SAFA

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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Protocol authorised by:

Name:	Dr Miriam Santer	**Role:**	Chief Investigator
Signature:		**Date:**	
Name:	Prof Gareth Griffiths	**Role:**	Director of SCTU
Signature:		**Date:**	
Name:		**Role:**	On behalf of Sponsor
Signature:		**Date:**	

MAIN TRIAL CONTACT

Chief Investigator and Medical Expert: Dr Miriam Santer

Primary Care and Population Sciences
University of Southampton
Aldermoor Health Centre
Aldermoor Close
Southampton
SO16 5ST

Tel: 023 8059 1789
Email: M.Santer@soton.ac.uk

Chief Investigator and Medical Expert: Dr Alison Layton

Harrogate and District NHS Foundation Trust
Lancaster Park Road
Harrogate
HG2 7SX

Tel: 01423 553 740 Ext: 3740
Email: Alison.Layton@hdft.nhs.uk

TRIAL COORDINATION CENTRE

For general trial and clinical queries e.g. participant queries, trial supplies, data collection, please contact in the first instance:

SAFA Trial Manager(s): Susanne Renz, PhD Tel: 023 8120 5538

Email: safa@soton.ac.uk

Address: Southampton Clinical Trials Unit
Southampton General Hospital
Tremona Road
SOUTHAMPTON
SO16 6YD

Tel: 023 8120 5154
Fax: 0844 774 0621
Email: ctu@soton.ac.uk
Web: www.southampton.ac.uk/ctu

SPONSOR

The University of Southampton is the research sponsor for this trial. For further information regarding sponsorship conditions, please contact the Director of Research and Development at:

Address: Head of Contracts, Policy and Governance
B28/2027 Highfield
University of Southampton
Highfield Road
SO17 1BJ

Tel: +44 (0)23 8059 5058
Web: https://www.southampton.ac.uk/research/ris.page

CO-INVESTIGATOR(S)

Co-Investigators can be contacted via Southampton CTU.
Dr Nick Francis (Cardiff University)
Prof Gareth Griffiths (Southampton CTU)
Prof Paul Little (University of Southampton)
Dr Ingrid Muller (University of Southampton)
Ms Jacqueline Nuttall (Southampton CTU)
Dr Matthew Ridd (University of Bristol)
Prof Tracey Sach (University of East Anglia)
Mrs Irene Soulsby (PPI contributor)

Dr Beth Stuart (University of Southampton)
Miss Karen Thomas (PPI contributor)
Prof Kim Thomas (University of Nottingham)

FUNDER

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Protocol Information

This protocol describes the SAFA trial and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non-trial participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but sites entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This trial will adhere to the principles of Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, in accordance with current Data Protection Regulations and all other regulatory requirements, as appropriate.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
DSUR	Development Safety Update Report
EQ-5D-5L	EuroQol Five Dimensions Five Level
GCP	Good Clinical Practice
GP	General Practitioner
HUI	Health Utilities Index
IB	Investigator Brochure
IGA	Investigator's Global Assessment
IMP	Investigational Medicinal Product
ISF	Investigator Site File
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
PIC	Participant Identification Centre
PPI	Patient and Public Involvement
QALYs	Quality Adjusted Life Years
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
SF-6D	Short Form Six Dimensions
SmPC	Summary of Product Characteristics
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

TRIAL SYNOPSIS

Short title:	SAFA
Full title:	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.

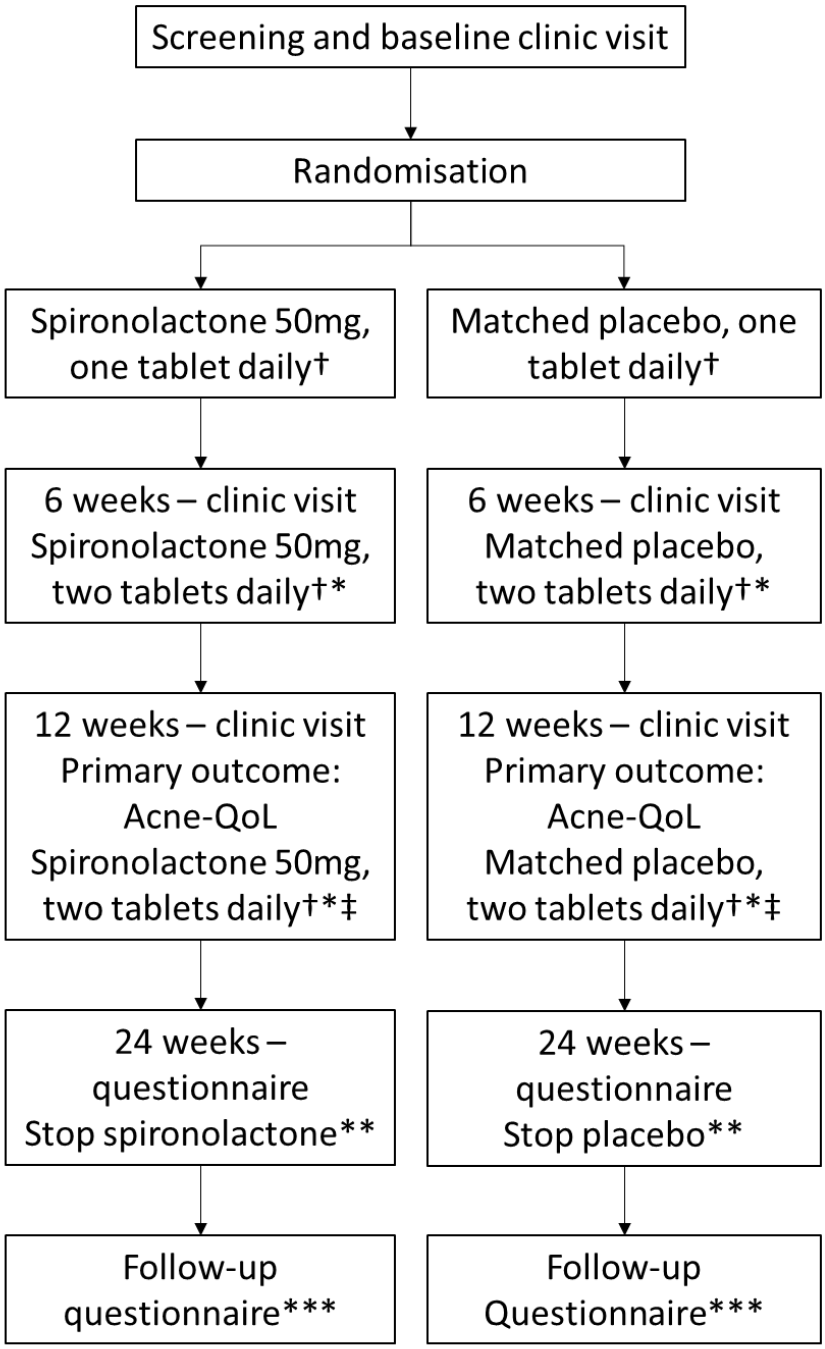
Phase:	3
Population:	Women aged 18 years and over with moderate or severe persistent facial acne (facial acne of sufficient severity to warrant treatment with oral antibiotics).
Primary Objective:	To determine the clinical effectiveness of spironolactone compared with placebo, in addition to standard care, in the treatment of moderate or severe persistent facial acne in adult women – initial treatment response (12 weeks).
Secondary Objectives:	1. To assess the clinical effectiveness of adding spironolactone to standard topical treatment, compared with placebo and standard topical treatment, for moderate or severe persistent facial acne in adult women. 2. To assess the cost-effectiveness of adding spironolactone to standard topical therapy for the management of moderate or severe acne in adult women over 24 weeks. 3. To assess the safety of adding spironolactone to standard topical treatment, compared with placebo and standard topical treatment, for moderate or severe persistent facial acne in adult women.
Rationale:	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 current trial seeks to answer the research question: Is oral spironolactone plus standard topical therapy superior to placebo plus standard topical therapy, at improving acne-related quality of life in adult women with moderate-severe persistent facial acne?

Trial Design:	Pragmatic multicentre double-blind randomised superiority trial
Sample size :	434 (217 per arm)
Revised sample size:	398 (199 per arm)
Investigational Medicinal Product:	Spironolactone
Dosage Regimen / Duration of Treatment:	Spironolactone/Placebo 1 x 50mg tablet for 6 weeks. Either staying at 1 tablet or increasing to 2 x 50mg tablets after 6 weeks. Total treatment duration of 24 weeks.

URL for Database:	https://www.imedidata.com
URL for randomisation:	https://prod.tenalea.net/ciru/DM/DELogin.aspx?refererPath=DEHome.aspx

Primary Outcome:	Acne-QoL symptom subscale score at 12 weeks
Secondary Outcomes:	• Acne-QoL symptom subscale score at 6 and 24 weeks • Acne-QoL other subscales (self-perception, role-emotional and role-social) and total score at 6, 12 and 24 weeks • Participant self-assessed improvement at 6, 12 and 24 weeks recorded on a 6-point Likert scale (with baseline photograph to assist recall) • Investigator's Global Assessment at 6 and 12 weeks, adjusted for baseline variables • Participant's Global Assessment at 6, 12 and 24 weeks, adjusted for baseline variables • Participant satisfaction with study treatment at 24 weeks (asked prior to unblinding) • Health-related quality of life using EQ-5D-5L at 6, 12 and 24 weeks • Cost at 6, 12 and 24 weeks and cost-effectiveness over 24 weeks
Other Outcomes:	• Acne-QoL symptom subscale score at up to 52 weeks • Acne-QoL other subscales (self-perception, role-emotional and role-social) and total score at up to 52 weeks • Participant self-assessed improvement at up to 52 weeks recorded on a 6-point Likert scale (with baseline photograph to assist recall) • Participant's Global Assessment at up to 52 weeks, adjusted for baseline variables • Adverse reactions (ARs) of special interest • Use of other oral treatments for acne during follow-up • Health-related quality of life using EQ-5D-5L at up to 52 weeks • High-level resource use data will be described at up to 52 weeks
Total Number of Sites :	GP practices as Participant Identification Centres in primary care and 5-8 secondary care dermatology clinic sites

TRIAL SCHEMA



† Allow use of topical therapy (creams/lotions/gels)
*Escalate dose if study tablet is tolerated, otherwise maintain on 1 tablet
‡ Add antibiotic taken by mouth/change topical therapy if response to study tablet is inadequate
**Participants will be informed of their treatment allocation after 24 weeks. Participants in either arm may seek to use spironolactone after this time.
***The follow-up questionnaire will be sent out 6 months or sooner after the 24-week timepoint.

SCHEDULE OF OBSERVATIONS AND PROCEDURES

Observation/procedure	Person undertaking the specified event	Timings of Visit/Contact (weeks)				
		Screening/ Baseline	Week 6 visit	Week 12 visit	End of Treatment Week 24 contact	End of Study Follow-up questionnaire[3]
Informed Consent	Nurse/ Other clinician[1]	X				
Eligibility evaluation	Other clinician	X				
Participant characteristics (age, height, weight, waist circumference, etc)	Nurse/Other clinician	X				
Blood pressure	Nurse/Other clinician	X				
Blood tests (serum potassium, eGFR)	Nurse/Other clinician	X				
Investigator's Global Assessment (IGA)	Nurse/ Other clinician	X	X	X		
Discuss use of contraception	Nurse/Other clinician	X	X	X		
Pregnancy test	Nurse/Other clinician	X				
Photograph(s) of face taken	Nurse/Other clinician	X				
Photograph given to participant	Nurse/Other Clinician	X		X (If a photo was stored at site)		
Letter to participant's GP (patient participation)	Nurse/Other clinician	X				
Medical history	Participant	X				
Self-assessment - Participants Global Assessment (adapted IGA)	Participant	X	X	X	X	X
Self-assessment – comparison with baseline photo - 6 Point Likert Scale	Participant		X	X	X	X
Acne Medication Use	Nurse/Other clinician/ Participant	X	X	X	X	X
Check participant is not using oral acne treatment	Nurse/Other clinician/ Participant		X	X		
Other Medication Use	Nurse/Other clinician/ Participant	X				
Acne-QoL	Participant	X	X	X	X	X
EQ-5D-5L	Participant	X	X	X	X	X
Resource use questionnaire	Participant	X	X	X	X	X

Return excess IMP to clinic	Participant		X	X	X (return via post)	
Spironolactone/Placebo Pill count	Nurse/Other clinician/ Participant		X	X	X	
Collection of ARs of special interest: Headache Dizziness/vertigo/ Light headedness Tingling Indigestion/heartburn/ Dyspepsia Diarrhoea Polyuria (passing much more urine than normal) Nausea/feeling sick Vomiting/being sick Tenderness of the breasts Breast enlargement Irregular menstrual periods Abdominal pain Weight gain Reduced libido (reduced interest in sex) Fatigue/tiredness Drowsiness/sleepiness	Participant/ Other clinician		X	X	X	
Serious Adverse Events	Other clinician (PI or delegate)		X	X	X	
Assessment of treatment response to determine dose adjustment[2]	Participant / Other clinician		X	X		
Letter to participant's GP (if dose is change)	Nurse/Other clinician		X	X		
Reminder to participant to report any subsequent adverse event(s) that might reasonably be related to participation in this trial (up to 52 weeks)	Nurse/Other clinician			X		
Ask participant if they would like to receive a summary of the study results, when available	Nurse/Other clinician			X		
Satisfaction with study treatment	Participant				X	

[1] Dermatologist or Clinical Research Fellow, in line with local procedures with demonstrable and appropriate level of training. Specific duties delegated by the PI and listed on the delegation log.

