. Allowing for 20% loss to follow up, we planned to recruit 434 participants (217 per arm).

Due to a lower than anticipated correlation of the Acne-QoL subscale at 12 weeks with baseline of 0.293 and a deflation factor of $1-\rho 2^{5}$, the target sample size decreased to 398 participants (199 per arm). This was approved in consultation with the study Steering Committees, Research Ethics Committee and the Funder.

More details on the sample size calculation is provided in section 8.2 in protocol.

2.3 Randomisation details

Participants were individually randomised using TENALEA. Participants were stratified by centre and by baseline acne severity (IGA < 3 versus 3 or more). This is a double-blind trial, where unblinding took place once the participant had completed 24 weeks of follow-up.

2.4 Timing of planned analyses

2.4.1 Interim analyses

No interim analysis was planned.

2.4.2 Final analysis

Final analysis will take place after all recruited participants have completed 24 weeks of follow up. End of study is defined as when the last participant has had their last data collected, cleaned and verified.

3 Statistical considerations

3.1 Definition of analysis populations

3.1.1 Intention-to-treat analysis population

The analysis will be based on a modified Intention-to-treat (ITT) population, which includes all participants who have been randomised to a treatment arm, regardless of compliance, and have completed data for the outcome and timepoint being analysed.

All analyses will be carried out in the modified ITT population, with the level of missing data reported, unless otherwise stated.

3.1.2 Per-protocol analysis population

We will undertake a complier-average causal effect (CACE) analysis which compares compliant participants in the intervention group, with those in the control group whose characteristics are similar enough to the intervention group compliers to suggest they too would have complied with the intervention, given the opportunity to do so.

Compliance for these analyses will be defined as taking at least 80% of the prescribed medication over the 12 to 24 week period. It would have been preferable to undertake the analysis over the initial 12 week period, in line with the primary outcome measure. However, because of disruption due to Covid, many participants did not return their medication for a tablet count, nor did they provide an estimate of their remaining medication. Due to a high level of missing data it is not possible, therefore, to undertake the analysis over this timeframe. It was felt that the CACE analysis over the 12 to 24 week period was still a useful secondary analysis.

To explore the sensitivity of this analysis to the definition of "compliance", we will also undertake sensitivity analyses assuming that compliance is taking 100% of the study medication and also assuming 50% of the study medication.

3.2 Analysis software

All analyses will be carried out using STATA SE 14 or above and/or SAS.

3.3 Methods for handling data

3.3.1 Withdrawal from trial

All data up until the point of patient withdrawal from trial treatment and further follow-up in the trial will be used in analyses unless the patient completely withdrew and does not wish for the data already collected prior to withdrawal to be used for the trial.

See more details on the types of withdrawal in the SAFA trial in section 5.7 of the protocol.

3.3.2 Missing data

For missing items within the Acne-QoL questionnaire, the guidance from the scoring manual will be followed.[6] If a patient has a partially completed domain (minimum 3 items completed, or 1-2 questions have missing responses), we will calculate the mean value within the domain for the answered items and replace missing values with the mean value. If more than this minimum is missing, then the domain score will be missing. For all other outcome measures, missing items will be treated as missing, in accordance with the scoring guidelines.

The primary analysis will be of complete cases. We will examine the structure and pattern of missing data and, if appropriate, will present a sensitivity analysis based on data imputed using a chained equations multiple imputation model. The imputation model would include the outcome measure, baseline value of the outcome, randomisation group, and all covariates included in the analysis model.

3.3.3 Assumption checking and alternative methods

Assumptions for linear regression models (linearity, normality, homoscedasticity) will be checked using scatter plots of standardized residuals against fitted values, and qq plots. If linear models are not appropriate a log-linear transformation will be used. If this is not appropriate, another suitable distribution (e.g. Poisson) will be considered. If no distribution fits the data, quantile regression models will be used.