[2]Dose escalated to 2 tablets per day if participant is tolerating side effects.

[3] The follow-up questionnaire will be sent out 6 months or sooner after the 24-week timepoint.

1 INTRODUCTION

1.1 BACKGROUND

Acne vulgaris 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%. For these patients, acne often persists into adulthood.[1] It has been estimated that about 30% of teenagers have acne that requires medical treatment.[2] Facial scarring occurs in approximately 20% of cases but the main impact is social, with levels of psychological disability equivalent to those seen in conditions such as asthma and diabetes.[2] Acne can have a negative impact on quality of life, with increased risk of depression and suicide.[3,4] Over 3% of people aged 13 to 25 years consult for acne each year.[5] In 2015, NHS England spent over £27m on prescriptions for acne (including rosacea),[6] but this is likely to be an underestimate as it does not include items, such as antibiotics, that are also prescribed for other indications and so do not appear in this figure.

First line treatment for moderate acne is fixed dose combination topical preparations, such as adapalene/benzoyl peroxide or adapalene/clindamycin.[2] However, non-adherence is common, possibly because topical treatments have to be used consistently for up to 8 weeks and adverse reactions (ARs) are common.[7] Patients therefore commonly seek second-line therapies, such as oral antibiotics, co-cyprindiol or combined oral contraceptives.[2] In severe acne (papulopustular acne with nodules and/or scarring), oral isotretinoin can be used in secondary care or sometimes in primary care under the supervision of a dermatologist. Oral isotretinoin is highly effective but is also highly teratogenic and there are concerns about a possible link between isotretinoin and depression or suicide.

A third of people who consult with acne are prescribed long courses of oral antibiotics.[8] Rising rates of antibiotic resistance suggest an urgent need for evidence to support alternatives.[9] Although the combined oral contraceptive pill is effective in females affected by acne [10] it is not licensed for this use in the UK and is contra-indicated for some or not tolerated by others. Co-cyprindiol is also effective in female acne [10] and is licensed for this but safety concerns mean it is not recommended for long-term use,[2,11] which can be frustrating for females who are keen to avoid a recurrence of their acne.

Spironolactone is a potassium-sparing diuretic that is widely used in the UK for indications including hypertension. It has been used off-license in female acne for over 30 years due to its anti-androgenic properties and American Guidelines suggest it has a role to play in the management of female acne therapy.[12] However, there is little convincing evidence of its benefit; need for evidence from randomised controlled trials (RCTs) of the effectiveness of spironolactone in this patient group is acknowledged.[13,14] If shown to be effective, spironolactone could reduce the use of antibiotics for acne in this female group, be cost-effective (cheaper than antibiotics) and would be more suitable for long-term use than other second line treatments.

1.2 RATIONALE AND RISK BENEFITS FOR CURRENT TRIAL

The current trial seeks to answer the research question: Is oral spironolactone plus standard topical therapy superior to placebo plus standard topical therapy, at improving acne-related quality of life in adult women with moderate or severe persistent facial acne? The chance of bias will be minimised by using a randomised, double-blind, parallel arm design.

The aim is to carry out a pragmatic trial whose findings will have strong external validity to answer the question about the effectiveness of spironolactone for adult female facial acne, informed by the PRECIS-2 tool.[15] Pragmatic design includes broad eligibility and recruitment strategies, a primary outcome that is relevant to participants, low intensity follow-up and an intention to treat analysis.

Participants

'Adult women' are defined as women aged 18 years or over for the purposes of this trial. Some acne studies have defined 'late onset or acne persisting as a continuum from adolescence in older women' as over 25 years but the clinical presentation of acne is similar in most cases above and below this age,[16] as is acne management.[2,12] Over 80% of women aged over 25 years with acne report that it started before the age of 25 and similar proportions of women above and below 25 years have symptoms of hyperandrogenism, suggesting no rationale for differing treatments [17]. Lastly, assessing the criteria for PCOS is challenging in adolescence, because PCOS symptoms often mirror the characteristics of normal puberty.[18]

There is no widely accepted definition of 'persistent' facial acne: for the purposes of this trial it has been defined as acne that has been present for at least 6 months. This figure was reached based on the results of surveys amongst people with acne and health professionals managing acne, assisted by the UK Dermatology Clinical Trials Network. One of the questions posed was around the most appropriate definition of 'persistent' acne and responses from both people with acne and health professionals suggested that 6 months or longer was appropriate.

Many studies use lesion counts or FDA Investigator's Global Assessment (IGA) to grade acne severity. Lesion counts are time-consuming, with wide inter-assessor variation and give little additional information to global assessments.[19] The IGA is a 5-point scale ranging from clear to severe (0 'Clear'; 1 'Almost clear'; 2 'Mild'; 3 'Moderate'; 4 'Severe').[20] SAFA will stratify participants in the basis of IGA < 3, compared with IGA 3 or higher.

Only 8.5% of women who consult with acne are referred to a dermatologist.[5] This percentage is likely to be higher amongst women requiring oral antibiotics for their facial acne, but women attending secondary care may be less willing to be randomised to spironolactone vs. placebo, as they may feel they have accessed secondary care in order to obtain oral isotretinoin, which is not generally prescribed in primary care. Recruitment for this trial will therefore be from primary and secondary care, as well as through community advertising. This approach has been successful in other pragmatic trials of skin conditions conducted by the co-applicants.[21]

Spironolactone

Concerns have been raised about teratogenicity of spironolactone but risk of harm to the foetus is not thought to be high,[11,12] and is likely to be lower than for other oral treatments for acne, such as tetracycline antibiotics, co-cyprindiol and significantly lower than with oral isotretinoin. Women of childbearing potential (WOCBP) at risk of pregnancy will have a pregnancy test at baseline. Participants will be advised that they must use appropriate contraception. Spironolactone is a category C drug and feminisation of the foetus is said to occur in the last trimester of pregnancy.[12] Consequently, if a participant inadvertently becomes pregnant during the study, the treatment can be stopped before reaching the third trimester. Women using hormonal contraception for 3 months or more may continue

to take these but we will ask participants not to start new hormonal treatment between baseline and assessment of primary outcome, as this could influence acne severity.

Spironolactone will be compared with placebo, but the trial will allow co-prescription of topical treatments in both arms for the following reasons. Firstly, the likely role of spironolactone in the acne care pathway would be as an alternative to oral antibiotics to be used in addition to topical therapies in treating acne that has shown insufficient response to topical therapies alone. Secondly, women with moderate or severe persistent facial acne may be unwilling to be randomised to placebo alone: in the survey of people with acne carried out by the UK Dermatology Clinical Trials Network, 51% (21/41) said they would not be happy to be randomised to placebo alone. One survey responder commented, "If I had severe acne I would not want to risk taking a placebo". Thirdly, amongst women with persistent facial acne requiring oral antibiotics it would be problematic to recruit women to a placebo-controlled trial with no effective treatment for 12 weeks in the control arm, as this may risk worsening of acne and possible scarring.

Topical treatments for acne are moderately effective [22] and greater changes in Acne-QoL have been found with clindamycin/BPO in moderate-severe acne [23] than for the combined oral contraceptive.[24] This could mask potential differences between arms if participants in a trial show greater adherence to topical therapies than would be the case during usual care. Therefore, we will not actively promote adherence to topical therapies but participants may continue to use them as prescribed by their usual clinical team if they wish to. We will ask women to report which topical therapies they are using and how frequently they are applying them.

2 STUDY OBJECTIVES

	Objective	Outcomes used to evaluate objective
Primary	To determine the clinical effectiveness of spironolactone compared with placebo in addition to standard care in the treatment of moderate or severe persistent facial acne in adult women – initial treatment response (12 weeks).	• Acne-QoL symptom subscale score at 12 weeks
Secondary	1. To assess the clinical effectiveness of adding spironolactone to standard topical treatment, compared with placebo and standard topical treatment, for moderate or severe persistent facial acne in adult women.	• Acne-QoL symptom subscale score at 6, 24 and up to 52 weeks • Acne-QoL other subscales (self-perception, role-emotional and role-social), and total score at 6, 12, 24 and up to 52 weeks • Participant self-assessed improvement at 6, 12, 24 and up to 52 weeks recorded on a 6-point Likert scale (with baseline photograph to assist recall) • Participant's Global Assessment at 6, 12, 24 and up to 52 weeks, adjusted for baseline variables

		• Investigator's Global Assessment (IGA) at 6 and 12 weeks, adjusted for baseline variables • Use of oral acne medication • Participant satisfaction with study treatment (asked prior to unblinding)
	2. To assess the cost-effectiveness of adding spironolactone to standard topical therapy for the management of moderate or severe acne in women.	• Health-related quality of life using EQ-5D-5L at 6, 12, 24 and up to 52 weeks • Comparison of Quality-Adjusted Life Years (QALYs) between arms, derived using the EQ-5D-5L and linear interpolation, adjusted for baseline variables • Comparison of cost, based on resource use data collected at the individual participant level at 6, 12, and 24, including use of other oral treatments for acne during follow-up up to 52 weeks • To use descriptive statistics to describe costs and utility at up to 52 weeks.
	3. To assess the safety of adding spironolactone to standard topical treatment, compared with placebo and standard topical treatment, for moderate or severe persistent facial acne in adult women.	• ARs of special interest • Serious adverse events

3 STUDY 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. The trial will include a 6 month internal pilot with clear stop-go criteria based on recruitment and retention rates:

Criteria assessed at 6 months	Proposed action
80% or more of target recruitment and retention.	Continue with main trial as planned.
50-80% of target recruitment and retention.	Trial Steering Committee discuss problems with the Trial Management Group and urgently implement remedies.
Less than 50% of target recruitment and retention.	Discuss plans with Trial Steering Committee and NIHR HTA. Consider stopping trial, unless remedies can plausibly be implemented.

3.1 STUDY OUTCOMES

3.1.1 Primary outcome

- Acne-QoL[24,25] symptom subscale score at 12 weeks

3.1.2 Secondary outcomes

- Acne-QoL symptom subscale score at 6 weeks and at end of treatment (24 weeks)
- Acne-QoL other subscales (self-perception, role-emotional and role-social), and total score, at 6, 12 and 24 weeks
- Participant self-assessed overall improvement at 6, 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[19]
- Investigator's Global Assessment (IGA) at 6 and 12 weeks
- Participant's Global Assessment at 6, 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
- Cost at 6, 12 and 24 weeks (participant report) and cost-effectiveness over 24 weeks

3.1.3 Other outcomes

- Acne-QoL symptom subscale score at up to 52 weeks
- Acne-QoL other subscales (self-perception, role-emotional and role-social), and total score, at up to 52 weeks
- Participant self-assessed overall improvement at up to 52 weeks recorded on a 6-point Likert scale
- Participant's Global Assessment at 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
- Cost and cost-effectiveness at 24 weeks (participant report)

The primary outcome will be measured at 12 weeks as this is when effectiveness of acne treatments is usually judged clinically. We will continue to follow participants to 52 weeks in total to investigate longer-term outcomes. We have chosen to measure the primary outcome at a single time point rather than repeated measures, because we anticipate that over half of participants will need up-dosing of spironolactone at 6 weeks and after this the onset of action may take a further 4–6 weeks.

Therefore, primary outcome measurement is most appropriate at 12 weeks. We will collect Acne-QoL symptom subscale score at 6 weeks in order to explore the numbers achieving treatment response at this time-point, but not to inform the primary outcome.

3.2 RATIONALE FOR DOSE REGIMEN OF SPIRONOLACTONE

A survey amongst health professionals and patients was carried out in order to inform trial design. The responses from 41 Dermatology consultants, 10 Dermatology nurses and 3 Dermatology SpRs were combined.

Of these 54 Dermatology health professionals, 22 prescribed spironolactone (9 rarely, 10 sometimes and 3 often). Most of those who responded stated that they would start at 50mg and increase up to 100-150mg depending on response. Several noted that this would depend on the patient's weight, with the starting dose lowered to 25mg if needed and allowing the dosage to increase up to 200mg. There was no consistency on the timeframe for these increases with 4 weeks, 6 weeks, 12 weeks and 6 months all being mentioned as review points.

A previous HTA study examining common treatments in the management of acne suggested that assessing efficacy at 6 weeks was ideal[19] – this informed the timing of follow up assessments and dose escalation. US guidelines note that trials have been carried out using spironolactone doses ranging from 50mg to 200mg daily.[12] No specific dose is recommended but it is noted that side effects are dose-related.[12]

A recent hybrid systematic review of RCTs and case series identified some very low-quality evidence which showed that a daily dose of 200mg was statistically significantly more effective than placebo versus inflamed lesions, but it also confirmed that this dose is associated with a significantly greater risk of adverse side effects than lower doses.[13]

Hence, there would appear to be no merit in using these higher doses for managing acne. Data from the multiple case series suggested that any future RCT examining lower doses is likely to generate results that confirm the effectiveness and better safety profile of doses ≤100 mg per day, which informed the dosage regimen.