3.4 Definition of key derived variables

3.4.1 Acne-QoL symptom subscale

- **The primary endpoint** is the Acne-QoL[2,3] symptom subscale score at 12 weeks. It is calculated from the total of the 5 questions from the acne symptoms domain of the Acne-QoL questionnaire by summing the items 15-19 (see Appendix 1).[6] The 5 questions are on a scale of 0-6 ("extensive, a whole lot, a lot, a moderate amount, some, very few, none" for items 15-17 and "extremely, very much, quite a bit, a good bit, somewhat, a little bit, and not at all." for items 18 and 19). Possible domain scores range from 0 to 30 and the MCID is considered to be 2 points.

- Described above definition of the Acne-QoL symptom subscale score applies to its secondary endpoint at 24 weeks, and its tertiary endpoints at 6 weeks and up to 52 weeks.

3.4.2 Other Acne-QoL subscales (self-perception, role-emotional and role-social)

- The three other domains of the Acne-QoL are measured as secondary endpoints at 12 and 24 weeks, and their tertiary endpoints at 6 weeks and up to 52 weeks. Each domain consists of the questions measured on a scale of 0-6 (extremely, very much, quite a bit, a good bit, somewhat, a little bit, and not at all). Possible domain scores range from 0 to 30.

    - Self-perception Acne- QoL symptom subscale score is calculated from the total of the 5 questions from the Acne- QoL questionnaire by summing the items 1, 3, 10, 2, and 6 (see Appendix 1).[6]
    - Role-emotional Acne- QoL symptom subscale score is calculated from the total of the 4 questions from the Acne- QoL questionnaire by summing the items 11-14 (see Appendix 1).[6]
    - Role-social Acne-QoL symptom subscale score is calculated from the total of the 5 questions from the Acne- QoL questionnaire by summing the items 4, 5, 7, 8 and 9 (see Appendix 1).[6]

3.4.3 Total Acne-QoL

- The total Acne-QoL score is calculated as the sum of all four subscales as defined above. This is used as a secondary endpoint at 12 and 24 weeks, and as a tertiary endpoint at 6 weeks and up to 52 weeks.

3.4.4 Participant's and Investigator's Global Assessment

- Participant's and Investigator's Global Assessment (PGA and IGA, respectively) at 6, 12 and 24 weeks (as secondary endpoints only) will be dichotomized as success or failure as recommended by the FDA (with success for IGA and PGA defined as clear or almost clear (grade 0 or 1) and at least a two-grade improvement from baseline; this represents a clinically meaningful outcome).

3.4.5 Participant's self-assessed overall improvement

- Participant's self-assessed overall improvement (as a comparison with baseline photo) is measured at 6, 12 and 24 weeks (as secondary endpoints) and up to 52 weeks (as tertiary endpoints) in the Self-Assessment Form as a single question "Using the photograph taken at your first visit if you have it, how do you think your acne today compares to your acne then?" on a 6-point Likert scale from 1 "Worse" to 6 "Completely Cleared".

3.4.6 Participant's satisfaction with study treatment

- Participant's satisfaction with study treatment (asked prior to revealing treatment allocation at 24 weeks as a single question "Do you think the tablets you received in this study have helped your skin?") is measured as a secondary endpoint on a scale from 0 (`not at all') to 5 (`a lot') with higher scores indicating increased satisfaction with treatment. Responses of "not sure" will be treated as missing and the proportion in this category will be reported.

Definitions of other key variables as tertiary endpoints include:

- Participant's reports on the use of other oral acne treatment (e.g. antibiotics, isotretinoin) between the end of the study treatment at 24 weeks and a follow-up at up to 52 weeks will be retrieved from the Acne Medication Use Form (only antibiotics) and Q2 Medication Form as a free-text variable. The categories described will be: Any topical treatment, oral isotretinoin, oral antibiotic, hormonal contraception, COC or Dianette, spironolactone obtained outside the study.