For most licensed indications for spironolactone, the British National Formulary states a starting dose of 100mg, titrated as required. Therefore, a starting does of 50mg in the SAFA trial seems conservative.

3.3 DEFINITION OF END OF TRIAL/STUDY

End of trial is defined as the date when the last point of data is collected for the last participant from their 24 week questionnaire.

End of study is defined as the date when the last point of data is collected for the last participant from their Follow-up questionnaire.

4 SELECTION AND ENROLMENT OF PARTICIPANTS

4.1 SETTING

Both primary and secondary care settings will be used, as well as community advertising. General Practices will be Participant Identification Centres (PICs). Secondary care sites will recruit and carry out the clinical assessments to ensure standardisation.

4.2 APPROACHING PARTICIPANTS

Secondary care

Secondary care recruitment will be through opportunistic invitation in out-patient clinics and through screening new referral letters. Where there is an available database and patients have given permission to be contacted about research potential participants may be contacted by the local site study team (research nurse, clinical research fellow or principal investigator) by mail-out or email. Posters will also be used to advertise the study

in out-patient departments and pharmacies within the organisations and local communities. The study may also be shared through a Trust website where possible as this informs members about research opportunities within the organisation. Close working with patient research ambassadors across the regional clinical research network and PPI groups will also be employed to support opportunities for participants to take part.

Primary care
Primary care recruitment will include opportunistic recruitment and database search and mail-out, based on electronic record of a diagnosis of acne vulgaris. Potential participants may also receive a courtesy telephone call from a member of their usual clinical team, informing them that they have been sent an information pack about the trial for their consideration. If a potential participant is interested, their usual clinical team will ask them to contact the local site study team for the initial invitation conversation.

Community
Community advertising will be through media local to recruiting centres or advertising in appropriate institutions, directing potential participants towards a website for information about the study and how to contact the local site study team if they are interested in taking part. The website will also hold a copy of the Participant Information Sheet, which potential participants can read if they would like to.

Social media
Tillison Consulting Limited will conduct a social media campaign advertising the trial to potential participants. This will include:

1. Building trial awareness and interest, for instance using the Google Display Network (Custom Affinity Audiences).
   This displays advertisements to people who have visited appropriate acne websites such as acnesupport.org or talkhealthpartnership.com/talkacne (PPI contributors advised on appropriate websites).
2. Setting up and optimising a Google Ads campaign.
   This approach will display advertisements to people searching Google for relevant search terms, such as the trial name or specific acne treatments.

Both approaches user banner adverts in an internet browser to direct interested parties to the trial website, which provides more information about the study and explains how to contact the local site study team if someone is interested in taking part. Potential participants will also be able to access the Participant Information Sheet, if they wish to.

The campaign will be piloted in regions surrounding 3 of the trial's hospital sites. We will continually monitor and assess the effect of social media advertising. If successful, the adverts will be expanded to include the regions surrounding the remaining sites.

Tillison can turn adverts off and on without delay. Usually, adverts are shown to an audience a few times, because people may miss them the first time.

People have ultimate control over what adverts they see in their browser. If an individual no longer wants to see the trial advert, they have the option of clicking a link that will close the advert and it will not be shown to that person again.

We may also use a targeted Facebook advert campaign in the future. People on Facebook who have shown an interest in acne or relevant organisations linked with the condition (such as PCOS, the charity Verity, or acne support sites) and who fit the profile

demographic (gender, age and location) will be shown adverts for the trial. If people are interested in this, they will be able to click a link taking them to the trial website.

If Facebook adverts are used, Tillison will use targeting methods to identify Facebook users in an appropriate region:

- Everyone in this location: People whose current city on their Facebook profile is that location, as well as anyone determined to be in that location via mobile device.
- People who live in this location: People whose current city from their Facebook profile is within that location. This is also validated by IP address and their Facebook friends' stated locations.

Facebook users will also be able to control which adverts they see and can click a link to close the advert and not see it again.

We may explore other ways of social media advertising, as appropriate.

4.3 CONSENT

Consent to enter the trial will be sought from each participant only after they have received a Participant Information Sheet and a full explanation of the study, and they have been allowed time to consider participating and had any questions answered satisfactorily. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the trial the clinician will remain free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the trial for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Upon completion of the informed consent form, a copy will be given to the participant, a copy stored in their medical notes, a copy sent to the SCTU and the original filed in the Investigator's Site File. The SCTU copy should be sent to monitorSCTU@soton.ac.uk using SafeSend (https://safesend.soton.ac.uk/) to allow for central monitoring. The informed consent forms will be password protected and stored in a secure electronic location if access to the SCTU office space is not possible (e.g. during a pandemic where governance guidance recommends working from home). SafeSend is the safest and most secure (data protection complaint) mechanism for the sites to send relevant contact information to SCTU as it is hosted by the University of Southampton and supports both in-transit and at-rest encryption.

Sending informed consent forms to SCTU via SafeSend is the preferred option. However, if SafeSend is not compatible with the local Trust, the site team have the option to send the informed consent forms to SCTU (uhs.sctu@nhs.net) via a secure NHS email address. Notice of having to use this option should be communicated to the Trial Manager as soon as site/local R&D become aware.

The participant's GP will also be sent a letter to inform them that their patient is taking part in the trial.

4.4 INCLUSION CRITERIA

- Women aged 18 years or over
- Facial acne vulgaris, symptoms present since at least 6 months

- Acne of sufficient severity to warrant treatment with oral antibiotics, as judged by the study clinician
- Women of childbearing potential at risk of pregnancy must be willing to use their usual hormonal or barrier method of contraception for the first 6 months of the study (whilst taking the study IMP) and for at least 4 weeks (approximately one menstrual cycle) afterwards
- Willing to be randomised to either study arm
- Willing and able to give informed consent
- Sufficient English to carry out primary outcome Acne-QoL (which has not been validated in other languages)

4.5 EXCLUSION CRITERIA

- Hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption
- Acne grade 0-1 using the Investigator's Global Assessment (i.e. clear or almost clear)
- Has ever taken spironolactone
- Currently taking potassium-sparing diuretic, ACE inhibitor, angiotensin II receptor blocker or digoxin
- Started, stopped or changed long-term (lasting more than 2 weeks) hormonal contraception, co-cyprindiol or other hormonal treatment within the past 3 months
- Planning to start, stop or change long-term (lasting more than 2 weeks) hormonal contraception, co-cyprindiol or other hormonal treatment within the next 3 months
- Pregnant/breastfeeding
- Intending to become pregnant in the next 6 months
- Androgen-secreting adrenal or ovarian tumour
- Cushing's syndrome
- Congenital adrenal hyperplasia
- Oral antibiotic treatment (lasting longer than a week) for acne within the past month
- Oral isotretinoin treatment within the past 6 months

Potential participants using long-term hormonal contraception, co-cyprindiol or other hormonal treatment will be included if they have been using this for 3 months or more prior to the baseline appointment. If they have recently started, stopped or changed hormonal treatments, or are intending to start, stop or change in the near future, they will be asked to wait for 3 months 'stabilisation' prior to baseline appointment.

Potential participants taking oral antibiotics will be asked to undergo a 1 month 'wash-out' period before attending their baseline appointment.

Potential participants taking isotretinoin will be asked to undergo a 6 month 'wash-out' period before attending their baseline appointment.

Blood tests will also be performed at baseline to determine participants' serum potassium level and estimated glomerular filtration rate (eGFR). Participants may start the trial IMP before the test results are known. Please see section 4.6 STOPPING CRITERIA for more information.

Spironolactone would be prescribed within the same consultation for patients attending normal care. The population in this study is likely to be healthier, and less likely to have urea or electrolyte abnormalities, than patients who are usually prescribed spironolactone. Initial discussions with sites around feasibility suggested that requiring potential participants to wait for their blood results prior to randomisation would form a significant barrier to recruitment and incur an unnecessary burden on participants and sites.

4.6 STOPPING CRITERIA

Participants may commence treatment before blood test results are known, but if there is an abnormality (serum potassium level is above the upper limit of the reference range for the laboratory processing the sample, or the eGFR is below 60 ml/min/1.73m^2), the participant must be contacted within 5 working days by telephone and told to stop taking the IMP. Local site study team to complete an End of Study form in the eCRF, giving the reason that the patient was a screen failure.

4.7 SCREEN FAILURES

Potential participants who are screen failures (i.e. do not complete a baseline visit because they are not eligible for the trial) will have their initials, year of birth and reasons for failure recorded on a screening form.

Participants who complete a baseline study visit, but who's serum potassium level is above the upper limit of the reference range for the laboratory processing the sample, or their eGFR is below 60 ml/min/1.73m^2 will also be classed as screen failures.

4.8 REGISTRATION/RANDOMISATION PROCEDURES

In each site, participants who meet the eligibility criteria for the study and for whom written informed consent has been obtained will be individually randomised (1:1 ratio) to either the active or the placebo treatment (see section 8.1 Method of Randomisation for more information). Sequentially numbered treatment packs, containing either spironolactone in tablet form or the matching placebo, will be sent to each site.

Following consent and baseline data collection randomisation and drug distribution will be managed via the online system TENALEA. TENALEA will determine the Participant Identification Number and track initial pack distribution; the site will maintain an accountability log for each bottle dispensed to the participant. The dermatologist, or nurse, allocating the pack, and the participant will remain blinded to which arm they have been allocated (placebo or spironolactone).

4.9 CONTRACEPTION

Spironolactone is a category C drug and feminisation of the foetus is said to occur in the last trimester of pregnancy.[12] Consequently, participants will be advised that they must use appropriate contraception. Due to the pragmatic trial design trial procedures will inform real-world-decision-making for women with acne, therefore the trial will include an approach to contraception that mirrors usual practice. Women of childbearing potential at risk of pregnancy will be asked to use their usual hormonal or barrier method of contraception during the first 6 months of the study (whilst taking the study IMP) and for at least 4 weeks (approximately one menstrual cycle) afterwards.

A pregnancy test will be conducted for all participants of childbearing potential at risk of pregnancy at their baseline visit, unless the study clinician documents why they do not think it is relevant for the participant to have a pregnancy test in the case report form and medical notes.

At the week 6 and week 12 visits, the study nurse or doctor will ask participants who were using contraception at the baseline visit to confirm that they are still using contraception. The clinician will also check that those not using hormonal treatments have not started using them, and that those using hormonal contraception have not changed type.

Participants who become pregnant will be asked to inform their local site study team as soon as possible (see section 7.5.6 for reporting procedures). Participants who become pregnant will not be able to continue taking part in the trial, meaning they will stop taking IMP, stop attending visits and won't complete follow-up questionnaires.

If an informed consent form for pregnancy follow-up is received, the SCTU Quality and Regulatory Team will maintain the responsibility for the follow-up of the pregnancy until pregnancy end.

If the informed consent form for pregnancy follow-up is not received, no further follow-up of the pregnancy can continue. The decline to consent or lack of receipt of consent should be clearly documented in the patient medical notes by site and within the trial documentation by the Trial Manager.

5 TRIAL OBSERVATIONS AND PROCEDURES

Site can send completed clinician and participant questionnaires to SCTU via SafeSend (https://safesend.soton.ac.uk/) in order for SCTU to assist with data entry if staff resources at site are low (e.g. during a pandemic). The questionnaires will be password protected and stored in a secure electronic location. SCTU personnel responsible for data entry will be added to the site delegation log and signed-off by local PI. SafeSend is the safest and most secure (data protection complaint) mechanism for sites to send the patient identifiable information to SCTU.

5.1 SCREENING PROCEDURES

Potential participants in SAFA will be found via advertising in local media and in the community, with advice to contact their local study team for an initial invitation conversation.

In secondary care, participants will be identified opportunistically in out-patient clinics and through screening new referral letters. Where there is an available database and patients have given permission to be contacted about research, potential participants may be contacted by mail out or email.

In primary care, a practice will identify participants opportunistically, or via database search and mail out based on a recorded diagnosis of acne and a relevant prescription within the past 6 months, with additional screening for suitability for invitation by a GP. The practice will advise participants to contact their local site study team for the initial invitation conversation, or the practice staff can offer to have the researcher contact the participant, as the participant prefers.

Regardless of how a participant has been identified and approached (section 4.2), the local site study team will conduct an initial invitation conversation either face-to-face or over the phone, depending on preference of the potential participant. Potential participants who are still interested in taking part following this initial conversation will be invited to a baseline clinic visit, which will include taking informed consent followed by the formal eligibility screen.

5.2 BASELINE VISIT

Informed consent

Eligibility evaluation

Pregnancy test

Contraception use

Medical History and participant characteristics:

- Height, weight and waist circumference
- PCOS characteristics
- Blood pressure
- Acne medication use
- Other medication use

Participant blood tests*:

- Renal function / estimated Glomerular Filtration Rate
- Serum potassium†

*Participants may commence treatment and if there is an abnormality they must be contacted within 5 working days by telephone.
† A repeat blood test may be required to account for spuriously raised potassium caused by haemolysis.

Participants will only have blood tests at the baseline visit; their serum electrolytes will not be continuously monitored. Routine potassium monitoring is unnecessary for healthy women taking spironolactone for acne.[26,27]

Participant questionnaires:

- Acne-QoL
- EQ-5D-5L
- Resource use

Acne Assessments

- Self-assessment – Participant's Global Assessment
- Photograph of participants' acne taken on an instant picture camera by clinician in standardised lighting, following the appropriate SOP
- Participants may send photos of their face to site as part of their baseline visit, providing the usual data protection measures of secure storage of the photo (once received) and prompt deletion (once no longer needed) are applied.
- Investigator's Global Assessment (IGA). Where possible, the IGA is to be performed by the same person at all visits.

NB. Self-assessments should be completed before clinical assessments where possible

IMP
The study IMP can be posted/delivered to the participant, if necessary.

Participants may send photos of their face to site as part of their baseline visit so that the clinician can score the IGA, providing the usual data protection measures of secure storage of the photos (once received) and prompt deletion (once no longer needed) are applied.

Other procedures

- Letter to participant's GP informing them of their patient's participation

The local site study team will collect contact details (including 1-2 phone numbers and an email address) from all participants to enable contact during the study and allow follow up phones calls. Contact details will be stored securely at site in a restricted locked environment, in accordance with the GDPR. Contact details will be shared securely with the SAFA study team at Southampton Clinical Trials Unit and stored securely. The study team at Southampton Clinical Trial Unit will access the contact details in case the local study team is unable to support participants whilst on the study (e.g. in case of a pandemic such as Covid-19). Contact details should be sent to the safa trial email account (safa@soton.ac.uk) using SafeSend (https://safesend.soton.ac.uk/). This is the safest and most secure (data protection complaint) mechanism for the sites to send the relevant contact information to the SAFA email account as it is hosted by the University of Southampton and supports both in-transit and at-rest encryption.

Participants will be asked to bring all of their current medication, including acne treatments, with them to the appointment. They will be issued with 7 weeks' worth of study IMP (i.e. one bottle containing 49 tablets), marked "Take 1-2 daily, as instructed by your study clinician" and will receive both written and verbal instructions from the study clinician for taking the medication. Participants will be instructed to take their total dose once daily in the morning to avoid diuresis later in the day/evening. Nurse prescribers, who are comfortable prescribing spironolactone with support from the local PI, may prescribe spironolactone providing this is usual practice at their site. Pharmacies/local site study team have the option to post the IMP to participants, providing systems are in place to monitor and account for dispensing the drug.

Participants should leave with a face-to-face visit date booked for 6 weeks' time with site contact details in case there is difficulty keeping the appointment. If participants are unable to make the original time/date of their next appointment, they will be asked to contact the local site study team to rearrange the visit. Participants will be asked to bring their IMP bottle to the subsequent visit.

Participants should be given their photograph to take home with them to aid recall when assessing change in their acne at later time points. A second photograph may be taken and kept in the Investigator's Site File, if the participant consents to this.

A participant's GP will also be sent a letter to inform them that their patient is taking part in the trial.

5.3 FOLLOW UP

Week 6 (face to face or remote visit) +7 days:

This visit may be conducted remotely and the study IMP posted/delivered to the participant, if necessary.

Participants may send photos of their face to site as part of their remote follow-up visit so that the clinician can score the IGA, providing the usual data protection measures of secure storage of the photos (once received) and prompt deletion (once no longer needed) are applied.

Participant questionnaires

- Acne-QoL
- EQ-5D-5L
- Resource use

Acne Assessments

- Clinical assessment of treatment response: Dose escalation to 2 tablets if the participant is tolerating any side effects.
- Self-assessment – Participant's Global Assessment
- Participant self-assessed overall improvement at 6 weeks recorded on a 6-point Likert scale (with baseline photo to aid recall, where available)
- Investigator's Global Assessment (IGA). Where possible, the IGA is to be performed by the same person who made the assessment at the baseline visit.

NB. Self-assessments should be completed before clinical assessments where possible

Other procedures

- Pill count
- Acne medication use
- ARs of special interest
- Serious Adverse Events
- Contraception check:
    - Nurse/Doctor to ask participants who were using contraception at the baseline visit to confirm that they are still using contraception.
    - Nurse/Doctor to check that participants not using hormonal contraception, co-cyprindiol or other hormonal treatment have not started using it.
    - Nurse/Doctor to check participants using hormonal contraception have not changed type.
- Nurse/Doctor to ask participants to confirm they are not taking oral treatment for their acne
- If participant's dose was changed - letter to participant's GP informing them of their patient's change in dose.

Participants will be instructed to return their baseline IMP bottle and any remaining study drug to the local site study team. Participants may have their dose of IMP increased from 1 tablet to 2 tablets per day, if they are tolerating any side effects. Participants will be issued with 7 weeks' worth of study IMP (one or two bottles of IMP with 49 tablets in each bottle, depending on whether they have been updosed to 2 tablets per day) marked "Take 1-2 daily, as instructed by your study clinician", and will receive written and verbal instructions from the study clinician for taking their study medication. Participants will be instructed to take their total dose once daily in the morning to avoid diuresis later in the day/evening. Nurse prescribers, who are comfortable prescribing spironolactone with support from the local PI, may prescribe spironolactone providing this is usual practice at their site. Pharmacies/local site study team have the option to post the IMP to participants, providing systems are in place to monitor and account for dispensing the drug.

Participants should leave with a face-to-face visit date booked for 6 weeks' time with site contact details in case there is difficulty keeping the appointment. If participants are unable to make the original time/date of their next appointment, they will be asked to contact the local site study team to rearrange the visit. Participants will be asked to bring their IMP bottle(s) to the subsequent visit.

After the week 6 visit, local site study teams may adjust the dose of IMP (increasing the dose to 2 tablets if the participant is tolerating any side effects, or lowering the dose to 1 tablet if side effects are unmanageable), following a telephone call with the participant. The local site study team will also either write or email the participant, giving written instructions for the new dose. If participants are unable to collect their extra bottle of IMP, pharmacies/local site study team have the option to post the bottle(s) of IMP to participants, providing systems are in place to monitor and account for dispensing the drug.

A participant's GP will be sent a letter to inform them of any change in the dose of study drug their patient is receiving.

Week 12 (face to face or remote visit) +7 days:

This visit may be conducted remotely and the study IMP posted/delivered to the participant, if necessary.

Participants may send photos of their face to site as part of their remote follow-up visit so that the clinician can score the IGA, providing the usual data protection measures of secure storage of the photos (once received) and prompt deletion (once no longer needed) are applied.

Participant questionnaires

- Acne-QoL
- EQ-5D-5L
- Resource use

Acne Assessments

- Clinical assessment of treatment response. If the participant is not already taking 2 tablets, dose escalation to 2 tablets if the participant is tolerating any side effects. 'Usual care' oral antibiotics/change of topical treatment also offered if the participant and study clinician judge together there has been inadequate treatment response.
- Self-assessment – Participant's Global Assessment
- Participant self-assessed overall improvement at 12 weeks recorded on a 6-point Likert scale (with baseline photo to aid recall)
- Investigator's Global Assessment (IGA). Where possible, the IGA is to be performed by the same person who made the assessment at the baseline visit.

NB. Self-assessments should be completed before clinical assessments where possible

Other procedures

- Pill count
- Acne medication use
- ARs of special interest
- Serious Adverse Events

- Participant given their second photograph (if site stored participant's photograph)
- Contraception check:
    - Nurse/Doctor to ask participants who were using contraception at the baseline visit to confirm that they are still using contraception.
    - Nurse/Doctor to check that participants not using hormonal contraception, co-cyprindiol or other hormonal treatment have not started using it.
    - Nurse/Doctor to check participants using hormonal contraception have not changed type.
- Nurse/Doctor to ask participants to confirm they are not taking oral treatment for their acne
- Nurse/Doctor to instruct each participant to report any subsequent event(s) that the participant, or the participant's GP, believes might reasonably be related to participation in this trial to the Nurse/Doctor.
- Nurse/Doctor to ask participant if they would like to receive a summary of the study results, when they are available. Answer to be recorded.
- If participant's dose was changed - letter to participant's GP informing them of their patient's change in dose.

Participants are to return their week 6 IMP bottle(s) and any remaining study drug to the local site study team. Participants will be issued with 12 weeks' worth of study IMP (one or two bottles of IMP with 84 tablets in each, depending on whether they have been updosed to 2 tablets per day) marked "Take 1-2 daily, as instructed by your study clinician", and will receive written and verbal instructions from the study clinician for taking their study medication. Participants will be instructed to take their total dose once daily in the morning to avoid diuresis later in the day/evening. Nurse prescribers, who are comfortable prescribing spironolactone with support from the local PI, may prescribe spironolactone providing this is usual practice at their site. Pharmacies/local site study team have the option to post the IMP to participants, providing systems are in place to monitor and account for dispensing the drug.

Participants will be reminded that there is no face-to-face visit at week 24, but that the local site study team will send questionnaires for them to complete.

After the week 12 visit, local site study teams may adjust the dose of IMP (increasing the dose to 2 tablets if the participant is tolerating any side effects, or lowering the dose to 1 tablet if side effects are unmanageable) following a telephone call with the participant. The local site study team will also either write or email the participant, giving written instructions for the new dose. If participants are unable to collect their extra bottle of IMP, pharmacies/the local site study team have the option to post the bottle(s) of IMP to participants, providing systems are in place to monitor and account for dispensing the drug.

A participant's GP will be sent a letter to inform them of any change in the dose of study drug their patient is receiving.

Week 24 questionnaires (end of treatment; remote data collection):

Participants stop taking the study drug/placebo.

Participant questionnaires

- Acne-QoL
- EQ-5D-5L
- Resource use

Acne assessments

- Self-assessment – Participant's Global Assessment
- Participant self-assessed overall improvement at 24 weeks recorded on a 6-point Likert scale (with baseline photo to aid recall)

Other procedures

- Pill count
- Acne medication use, including use of other oral acne treatments during follow-up
- ARs of special interest
- Serious Adverse Events
- Participants will be asked about their satisfaction with their study treatment prior to unblinding

Participants will be asked to return their questionnaire, as well as all unused IMP and packaging to their local site study team. They will be given a prepaid addressed padded envelope for this purpose.

After week 24 visit (up to week 28)

Treatment allocation revealed to participants and their GP via standardised written letters sent from the participant's local site study team.

Follow-up questionnaires (end of follow-up; remote data collection):

Participant questionnaires

- Acne-QoL
- EQ-5D-5L
- Resource use

Acne assessments

- Self-assessment – Participant's Global Assessment
- Participant self-assessed overall improvement at up to 52 weeks recorded on a 6-point Likert scale (with baseline photo to aid recall)

Other procedures

- Acne medication use, including use of other oral acne treatments during follow-up

Participants will be asked to return their questionnaire to their local site study team. They will be given a prepaid addressed envelope for this purpose.

5.4 DEVIATIONS AND SERIOUS BREACHES

Any study protocol deviations/violations and breaches of Good Clinical Practice occurring at sites should be reported to the SCTU and the local R&D Office immediately. SCTU will then advise of and/or undertake any corrective and preventative actions as required.

Sponsor will be notified immediately of any serious protocol deviations/violations and serious breaches.

All serious protocol deviations/violations and serious breaches of Good Clinical Practice and /or the study protocol will immediately be reported to the regulatory authorities and other organizations, as required in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

5.5 TRIAL DISCONTINUATION

In consenting to the study, participants have consented to the study intervention, follow-up and data collection. Participants may be discontinued from the study procedures at any time.

5.5.1 Reasons for trial/trial treatment discontinuation

A participant may withdraw, or be withdrawn, from trial treatment for the following reasons:

- Intolerance to treatment: Any clinical adverse event (AE) which, in the opinion of the PI or delegate named on the delegation log, indicates that continued participation in the study is not in the best interest of the participant.
- Clinician's decision
- Termination of the study by Sponsor
- Pregnancy
  *In the case of pregnancy, the PI or delegate named on the delegation log must immediately notify the Sponsor of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner.

Full details of the reason for trial discontinuation should be recorded in the eCRF and medical record.

5.6 WITHDRAWAL

The participant/legal representative is free to withdraw consent from the trial at any time without providing a reason.

Participants may withdraw or be withdrawn from one of three levels:

- Participant withdrawal (**Level 1**) from trial treatment – participants stop trial treatment but remain in follow-up
- Participant withdrawal (**Level 2**) from trial treatment and further follow-up - participants stop trial treatment and will not be contacted for follow up purposes
- Participant completely withdraw (**Level 3**) from the trial and does not wish for data to be used – participants stop the trial treatment, any follow-up activity and data not used within the analysis

If a participant wishes to withdraw from trial treatment, investigators should explain the importance of remaining on trial follow up for the purposes of data capture only. Where possible, participants who have withdrawn from trial treatment should remain in follow-up as per the trial schedule. If participants additionally withdraw consent for this, they should revert to standard clinical care as deemed by the responsible clinician. An End of Study eCRF should be completed for each participant who withdraws from the study, recording the date and reason for withdrawal, if known.

5.7 BLINDING AND PROCEDURES FOR EMERGENCY UNBLINDING

Participant allocation will be provided to an independent pharmacy (University Hospital Southampton Pharmacy) via a Concealment list provided by the SCTU statistics team.