3.5 General principles for reporting and analysis

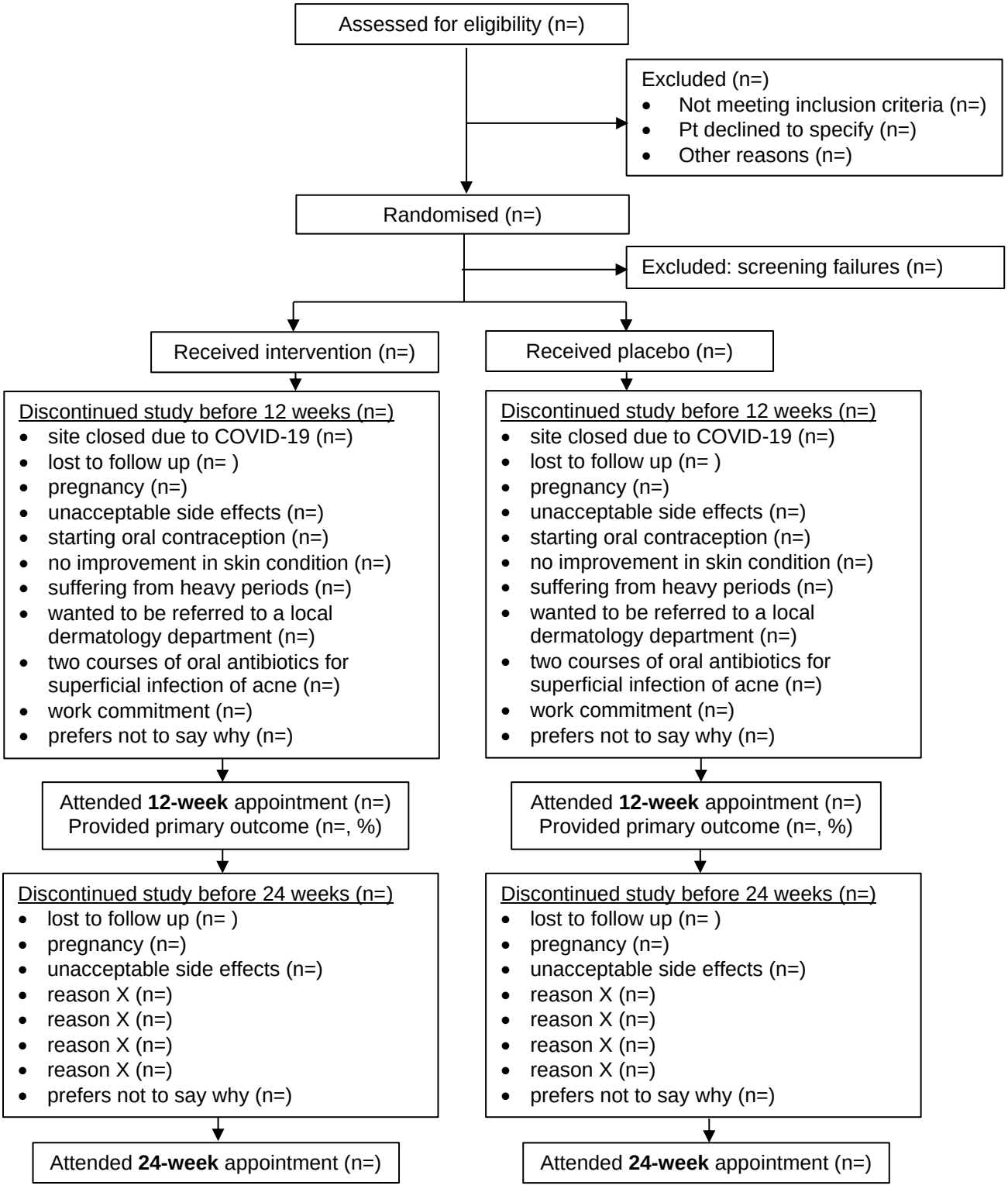
- Summary statistics will consist of frequencies and percentages for categorical variables, means, ranges and standard deviations for normally-distributed continuous variables, and medians and inter-quartile ranges for continuous variables with a skewed distribution.
- One decimal place will be used for percentages, means, ranges, standard deviations, medians and inter-quartile ranges.
- Where multiple answers are provided (e.g. Other treatments received), the percentages will reflect the number of each type of reported answers rather than participants, where the denominator will be the number of patients in the treatment or control group.
- Treatment group will be labelled in the tables as 'Spironolactone' versus the control group labelled as 'Placebo'. Total column will be included in the tables as the last column.
- All tests will be two-tailed with point estimates, 95% confidence intervals and exact p-values for the treatment effect presented.
- Coefficients, standard errors, p-values and 95% confidence intervals will be reported with two decimal points each in a separate column for the linear regression models.
- Odds ratios, standard errors, p-values and 95% confidence intervals will be reported with two decimal points each in a separate column for the logistic regression models. The level of statistical significance will be taken at 5%.
- No formal adjustment for multiple significance testing will be applied.