In the case of adverse events in which participant care would vary dependent on treatment allocation, emergency unblinding may be performed by the independent pharmacy staff. If participant allocation is disclosed, sites should report to SCTU the date, time, reason for unblinding, name of person requesting the code break, and name of person breaking the code. Unblinding reports should be filed in the participant's medical records at site and in the trial master file (without disclosing the treatment allocation). The trial manager or senior trial manager will ensure that the statistician and senior statistician are fully informed of all cases of unblinding.

Deaths and SAEs will be reviewed in a blinded manner. If a SAE is unexpected (i.e. not in line with the approved reference safety information within the Summary of Product Characteristics [SmPC] for spironolactone) and considered drug related the trial statistician and Quality and Regulatory team (SCTU) will be able to unblind the participant's treatment assignment.

All further details will be outlined in the study specific procedure for unblinding.

6 TREATMENTS

6.1 TREATMENT SCHEDULE

Participants will be randomised to a patient pack which will contain either spironolactone or placebo. Participants will be treated for 24 weeks.

Baseline (Day 0):
All participants

- Spironolactone/Placebo 50mg. One tablet to be taken once daily for 6 weeks.

6 week visit +7 days
All participants have a 6 week dose escalation review:

- Dose kept at 50mg: one tablet to be taken once daily for a further 6 weeks.

Or

- Dose increased to 100mg: two tablets to be taken once daily for a further 6 weeks.

12 week visit +7 days
All participants have a 12 week dose review. Based on current prescription, they receive either:

- 50mg**:** one tablet to be taken once daily in the morning for a further 12 weeks.

Or

- 100mg: two tablets to be taken once daily in the morning for a further 12 weeks.

24 weeks
All participants complete their course of study drug.

6.1.1 Dose adjustment

In both arms dose escalation will be offered at 6 weeks increasing if the participant is tolerating any side effects. These side effects of special interest have been taken from the SmPC and based on previous spironolactone research.[13] These side effects are recorded in the eCRF. In both arms this would mean increasing their study drug from 'one to be taken

daily' to 'two to be taken daily'. Participants will receive written and verbal instructions for taking their study medication from the study clinician.

The reason for dose escalation is to avoid side effects from spironolactone, which can cause gastro-intestinal disturbances, dizziness, gynaecomastia and menstrual disturbances, particularly at higher doses. The choice of spironolactone dosage was based on responses by dermatologists to a survey carried out by the UK Dermatology Clinical Trials Network, and is in line with US guidelines.

After 6 weeks, local site study teams may adjust the dose of IMP (increasing the dose to 2 tablets if the participant is tolerating any side effects, or lowering the dose to 1 tablet if side effects are unmanageable) at any time following a telephone call with the participant. The local site study team will also either write or email the participant, giving written instructions for the new dose. If participants are unable to collect their extra bottle of IMP, pharmacies/the local site study team have the option to post the bottle(s) of IMP to participants, providing systems are in place to monitor and account for dispensing the drug.

Important information on additional treatment of participant's acne
Prior to the primary outcome assessment at 12 weeks, participants in both arms will receive 'usual care' from their usual clinician, including topical treatments, but **excluding** oral treatments such as oral antibiotics, or isotretinoin. However, use of topical treatments should reflect 'usual care', i.e. the local site study team will make no particular effort at promoting adherence.

Local site study teams will unblind participants to treatment allocation after 24 weeks, while carefully recording medication use to 52 weeks through questionnaires to participants. Participants in either arm may seek to use spironolactone after 24 weeks. Local site study teams will send a letter to all participants' GPs informing them which treatment their patient received. The letter will suggest potential action for the GP, if their patient asks to be prescribed spironolactone.

6.2 IMP SUPPLY

Spironolactone and placebo are considered investigational medicinal products (IMPs) for the purpose of this protocol.

MODEPHARMA will arrange the sourcing of Spironolactone tablets, placebo manufacture, randomised double-blind IMP packaging, final QP release, storage and distribution of the IMPs. The study medication will be shipped directly from the final QP releasing site to the trial sites following site initiation.

Please refer to the SmPC and Investigational Medicinal Product Dossier (IMPD) for more details about the active and placebo IMPs.

Ratiopharm Spironolactone does not have any special storage conditions (Please see Appendix 1: 6.4 Special Precautions For Storage). Storage can be either within the Site Pharmacy or the dermatology clinic (within in a secure locked cabinet labelled specially for SAFA study drug).

Re-ordering will be via TENALEA.

A detailed IMP/reordering guidance document will be provided to sites.

6.3 ADMINISTRATION

Participants will be given bottles containing 50mg dose tablets at their baseline visit (1 bottle of tablets (49 tablets in each) for 7 weeks); 6 week visit (either 1 bottle of tablets or 2 bottles of tablets (49 tablets in each) for 7 weeks – treatment response dependant); and 12 week visit (either 1 bottles of tablets or 2 bottles of tablets (84 tablets in each) for 12 weeks – based on current prescription). Participants will receive written and verbal instructions for taking their study medication.

6.4 ACCOUNTABILITY

It is the local site study team's responsibility to establish a system for handling study treatments, including investigational medicinal products, so as to ensure that:

- Deliveries of such products from the final QP releasing site are correctly received by a responsible person.
- Such deliveries are recorded.
- Study treatments are handled and stored safely and properly as stated on the label.
- Spironolactone/matching placebo is only dispensed to study participants in accordance with the protocol.
- Participants return all unused medication and empty containers to the local site study team.

The safety profile of spironolactone is well known and it is not a high risk drug. Consequently, we have taken a pragmatic approach to drug accountability. We will ask participants to bring any remaining study medication with them to their week 6 and week 12 clinic visits, and to post any remaining medication back to their local site study team at week 24, using the pre-paid envelope provided. The eCRF will capture the participant identification number of the person to whom the Spironolactone/matching placebo was dispensed, the quantity and date of dispensing and the date any unused Spironolactone/matching placebo was returned to the local site study team.

All unused or returned medication, after drug accountability, should be destroyed and documented according to local procedures at the study site, once written instruction to proceed has been issued by SCTU. Spironolactone/matching placebo and label accountability records will be maintained by the study site personnel.

6.5 CONCOMITANT MEDICATIONS

Information on oral acne treatment received by the participant from 3 months prior to starting trial treatment and up to 28 weeks after the last dose of spironolactone/placebo will be recorded in the eCRF.

6.6 PROHIBITED AND RESTRICTED THERAPIES DURING THE TRIAL

- Ideally, participants should not change their topical treatment during the first 12 weeks of the study.
- Use of topical treatment to reflect 'usual care'; the local site study team will not actively promote adherence to topical therapies.
- Participants should not start, stop or change long-term (lasting for more than 2 weeks) hormonal contraception (or other hormonal treatment) during the first 12 weeks of the study.

- Participants should not take oral antibiotics, which could be prescribed for the management of acne, for more than 2 weeks' continuous use during the first 12 weeks of the study.
- No isotretinoin to be taken by participants during the first 24 weeks of the study.

All uses of prohibited and restricted therapies will be recorded in the trial's eCRF and deviation log. Participants will remain in the trial.

6.7 DOSE DELAYS AND MODIFICATIONS FOR TOXICITY

Participants will be provided with 7 days' worth of excess tablets in their baseline and 6 week bottles to allow flexibility when booking their next clinic appointment. However, SAFA is a 'usual care' trial, so if participants miss a tablet or are unable to make their next clinic appointment before their tablets run out, they will continue in the study as planned. Any missed tablets will be captured in the pill count and eCRF.

In the event of an AR of special interest, supportive therapy should be given according to local policies. Menstrual irregularities are the most common adverse effect and these are dose dependent. If participants tolerate 1 tablet but not 2 tablets the dose will be reduced (see section 6.1.1).

7 SAFETY

7.1 DEFINITIONS

The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, provides the following definitions relating to adverse events in trials with an investigational medicinal product:

Adverse Event (AE): any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered.
All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as ARs. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure (IB) for an unapproved investigational product or SmPC for an authorised product*).*
When the outcome of the AR is not consistent with the applicable product information this AR should be considered as unexpected. Side effects documented in the IB/SmPC which occur in a more severe form than anticipated are also considered to be unexpected. Reports which add significant information on specificity or severity of a known documented adverse event are to be considered unexpected.

Serious Adverse Event (SAE) or **Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR):** any untoward medical occurrence or effect that at any dose:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing hospitalisation***
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**
- Important medical events**.

* Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
**Other important medical events may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

Note: *It is the responsibility of the PI or delegate named on the delegation log to grade an event as 'not serious' (AE) or 'serious' (SAE).*

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected AR related to an IMP that is both unexpected and serious.

7.2 SERIOUSNESS

A complete assessment of the seriousness must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the PI.

All adverse events that fulfil the criteria definition of 'serious' in protocol section 7.1 and are not included in the exceptions list below must be reported to the SCTU using the trial specific Serious Adverse Event Report Form. Specific exceptions to this (as listed below) should be recorded as AEs rather than SAEs.

All SAEs must be reported immediately by the PI or delegate at the participating centre to the SCTU.

7.2.1 Exceptions:

For the purposes of this trial, the following SAEs **do not** require reporting to SCTU using the Serious Adverse Event Report Form:

- Hospitalisations for elective treatment of a pre-existing condition

7.3 CAUSALITY

A complete assessment of the causality must always be made by a medically qualified doctor who is registered on the delegation of responsibility log to undertake this duty; this is usually the PI.

If any doubt about the causality exists the local PI should inform Southampton Clinical Trials Unit (SCTU) who will notify the Chief Investigator. Other clinicians may be asked for advice in these cases.

In the case of discrepant views on causality between the PI and others, SCTU will classify the event as per the worst case classification and if onward reporting is required, the MHRA will be informed of both parties points of view.

Relationship	Description	Denoted
Unrelated	There is no evidence of any causal relationship	SAE
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	SAE
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	SAR/ SUSAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR/ SUSAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR/ SUSAR

7.4 EXPECTEDNESS

Expectedness assessments are made against the approved reference safety information (RSI). The RSI for this trial is specified within the document versions listed in the tables below:

Name of Product	SmPC	Section /Table No.	Manufacturer	Last updated
Spironolactone-ratiopharm 50mg/100mg Tablets	010455-19858	4.8 Undesirable effects	Ratiopharm GmbH (Germany)	JAN-2016 Located in Appendix 1

The nature or severity of the event should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available then the AE should be recorded as 'unexpected'.

7.5 REPORTING PROCEDURES

There are a number of avenues where SAEs could be identified:

1. Participants' GPs: Participants' GPs will be informed of their patient's participation and will be asked to notify the local site study team of any event that falls within the serious classification (section 7.1).

2. The local site study team: Teams will ask the participant at the 6 week and 12 week follow-up visits whether they have been hospitalised, and if so where; the team will obtain relevant information and contact the participant's GP should further information

be required. The eCRF will also collect information on ARs of special interest, including their duration and severity.

3. Participant reported: At the 24 week follow up contact, participants will be asked within the follow up questionnaire if they have been to hospital, and if so where they were hospitalised. The local site study team will obtain relevant information and contact the participant's GP should further information be required. The eCRF will also collect information on ARs of special interest, including their duration and severity.

Upon occurrence of an SAE notified by the GP, identified at the follow up visits or participant reported at 24 weeks, the PI or named delegate listed on the delegation log will assess seriousness and causality. Any delegated member of local site study team will take the reporting action described in Sections 7.5.3 and 7.5.4.

7.5.1 Non-serious AEs/ARs

Given the safety profile of spironolactone is well known and it is not a high risk drug, non-serious AEs/ARs will not be recorded as part of the safety profile of the study drug, and will be managed according to current clinical practice. ARs of special interest will be collected to inform the dosing of the study drug (see section 6.1.1 and listed in the Schedule of Observations and Procedures).

7.5.2 Assessment of intensity

The intensity of all SAEs should be assessed by the PI or delegate named on the delegation log according the following definitions:

1. Mild – asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Does not interfere with participant's usual function
2. Moderate – minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL) (such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc)
3. Severe – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (such as bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
4. Life-threatening consequences; urgent intervention indicated.
5. Death related to AE

(A semi-colon indicates 'or' within the description of the grade).

It should be noted that the severity and seriousness of an AR are not the same classification, such that an AE classified as severe (for example a headache) is not necessarily an SAE (unless it also meets the definition of an SAE in section 7.1)

7.5.3 Reporting to SCTU

For all SAEs, SARs and SUSARs an SAE report form should be completed with as much detail as possible (including any relevant anonymised treatment forms and/or investigation reports) and faxed/emailed to SCTU immediately but at least within 24 hours of site becoming aware of the event.

Or

Contact SCTU by phone for advice and then fax or email a scanned copy of the SAE report form completed as above.

SAE REPORTING CONTACT DETAILS

Please email or fax a copy of the SAE form to
SCTU within 24 hours of becoming aware of the event

Fax: 0844 774 0621 or Email: ctu@soton.ac.uk

FAO: Quality and Regulatory Team

For further assistance: Tel: 023 8120 4138 (Mon to Fri 09:00 – 17:00)

The SAE report form asks for nature of event, date of onset, severity, outcome, causality and expectedness. The responsible investigator (or delegate) should assign the seriousness, causality and expectedness of the event with reference to the approved IMP IB/SmPC and provide version used for the assessment.
The event term should be the most appropriate medical term or concept (which the SCTU will code to MedDRA) and grades given in accordance with the NCI CTCAE v5.