4 Planned analyses and reporting

Section 4 of the SAP provides more detailed description of all the analysis and results to be reported.

4.1 Disposition of the study population

Figure 4.1 Consort diagram



Withdrawal information including the primary reasons of discontinuation will be summarised and presented by where this is known.

4.2 Baseline and demographic characteristics

Baseline and demographic characteristics will be tabulated by randomised group using the summary statistics (frequencies and percentages for categorical characteristics, or means with ranges and standard deviations for continuous characteristics with a normal distribution, or medians with inter-quartile ranges for continuous characteristics with a skewed distribution).

Baseline and demographic characteristics will include:

- Stratification characteristics used in randomisation, which are the recruitment centre and severity at baseline (IGA<3 vs IGA≥3);

- Demographic information recorded on baseline characteristics form (age at baseline in years, height in cm, weight in kg, BMI, waist circumference in cm, and where did the participant hear about the study);

- Disease assessment information as recorded on self-assessment at baseline, IGA form and contraception form (How would you describe the acne on your face at the moment?; Do you have flares or breakouts in your acne before or during your period?; Using the IGA scale for acne, how would you describe the participant's facial acne?; Is the participant currently using any hormonal contraception? If 'Yes', please state which contraception);

- Medical history information as recorded on medical history form (How long have you had your current episode of acne?; Age acne started (years);

- PCOS diagnosis and suspected PCOS. Suspected PCOS will be derived based on the Rotterdam criteria[7]: Suspected PCOS will be defined as having two or more of: oligo/anovulation(missed / infrequent periods), hyperandrogenism (evidence of excess facial and body hair or female pattern baldness) or polycystic ovaries on ultrasound. Since ultrasound was not performed in this study, participants will need to have both of the other criteria to qualify has having suspected PCOS.

- Acne Medication recorded on Acne Medication Use form (Previously or currently using topical treatments (creams/lotions/gels): Benzoyl peroxide, Azelaic acid, Topical adapalene, Antibiotics, Combination, or Other treatment; If tropical treatments have been prescribed, how often are they used?).

- Baseline values of all outcome measures.

4.3 Treatment information

Treatment information will be tabulated by randomised group using the summary statistics (frequencies and percentages for categorical characteristics, or means with ranges and standard deviations for continuous

characteristics with a normal distribution, or medians with inter-quartile ranges for continuous characteristics with a skewed distribution).

- Dose escalation:
    a. How many patients were advised to increase the dose to two tablets (100 mg dose) per day at 6 week visit?
    b. How many patients had one tablet (50mg dose) and two tablets (100 mg dose) per day between 6 week and 12 week visit?
    c. How many patients had one tablet (50mg dose) and two tablets (100 mg dose) per day between 12 week and 24 week visit?

4.4 Primary endpoint

For the primary outcome, summary statistics will be presented for each group. A linear regression model will be used to analyse the between group difference in the Acne-QoL symptom subscale at 12 weeks. The model will be adjusted for randomisation stratification variables (centre, baseline severity (IGA < 3 versus 3 or more)), baseline variables (including baseline Acne-QoL symptom subscale score, use of topical treatments/hormonal contraception/co-cyprindiol, age, and PCOS status). A 95% confidence interval for the least squares mean difference between arms in Acne-QoL symptom subscale at 12 weeks will be calculated. As a sensitivity analysis, this primary outcome analysis will be repeated using multiple imputation for missing data.

Ethnicity data was not collected on the original CRFs but is being obtained retrospectively from sites. If sufficient data on ethnicity is available to retain 90% power (i.e. at least 80% of participants contributing primary outcome data to the model) then we will include ethnicity as a covariate in the model.