Additional information should be provided as soon as possible if the event has not resolved at the time of reporting.

In addition to the definition above, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. Elevations in liver biochemistry that meet Hy's Law criteria are reported as SAEs, using the important medical event serious criterion if no other criteria are applicable.

7.5.4 Follow up and post-trial SAEs

The reporting requirement for all SAEs affecting participants applies for all events occurring from Informed Consent up to the 24 week contact.

All unresolved SAEs should be followed by the PI or delegate named on the delegation log until resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the local site study team should instruct each participant to report any subsequent event(s) that the participant, or the participant's GP, believes might reasonably be related to participation in this trial. The PI or delegate named on the delegation log should notify the trial sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated trial participation that may reasonably be related to this trial.

7.5.5 Non-serious AEs

All adverse events (unless specified as exceptions in this protocol) should be recorded in the relevant eCRF and submitted to SCTU.

7.5.6 Pre-existing conditions

Medically significant pre-existing conditions (prior to informed consent) should not be reported as an AR of special interest unless the condition worsens during the trial. Any SAEs which occur after informed consent is taken should be recorded on the SAE eCRF as per safety reporting section.

7.5.7 Pregnancy

Spironolactone is a category C drug and feminisation of the foetus is said to occur in the last trimester of pregnancy.[12] Concerns have also been raised about teratogenicity of spironolactone but risk of harm to the foetus is thought to be lower than for oral tetracyclines, which are also commonly used in acne.[12,28] The local site study team will carry out pregnancy tests at baseline, and advise participants of childbearing potential at risk of pregnancy that they must use their usual hormonal or barrier method of contraception during the first 6 months of the study (whilst taking the study IMP) and for at least 4 weeks (approximately one menstrual cycle) afterwards.

If a participant becomes pregnant whilst taking part in the trial or during a stage where the foetus could have been exposed to an IMP, the local site study team must inform the Trial Manager as soon as they become aware of the pregnancy. The pregnancy itself is not an SAE, however, the outcome of the pregnancy may be an SAE.
When made aware of the pregnancy the Trial Manager will inform the Chief Investigator, and liaise with the local site team. All tasks to be carried out once a pregnancy notification is received are detailed below:

- **Site**
  - Confirm with the participant and provide information to Trial Manager
    - the date of the positive pregnancy test/how many weeks pregnant the participant is
    - the last date the participant took IMP
    - the date of their last period
    - If the participant requested to be unblinded
  - Confirm to Trial Manager
    - whether the patient was advised at baseline and follow-up visits (if applicable) that they must use appropriate contraception as per protocol
    - that the study nurse/clinician checked that if the participant was taking contraception at baseline, the participant was still taking the contraception at their follow-up visits
  - Complete forms in RAVE data base
    - End of Treatment form (date the participant has stopped taking the IMP)
    - End of Study form (date the site was made aware of the pregnancy)
    - Pregnancy notification form (it asks whether consent for the pregnancy follow-up has been obtained from the participant)
  - If possible, IMP should be returned to site for drug reconciliation to be completed
  - If permission to unblind given by Chief Investigator, Trial Manager asks site team to complete and return the trial unblinding request form (if participant wishes to be unblinded) and send to ctu@soton.ac.uk
  - Site team provide the participant with the Pregnancy Patient Information Sheet and Informed Consent Form

- If the participant is happy for her pregnancy to be followed up, site team send a copy of the signed Informed Consent Form to SCTU via SafeSend (https://safesend.soton.ac.uk/). SafeSend is the safest and most secure (data protection complaint) mechanism for the sites to send the relevant contact information to the SAFA email account as it is hosted by the University of Southampton and supports both in-transit and at-rest encryption.
- Sending documents with patient identifiable information to SCTU via SafeSend is the preferred option. However, if SafeSend is not compatible with the local Trust, the site team have the option to send the questionnaires and informed consent forms to SCTU (uhs.sctu@nhs.net) via a secure NHS email address. Notice of having to use this option should be communicated to the Trial Manager as soon as site/local R&D become aware.

  - Site study team must ensure that the participant and the participant's healthcare professional are aware that follow up information is required on the outcome of the pregnancy (if participant gives informed consent for this). If the participant leaves the area, their new healthcare professional should also be informed.

- **Trial Manager to email Chief Investigator**
  - how many weeks the patient is pregnant
  - last date of IMP taken
  - ask to confirm if there is a risk to the foetus
  - ask if they require additional information (depending on consent being provided) and if there is any information which should be passed to the treating team or mother
  - Ask for permission to reveal treatment allocation (if this has been requested by site and/or if the participant has requested to be unblinded)
- **Trial statistician**
  - Trial Manager informs the TS once permission to unblind has been given by Chief Investigator and the unblinding request form has been received, trial statistician will liaise with site regarding the unblinding of the pregnant participant
  - PLEASE NOTE: SCTU trial management team must remain blinded to treatment allocation.
- **SCTU Quality and Regulatory team**
  - Trial Manager informs the team that a pregnancy notification was received
  - The Quality and Regulatory team will be responsible for pregnancy follow-up if the participant gives permission by signing the informed consent form
  - Information asked during the pregnancy follow-up are:
    - Date of last menstrual period
    - Estimated date of delivery given by midwife/obstetric team
    - Eventual date of delivery
    - Outcome of pregnancy
- **Report to sponsor**
  - Trial manager completes pregnancy report to sponsor summarising the conversions with site and Chief Investigator
  - Completed report will be sent to via email to the sponsor

If consent to pregnancy follow up is not received, no further follow-up of the pregnancy can continue. The decline to consent or lack of receipt of consent should be clearly documented

in the patient notes (TM should advise site of this) and within the trial documentation by the TM.

7.6 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO REC

SCTU will notify the necessary REC of all SUSARs occurring during the trial according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days.

SCTU submit all safety information to the REC in annual progress report and the annual Development Safety Update Report (DSUR).

7.7 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO MHRA

SCTU will notify the necessary competent authorities of all SUSARs occurring during the trial according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days.

SCTU submit the DSUR to MHRA annually.

8 STATISTICS AND DATA ANALYSES

8.1 METHOD OF RANDOMISATION

Participants will be individually randomised using TENALEA. Participants will be stratified by centre and by baseline severity (IGA < 3 versus 3 or more).

8.2 SAMPLE SIZE

Based on comparison of the Acne-QoL between arms at 12 weeks, power 90%, alpha 0.05 and seeking a difference between arms of 2 points on the symptom subscale (s.d. 5.8, effect size 0.35), 346 participants are needed. Allowing for 20% loss to follow up gives a total 434 participants (217 per arm). Allowing for a correlation with baseline of 0.293 and a deflation factor of 1-ρ2[29], gives a total sample size (including allowing for 20% loss to follow up) required of 398 participants. A difference of 2 points on the symptom subscale and a standard deviation of 5.8 (equivalent to an effect size 0.35) is in line with that reported in trials in a similar patient group and with the MCID reported for Acne-QoL.[24,30]

8.3 INTERIM ANALYSIS

No interim analysis is planned.

8.4 STATISTICAL ANALYSIS PLAN (SAP)

The study will be reported in accordance with CONSORT guidelines. A detailed statistical analysis plan will be written and reviewed prior to the trial database being frozen. All data and appropriate documentation will be stored for a minimum of 25 years after the completion of the trial, including the follow-up period. All assumptions underlying regression modelling applied will be checked and alternative analysis methods used (e.g. transformation or non-parametric methods) if the assumptions are not met.

Study populations:
Modified Intention-to-treat (ITT) population – consists of all participants who have consented and been randomised to a treatment arm and have complete data for the outcome being analysed. All analyses will be carried out in the modified ITT population, with the level of missing data reported, unless otherwise stated.

Analyses:
For the primary analyses, descriptive statistics will be obtained for the randomisation arms to characterise recruited participants and assess baseline comparability.

For the primary outcome, a linear regression model will be used to analyse Acne-QoL symptom subscale at 12 weeks, adjusting for baseline variables (including baseline Acne-QoL symptom subscale score, use of topical treatments) , use of hormonal contraception/co-cyprindiol) and randomisation stratification variables (centre, baseline severity (IGA < 3 versus 3 or more)). 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 analysis will be repeated using multiple imputation for missing data.

The same analysis methods will be used to summarise Acne-QoL symptom subscale at other time points (6 weeks, 12 weeks and 24 weeks) and for the other Acne-QoL subscales (self-perception, role-emotional and role-social) and total score.

Participant's and investigator's global assessment and participants' comparison with baseline photo at 6, 12 and 24 weeks will be dichotomized as success or failure as recommended by the FDA (with success for IGA and participants global assessment 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). The dichotomized outcomes will be summarised by frequencies and percentages and compared by arm using logistic regression adjusting for baseline assessment, use of hormonal contraception/co-cyprindiol), use of topical treatment and randomisation stratification factors.

ARs of special interest and SAEs 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.

Subgroup analyses will investigate how the treatment effect differs by whether participants have symptoms consistent with PCOS as recorded at the baseline visit. It is acknowledged the trial is not powered for this subgroup analysis.

The analysis of the final follow up data wil primarily be analysed descriptively as participants will potentially have been off treatment for up to 6 months.

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

9 HEALTH ECONOMICS

If clinically effective, then spironolactone is likely to be cost-effective for acne as it is cheaper than current alternatives, such as doxycycline.[11]

To demonstrate this, if the intervention is found effective, a within-trial cost-effectiveness analysis will be undertaken to assess value for money of spironolactone plus standard care versus standard care for women aged 18 years and over with moderate or severe persistent

facial acne from the perspective of the NHS (as personal social service resource use is unlikely to be incurred for the condition and participant population in the study).[31]

Cost and cost-effectiveness, including intervention and wider NHS resource use, will be recorded in the trial eCRF for the former whilst wider NHS resource use will be captured in participant questionnaires at baseline, 6, 12, and 24 weeks. Cost and cost-effectiveness will be valued using published unit costs[32-34] for a common recent price year to estimate mean cost per participant in each arm. The potential importance of taking a broader perspective will be considered in a secondary analysis incorporating participant out of pocket costs related to acne and any productivity/employment impacts for people with persistent acne. Questions capturing these will be incorporated into the resource use questionnaires developed for the trial.

Participants will be asked to complete the EQ-5D-5L [35,36] at baseline, 6, 12, and 24 weeks. The EQ-5D was chosen as the limited published evidence available supports the use of the EQ-5D for Acne. Yang et al (2015) systematically searched for evidence on the reliability, validity and responsiveness of three generic preference-based measures (EQ-5D, SF-6D and HUI) in skin conditions.[36] They only found evidence to support the use of the EQ-5D in skin diseases; they found no studies looking at measurement properties for the Short-Form six-dimensions (SF-6D) or Health Utilities Index (HUI) in skin disease.[36] For acne there is one paper by Klassen et al (2000) who found that problems on the EQ-5D domains were substantially higher in the acne sample receiving specialist care than in an age truncated population sample (aged 20-39 years) particularly on the pain/discomfort (42.1% in the acne sample versus 17.7% in an age-truncated population sample) and anxiety/depression domains (52.8% versus 12.5% respectively).[35] It also found the EQ-5D to be responsive to change, with moderate effect sizes at 4 and 12 months (-0.44 and -0.53 respectively).[35] The authors stated "The present study demonstrates that health problems in acne patients could be detected by means of the EQ-5D despite its limited scope. In addition, treatment was shown to be effective by means of this measure."[35] The EQ-5D-5L can be valued in a number of ways with NICE (2017)[37] currently recommending using the 3L valuation set and the mapping function developed by Van Hout et al (2012)[38], where data has been collected using the 5L descriptive system, for the reference case analysis. We will value the EQ-5D-5L in our primary analysis in line with NICE recommendations at the time of analysis. If appropriate, the EQ-5D-5L may be valued in more than one way in secondary analyses in order to explore the impact of the different approaches available on the results and conclusions reached (Devlin et al 2018).[39] QALYs (estimated using EQ-5D-5L [35,36]) for the trial period will be estimated using linear interpolation and area under the curve with and without baseline adjustment.[40]

Klasson et al did, however, find clinical measures to be more responsive to change than the generic measures (shown by larger effect sizes) and concluded that it is desirable to combine generic preference based measures with the use of disease specific measures. The primary outcome measure in this study is the disease-specific Acne-QoL. Whilst this measure does not have utility weights available, a secondary cost effectiveness analysis using this instrument will be presented as appropriate, though it should be noted that it is unclear what incremental cost per unit of change on the Acne-QoL represents good value for money.

The primary economic evaluation will be an Incremental cost utility analysis from an NHS perspective, as this enables the cost effectiveness to be compared across a range of health conditions and interventions such that decision makers can use the information to inform prioritisation of health care. This analysis will be conducted and presented using established methods.[41,42]

If Spironolactone is not found to be clinically effective a full economic evaluation will not be conducted. Instead, estimates of mean costs and utility per participant will be presented at the various study time points as these may be informative for other researchers undertaking future economic studies or economic modelling in this clinical area.

A detailed Health Economic Analysis Plan will be written and reviewed prior to the trial database being locked.