4.5 Secondary and tertiary endpoints

The Acne-QoL symptom subscale score, as well as other three Acne-QoL subscales (self-perception, role-emotional and role-social) and the total score, at 24 weeks will be analysed using the same approach as for the primary endpoint. These outcomes will be described at 6 weeks and up to 52 weeks as tertiary endpoints and the trend in the groups over time illustrated graphically.

Participant's and Investigator's Global Assessment (PGA and IGA, respectively) at 12 and 24 weeks (as secondary endpoints only) will be analysed as dichotomized outcomes using logistic regression adjusting for the respective baseline values and the same covariates as the primary endpoint.

Participant's self-assessed overall improvement (as a comparison with baseline photo recorded on a 6-point Likert scale) 12 and 24 weeks (as secondary endpoints) will be analysed as a continuous outcome using linear regression, controlling for the same covariates as the primary endpoint. If the distribution is highly skewed, this will be dichotomised into score 1-3/4-6 and analysed using a logistic regression modelling approach.

Analysis of tertiary endpoints at 6 and 52 weeks will be descriptive.

Participant's satisfaction with study treatment (asked prior to revealing treatment allocation at 24 weeks as a single question "Do you think the tablets you received in this study have helped your skin?") as a secondary endpoint will be analysed using the same approach as for the primary endpoint. If the distribution is highly skewed, this will be dichotomised into agree/disagree and analysed using a logistic regression modelling approach. Those who were not sure will be treated as missing.

Analysis of other tertiary endpoints will include:

- Adverse reactions of special interest as set out in the protocol will be summarised by arm with frequencies and percentages and compared with Pearson's χ^2 tests. Logistic regression modelling will also be used to adjust for any important differences in topical treatment use by arm.
  These are: headache, dizziness, tingling, indigestion, polyuria, nausea, vomiting, tenderness of the breasts, breast enlargement, irregular menstrual periods, abdominal pain, weight gain, reduced libido, fatigue and drowsiness.
- Participant's reports on the use of other oral acne treatment (e.g. antibiotics, isotretinoin) as set out in section 3.4.6 between the end of the study treatment at 24 weeks and a follow-up at up to 52 weeks will be summarised by arm with frequencies and percentages.

4.6 Additional analyses

Exploratory subgroup analyses will investigate how the treatment effect differs by whether participants have symptoms consistent with PCOS as recorded at the baseline visit, by age (below 25 years and 25 years and over), by BMI (as a continuous variable and also as a categorical variable considering BMI≤25 or BMI>25), by higher and lower IGA scores at baseline (as per stratification), by the use of hormonal co-treatments (yes/no) and by the use of topical co-treatments (yes/no).

Additional analysis will explore whether there are any differences in the primary endpoint data recorded before and during the COVID-19 pandemic.

If sufficient data is available (more than 5 participants per cell) we will provide a descriptive analysis of the outcome measures by ethnic group. Whilst there will be insufficient power in this study to explore these subgroups, this information may prove useful for future meta-analyses.

A full economic evaluation of the trial will also be carried out. Details of this analysis will be set out in a separate Health Economic Analysis Plan (HEAP).

4.7 Safety reporting

Adverse events (AEs), ARs of special interest and SAEs for the full population will be summarised descriptively according to randomised group. Overall AEs will be also summarised by CTCAE Grade according to randomised group. No statistical comparisons will be undertaken on these data with an exception of those of special interest (see 4.6).

5 References

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6 Appendix

Appendix 1. Content Areas of Acne-QoL Domains

Self Perception		**Role-emotional**	
1	Feel unattractive	5	Spending time treating face
3	Feel self-concious	9	Need to have meds or cover-up available
10	Self-confidence affected	8	Meds won't clear face fast enough
2	Feel embarrassed	7	Not looking your best
6	Dissatisfied with self appearance	4	Feel upset
Role-Social		**Acne Symptoms**	
12	Going out in public	15	Bumps on face
11	Meeting new people	16	Bumps full of pus
14	Interacting with opposite sex (or same sex if gay) a problem	17	Scabbing from acne
13	Socializing with people a problem	18	Concerned with scarring
		19	Oily skin

Source: p.7, Acne-specific Quality of Life Questionnaire (Acne-QoL) Manual & Interpretation Guide (2003)