10 REGULATORY

10.1 CLINICAL TRIAL AUTHORISATION

This trial has a Clinical Trial Authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA).

11 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the study should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the study without giving reasons must be respected.

After the participant has entered the study, the clinician may give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the study for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from protocol treatment and study follow-up without giving reasons and without prejudicing their further treatment.

11.1 SPECIFIC ETHICAL CONSIDERATIONS

None.

11.2 ETHICAL APPROVAL

The study protocol has received the favourable opinion of Wales REC 3 Research Ethics Committee in the approved national participating countries.

11.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the local site study team should comply with applicable regulatory requirements and should adhere to the principles of GCP.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to the participant by appropriately delegated staff with

knowledge in obtaining informed consent with reference to the Participant Information Sheet. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. The participant will be given the opportunity to ask any questions that may arise and provided the opportunity to discuss the trial with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

11.4 CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the trial. The local site study team must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On CRFs and eCRFs participants will not be identified by their names, but by an identification code.

12 SPONSOR

SCTU, Chief Investigator and other appropriate organisations have been delegated specific duties by the Sponsor and this is documented in the trial task allocation matrix.

The duties assigned to the trial sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

12.1 INDEMNITY

The University of Southampton's public and professional indemnity insurance policy provides an indemnity to UoS employees for their potential liability for harm to participants during the conduct of the research. This does not in any way affect an NHS Trust's responsibility for any clinical negligence on the part of its staff.

12.2 FUNDING

The NIHR Health Technology Assessment Programme is funding this study.

12.2.1 Site payments

The payments assigned to the trial sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

This study is automatically eligible for the NIHR portfolio. This enabled trusts to apply to their comprehensive local research network for service support costs, if required.

12.2.2 Participant payments

Participants will not be paid for participation in this study.

12.3 AUDITS AND INSPECTIONS

The study may be participant to inspection and audit by University of Southampton (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, UK Policy Framework for Health and Social Care Research, applicable contracts/agreements and national regulations.

13 TRIAL OVERSIGHT GROUPS

The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by the Trial Management Group, the Trial Steering Committee and the Data Monitoring and Ethics Committee.

13.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the study, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the study.

The SAFA TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

13.2 TRIAL STEERING COMMITTEE (TSC)

The TSC act as the oversight body on behalf of the Sponsor and Funder. The TSC will meet at least yearly. The majority of members of the TSC, including the Chair, should be independent of the trial.

The SAFA TSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TSC, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

13.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC) /DATA MONITORING AND ETHICS COMMITTEE (DMEC)

*(**NB** for the purposes of this protocol, IDMC and DMEC refer to the same committee, and these terms can be used interchangeably).*

The aim of the IDMC is to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the study.

The SAFA DMEC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the DMEC, including the timing of meetings, methods of providing information to and from the DMEC, frequency and format of meetings, statistical issues and relationships with other trial committees.

14 DATA MANAGEMENT

Participant data will be entered remotely at site and retained in accordance with current Data Protection Regulations. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data is pseudo anonymised by assigning each participant a participant identifier code which is used to identify the participant during the study and for any participant- specific clarification between SCTU and site. The site retains a participant identification code list which is only available to site staff.

The Informed Consent Form and Participant Information Sheet will specify the participant data to be collected and how it will be managed or might be shared; including handling of all Participant Identifiable Data (PID) and sensitive PID adhering to relevant data protection law.

Trained personnel with specific roles assigned will be granted access to the eCRF. Electronic CRF completion guidelines will be provided to sites to aid data entry of participant information.

Only the PI and personnel authorised by them should enter or change data in the eCRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the eCRF. The original laboratory reports must be retained by the site for future reference.

A Data Management Plan (DMP) providing full details of the study specific data management strategy for the trial will be available and a Trial Schedule with planned and actual milestones, CRF tracking and central monitoring for active trial management created.

Data queries will either be automatically generated within the eCRF, or manually raised by the local site study team, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the trial after all queries have been resolved and the database frozen, the PI will confirm the data integrity by electronically signing all the eCRFs. The eCRFs will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

Data may be requested from the Data Access Committee at SCTU. Any request will be considered on a monthly basis.

15 DATA SHARING REQUESTS FOR RESULTS THAT ARE AVAILABLE IN THE PUBLIC DOMAIN

In order to meet our ethical obligation to responsibly share data generated by interventional clinical trials, SCTU operate a transparent data sharing request process. As a minimum, anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site, www.southampton.ac.uk/ctu] to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

16 MONITORING

16.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data queries will be produced at SCTU in the trial database. Sites will respond to the queries providing an explanation/resolution to the discrepancies and return the data query forms to SCTU within the required timeframe. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring features in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan.

16.2 CLINICAL SITE MONITORING

The Trial will be monitored and audited in accordance with SCTU procedures. All trial related documents will be made available on request for monitoring and audit by SCTU, UoS and REC and for inspection by other relevant bodies. Prior to the trial start, the centre will be advised of the anticipated frequency of the monitoring visits. The Site Lead will receive reasonable notification prior to any monitoring visits.

16.2.1 Source Data Verification

On receipt of a written request from SCTU, the PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account current Data Protection Regulations). Access should also be given to study staff and departments (e.g. pharmacy).

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the study, including representatives of the Competent Authority. Details will remain confidential and participants' names will not be recorded outside the study site.

16.3 SOURCE DATA

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

16.4 AUDITS AND INSPECTIONS

The trial may be participant to inspection and audit by University of Southampton (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

17 RECORD RETENTION AND ARCHIVING

Trial documents will be retained in a secure location during and after the trial has finished.

The PI or delegate named on the delegation log must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. After trial closure the PI will maintain all source documents and trial related documents. All source documents will be retained for a period of 25 years following the end of the trial.

Sites are responsible for archiving the ISF and participants' medical records.

The Sponsor is responsible for archiving the TMF and other relevant trial documentation.

18 PUBLICATION POLICY

Data from all centres will be analysed together and published as soon as possible.

Individual investigators may not publish data that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors then a 'writing committee' will be identified.

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20 APPENDIX 1 DRUG INFORMATION FROM SMPC – TABLET FORMULATION

SUMMARY OF PRODUCT CHARACTERISTICS: SPIRONOLACTONE-RATIOPHARM 50MG / 100MG TABLETS (GERMAN-ENGLISH TRANSLATION)

The translation refers to the following document:

- Publisher: Ratiopharm GmbH (Germany)
- Document title: Fachinformation Spironolacton-ratiopharm® 50mg/100mg Tabletten
- Document date: Jan 2016 Publication language: German Sections translated: 1 - 11
- Summary of Product Characteristics
- Spironolactone-ratiopharm® 50 mg / 100 mg tablets
- FACHINFORMATION 4010455-19858

Summary of Product Characteristics
Spironolactone-ratiopharm® 50 mg / 100 mg tablets

1. NAME OF THE MEDICINAL PRODUCT

Spironolactone-ratiopharm® 50 mg tablets

Spironolactone-ratiopharm® 100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Spironolactone-ratiopharm® 50 mg tablets

Each tablet contains 50 mg spironolactone.

Spironolactone-ratiopharm® 100 mg tablets

Each tablet contains 100 mg spironolactone.

Excipient with known effect: lactose

Full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Spironolactone-ratiopharm® 50 mg tablets

White, round, biconvex tablet with a score on one side

Spironolactone-ratiopharm® 100 mg tablets

White, round, biconvex tablet with cross-hatch notch on one side

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Primary hyperaldosteronism, unless surgery is indicated
- Oedema and / or ascites in diseases associated with secondary hyperaldosteronism

4.2 Posology and method of administration

Posology

The dosage should be determined individually, depending on the severity and extent of the disease. The following dosing recommendations apply:

Adults

For adults, the **initial dose is 100-200** mg spironolactone per day, divided into 1 - 2 single doses over 3 - 6 days. If insufficient, the dose may be increased to a maximum of 400 mg spironolactone per day.

As a **maintenance dose** usually 50-100 mg spironolactone to a maximum of 100-200 mg spironolactone are sufficient. The maintenance dose may be administered daily, every 2nd or every 3rd day, as needed.

Paediatric population

Due to its high content of active ingredient, Spironolactone-ratiopharm® tablets are unsuitable for use in infants.

There are no controlled clinical trials for dosing in newborns and children. Medical guidelines recommend the following dosages:

- Newborns: 1 - 2 mg / kg daily, divided into 1 - 2 single doses; up to 7 mg / kg daily with resistant ascites.
- Children from 1 month to 12 years: 1 - 3 mg / kg daily, divided into 1 - 2 single doses; up to 9 mg / kg daily with resistant ascites.
- Adolescents from 12 to 18 years: 50 - 100 mg daily, divided into 1 - 2 single doses; up to 9 mg / kg daily (maximum 400 mg daily) in resistant ascites.

Method of administration

The tablets should be swallowed whole with sufficient liquid (e.g. a glass of water).

The duration of treatment depends on the type and severity of the disease. It should be limited to as short a period as possible. The need for long-term therapy should be reviewed periodically. Children should not be given spironolactone for more than 30 days.

4.3 Contraindications

Spironolactone-ratiopharm® tablets should not be used with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Anuria
- Acute renal failure
- Severe renal insufficiency with oliguria and anuria (creatinine clearance below 30 ml / min per 1.73 m2 body surface area and / or serum creatinine above 1.8 mg / dL)
- Hyperkalaemia
- Hyponatremia
- Hypovolemia or dehydration
- Pregnancy and during breast feeding

4.4 Special warnings and precautions for use

Particularly careful medical supervision is required in:

- moderate kidney impairment (creatinine clearance between 60 and 30 ml / min or serum creatinine between 1.2 and 1.8 mg / dl)

- patients prone to acidosis and / or hyperkalaemia as a result of their underlying disease (e.g. patients with diabetes mellitus)
- hypotension

Potassium supplementation in the form of medications should not be given or a potassium rich diet should generally not be consumed during spironolactone therapy. Excessive potassium intake may cause hyperkalaemia in patients receiving spironolactone.

Co-administration of spironolactone with medicinal products known to cause hyperkalaemia (potassium-sparing diuretics [e.g. amiloride, triamterene], ACE inhibitors, angiotensin II antagonists, non-steroidal anti-inflammatory drugs [NSAIDs], trimethoprim / sulfamethoxazole [cotrimoxazole]), can lead to severe hyperkalemia.

In case of severe renal insufficiency (glomerular filtration rate below 30 ml / min and / or serum creatinine above 1.8 mg / dl), Spironolactone-ratiopharm® tablets are not only ineffective but even harmful, as the glomerular filtration rate is further reduced.

In renal impairment with serum creatinine levels between 1.2 and 1.8 mg / dl and creatinine clearance between 60 and 30 ml / min per 1.73 m2 of body surface and concomitant use of any medicinal products that cause an increase serum potassium levels, treatment with Spironolactone-ratiopharm® tablets should besubjected to frequent monitoring of serum potassium.

When administering Spironolactone-ratiopharm® tablets, periodically check the serum electrolytes (especially potassium, sodium, calcium, bicarbonate), serum creatinine, urea and uric acid, as well as the acid-base status.

All patients treated with diuretics should be monitored for fluid or electrolyte disturbances, e.g. Hypomagnesaemia, hyponatremia, hyperchloraemic alkalosis and hyperkalemia. In patients that vomit more frequently or receive parenteral liquids, the determination of serum and urine electrolytes is particularly important. Warning signs or symptoms of fluid or electrolyte disturbances, regardless of the cause, are weakness, drowsiness, muscle pain or cramps, muscle weakness, atonic paralysis of the extremities, hypotension, and gastrointestinal complaints such as nausea and vomiting. Hyperkalaemia may occur in patients with impaired renal function or excessive potassium intake, causing cardiac arrhythmias that can lead to death. Therefore, during a spironolactone treatment, potassium supplementation should usually not be used.

Patients have been reported to have reversible hyperchloraemic metabolic acidosis, usually in conjunction with hyperkalaemia.

Hyponatraemic hyperhydration may be induced or worsened.

There may be a transient increase in urea nitrogen in the blood during treatment with spironolactone, especially in patients with pre-existing renal impairment. Spironolactone can cause mild acidosis.

The weight loss caused by increased urinary output should not exceed 1 kg / day, regardless of the extent of urinary output.

Chronic diuretic abuse may result in pseudo-Bartter syndrome resulting in oedema. The oedema is an expression of a renin increase with secondary hyperaldosteronism.

Spironolactone-ratiopharm® tablets may cause interference with certain diagnostic tests (e.g. RIA determination of digoxin serum concentration).

Patients should be aware of adequate fluid intake during treatment with Spironolactone-ratiopharm® tablets.

The use of Spironolactone-ratiopharm® tablets may lead to positive results in doping control. The use of Spironolactone-ratiopharm® tablets as a doping agent may endanger your health.

Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Spironolactone-ratiopharm® tablets.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions between the present and other medicinal products should be noted:

The simultaneous use of Spironolactone-ratiopharm® tablets and potassium supplements (e.g. potassium chloride), ACE inhibitors (e.g. captopril, enalapril), angiotensin II antagonists (e.g. candesartan, valsartan) or potassium-sparing medicines (e.g. Triamterene, Amiloride) may lead to an increase in serum potassium up to severe, possibly life-threatening hyperkalemia and should therefore be avoided.

The combination of non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid (aspirin), indomethacin) with Spironolactone-ratiopharm® tablets may lead to severe hyperkalaemia.

In addition to these medicinal products, which are known to cause hyperkalemia, co-administration of trimethoprim / sulfamethoxazole (cotrimoxazole) with spironolactone may also result in clinically relevant hyperkalaemia.

When concomitant with ACE inhibitors, furosemide and spironolactone can cause acute renal failure.

If antihypertensive medicinal products are used in addition to Spironolactone-ratiopharm® tablets, an increased blood pressure reduction is to be expected. In particular, concomitant treatment with Spironolactone-ratiopharm® tablets and ACE inhibitors (e.g. captopril, enalapril) poses the risk of a massive fall in blood pressure until shock, as well as the risk of renal impairment, which can rarely lead to acute renal failure. Diuretic therapy should therefore be discontinued 2 to 3 days before initiating therapy with an ACE inhibitor to avoid the possibility of hypotension at the start of therapy.

Spironolactone-ratiopharm® tablets and carbenoxolone can affect each other in their effect. Large amounts of liquorice in this regard act like carbenoxolone.Non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid (aspirin), indomethacin), salicylates, and phenytoin may attenuate the diuretic effects of Spironolactone-ratiopharm® tablets. In patients who develop hypovolemia or dehydration while receiving Spironolacton-ratiopharm® tablets, concomitant administration of non-steroidal anti-inflammatory medicinal products may induce acute renal failure.

Concomitant use of Spironolactone-ratiopharm® tablets and other diuretics may lead to increased diuresis and an increased blood pressure drop.

Co-administration of digoxin and spironolactone may result in increased digoxin plasma levels by prolonging the digoxin half-life.

There are several literature reports that spironolactone or its metabolites may interfere with RIA determination of digoxin serum concentration. However, neither the extent nor clinical significance of this effect (which may be content specific) has been fully established.

Neomycin may delay the absorption of Spironolactone-ratiopharm® tablets.

4.6 Pregnancy and lactation

Spironolactone-ratiopharm® tablets should not be used during pregnancy and lactation.

Pregnancy

There is no adequate data from the use of spironolactone in pregnant women. Animal studies have revealed feminization of the genitalia of male offspring and evidence of endocrine disruption in female and male offspring (see section 5.3). In humans, antiandrogenic effects have been demonstrated. Spironolactone is therefore contraindicated in pregnancy.

Lactation

There is no data available on the excretion of spironolactone in breast milk. The pharmacologically active major metabolite canrenoate has been detected in breast milk (milk-plasma concentration ratio 0.7). Therefore, spironolactone is contraindicated during breast-feeding. Nevertheless, should treatment be necessary, the baby must be weaned.

4.7 Effects on ability to drive and use machines

This medicinal product, even when used as intended, may alter the ability to react so far as to impair the ability to drive or operate machinery or work safely. This applies to a greater extent at the start of treatment, dose increase and change of preparation and in conjunction with alcohol.

4.8 Undesirable effects

The evaluation of side effects is based on the following frequencies:

- Very common: ≥ 1/10
- Common: ≥ 1/100 to <1/10
- Uncommon: ≥ 1 / 1,000 to <1/100
- Rare: ≥ 1 / 10,000 to <1 / 1,000
- Very rare: <1 / 10,000
- Not known: frequency cannot be estimated based on available data

Diseases of the blood and lymphatic system

Uncommon: thrombocytopenia by spironolactone-induced antibodies

Rare: eosinophilia in cirrhotic patients, agranulocytosis

Immune system disorders

Uncommon: allergic reactions; also as skin and mucous membrane reactions (see "Skin and subcutaneous tissue disorders")

Endocrine disorders

Rarely: deepening of the pitch (women), increase in the pitch (men), voice changes (also in the form of hoarseness); do not regress in some patients even after discontinuation of spironolactone

Metabolic and nutritional disorders

Common: life-threatening hyperkalemia (especially in renal impairment); may lead to hyperkalemic paralysis (muscle paralysis); hyperuricemia; can lead to gout attacks in predisposed patients.

Uncommon: Reversible increase in nitrogen-containing urinary substances (urea, creatinine)

Not known: disturbances in fluid and electrolyte balance (especially in renal impairment); hyponatremia; hypomagnesaemia; hyperchloraemia; hypercalcaemia; hypovolemia; hyperchloremic metabolic acidosis

Psychiatric disorders

Uncommon: confusion

Unknown: apathy, lethargy

Diseases of the nervous system

Uncommon: headache or pressure in the head, drowsiness, ataxia, weakness, dizziness

Not known: tiredness

Eye diseases

Not known: blurred vision

Heart disease

Common: cardiac arrhythmias

Vascular

Not known: Orthostatic regulatory disorders or hypotension resulting in circulatory collapse, circulatory disorders, thrombosis and embolism (especially in the elderly)

Gastrointestinal disorders

Uncommon: dry mouth, gastrointestinal discomfort (e.g., upper abdominal discomfort, nausea, vomiting, diarrhea, gastrointestinal spasms), gastric bleeding and gastrointestinal ulcers (also with bleeding)

Not known: thirst, loss of appetite

Liver and biliary disorders

Very rare: Hepatotoxicity with increase in liver enzymes and histologically proven hepatitis

Skin and subcutaneous tissue disorders

Uncommon: Skin reddening, itching, skin rash, urticaria

Very rare: maculopapular or erythematous rash, erythema annulare, lichen planus-like skin lesions, hair loss to alopecia

Not known: lupus erythematosus-like syndrome, hirsutism in women, pemphigoid

Musculoskeletal, connective tissue and bone disorders

Uncommon: muscle cramps (calf cramps)

Very rare: osteomalacia

Not known: General muscle weakness

Diseases of the kidneys and urinary tract

Not known: Renal failure increased urine output may cause discomfort or exacerbate existing conditions in patients with urinary tract obstruction

Reproductive system and breast disorders

Common: Mostly reversible gynecomastia, increased nipple sensitivity and breast tenderness

Uncommon: potency disorders

Rarely: mastodynia, menstrual disorders such as intermenstrual bleeding and amenorrhea

Not known: impotence

Reporting of suspected adverse reactions

The reporting of suspected adverse reactions after approval is of great importance. It allows continuous monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are required to report any suspected adverse reactions to the Federal Institute for Drugs and Medical Devices, Dept. Pharmacovigilance, Kurt-Georg-Kiesinger Allee 3, D-53175 Bonn, website: www.bfarm.de.

4.9 Overdose

Symptoms of overdose

The clinical picture of acute or chronic overdose depends on the extent of water and electrolyte loss. Overdose can lead to hypotension, orthostatic regulatory disorders and electrolyte imbalances (hypo- or hyperkalemia, hyponatraemia). Significant fluid and sodium losses due to dehydration and hypovolaemia may result in somnolence and confusion, cardiac arrhythmias, circulatory collapse, hemoconcentration with thrombosis, and acute renal failure. Rapid water and electrolyte losses can cause delirium. Hyperkalemia can lead to cardiac arrhythmias (e.g., AV block, atrial fibrillation, ventricular fibrillation), cardiac arrest, ECG changes (tall, peaked T-waves and widening of the QRS complex), hypotension with peripheral circulatory collapse, and neurological disorders (flaccid paralysis, apathy, confusional states).

Therapeutic measures in case of overdose

In case of overdose or signs of hypovolemia (hypotension, orthostatic regulatory disorders) treatment with Spironolactone-ratiopharm® tablets must be discontinued immediately.

In case of short-term intake, measures of primary elimination of toxins (induced vomiting, gastric lavage) or absorption-reducing measures (activated charcoal) can be used to reduce the systemic intake of Spironolactone-ratiopharm® tablets.

In severe cases, the vital parameters must be monitored under intensive care conditions, and repeated monitoring of water, electrolyte and acid-base balance and of urine-containing substances must be carried out and abnormalities corrected if necessary.

Therapeutic measures

- in hypovolemia and hyponatremia: sodium and volume substitution
- in circulatory collapse: shock positioning, if necessary shock therapy
- in hypokalemia: potassium substitution
- in hyperkalemia: severe hyperkalemia must be given immediate intensive care

Normalization of the ratio between intracellular and extracellular potassium concentration

Sodium bicarbonate increases cell uptake by a direct mechanism: infusion of 50-100 ml of a 1 molar (8.4%) sodium bicarbonate IV solution (onset of action: after a few minutes, duration of action: several hours).

The potassium influx into the cell is promoted especially by glucose: For example, infuse 200 ml of a 25% (1.4 mol / l) glucose solution and 25 IU of regular insulin (1 IU of regular insulin per 2 g of glucose) IV within 30 - 60 minutes (duration of action: several hours).

Elimination of any potentially existing excess potassium

After the emergency measures mentioned above, excess potassium should be eliminated from the body through longer-term measures. If the renal excretion cannot be increased (e.g. by injection of furosemide), extrarenal elimination pathways should be chosen. Here the oral administration of cation exchange resins (e.g. Resonium A or Calcium Resonium) is recommended:

1 g of the resins binds about 1 mmol of potassium in the intestinal lumen. The bound potassium is excreted with the faeces.

If no normalization of the extracellular potassium concentration can be achieved with the above-mentioned measures, peritoneal dialysis or hemodialysis is unavoidable.

A specific antidote to spironolactone is unknown.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Potassium-sparing diuretics; Aldosterone antagonist

ATC code: C03DA01

Spironolactone competitively blocks the binding of aldosterone to its cytoplasmic receptor in the late-distal tubule and collecting tube. As a result, aldosterone cannot penetrate into the cell nucleus via its receptor, thereby preventing the synthesis of the aldosterone-induced proteins. This counteracts the essential aldosterone effect, sodium reabsorption and potassium secretion. Aldosterone receptors are found in renal and extrarenal areas, for example, in the salivary glands and in the intestine.

Spironolactone develops its own activity only in the presence of endogenous or exogenous aldosterone. The effect can be reversed by increasing aldosterone levels. Neither production nor excretion of aldosterone is reduced in therapeutic doses. Only in extremely high doses does spironolactone inhibit the biosynthesis of aldosterone.

Spironolactone increases sodium and chloride excretion and, to a lesser extent, calcium excretion; The potassium and ammonium excretion as well as the acidity of the urine are reduced.

Spironolactone reduces renal magnesium excretion.

When used alone, spironolactone has only a low diuretic efficacy. Additional administration of thiazides or loop diuretics can further increase natriuresis.

Spironolactone may increase serum urea concentrations by lowering the glomerular filtration rate. A hypotensive effect in hypermineralocorticoid syndromes or in various diseases with primary or secondary hyperaldosteronism has been proven.

The clinical onset occurs in continuous administration gradually, with a maximum effect after 2 - 3 days or later; the maximum diuretic effect can possibly also occur after 2 weeks.

5.2 Pharmacokinetic properties

Absorption

After oral administration, spironolactone is rapidly absorbed to approximately 73%. When taken with a meal, the absorption of spironolactone is increased. This results from an increase of the serum concentration of the parent substance by 50-100%.

Distribution

The plasma protein binding of spironolactone and canrenone is 90% (equilibrium dialysis) or 98% (ultrafiltration) depending on the methodology.

Metabolism

Spironolactone undergoes a pronounced first-pass effect when administered orally and is metabolised to 7-α-thiospirolactone, canrenone or canrenoate, 7-α-thiomethylspirolactone or 6-β-hydroxy-7-α-thiomethylspirolactone, mainly in the liver and kidneys. The first three metabolites have a relative antimineralocorticoid activity of 26.68 and 33%, respectively, compared to the parent compound. After oral administration of spironolactone, maximum plasma concentrations of spironolactone are measured after 1-2 hours and maximum plasma concentrations of the metabolites after about 2-3 hours.

At low dosages (50 to about 200 mg), the area under the canrenone serum concentration-time curve increases linearly with dose, while higher dosages lead to relatively lower concentrations, most likely due to a reduction in the enzymatic conversion of spironolactone into its metabolites.

The steady-state levels of canrenone are between 50 and 188 ng / ml. Steady-state concentrations for canrenone are reached after about 3 to 8 days after daily administration of spironolactone. In patients with cirrhosis of the liver and ascites, these are only reached after 14 days.

Elimination

The excretion occurs predominantly in the urine, to a lesser extent via the bile. The proportion of unchanged spironolactone is low. Only metabolites are found in urine, especially canrenone and its glucuronide ester and 6-β-hydroxysulfoxide. After a single oral dose of radiolabelled spironolactone, 47-57% appears in urine and 35-41% appears in the stool within 6 days. After oral administration of spironolactone, the elimination half-life for spironolactone is 1-2 hours, while the metabolites are excreted more slowly. The terminal elimination half-lives are about 20 hours for canrenone, about 3 hours for 7-α-thiomethylspirolactone and about 10 hours for 6-β-hydroxy-7-α-thiomethylspirolactone.

Spironolactone and its metabolites penetrate the placental barrier. Canrenon passes into breast milk.

5.3 Preclinical safety data

Chronic toxicity / subchronic toxicity

Subchronic and chronic toxicity studies of spironolactone have been performed on various animal species (rat, dog, monkey). In the study on the rat, an increased incidence of thyroid and testicular adenomas was found in the high dose.

Mutagenic and tumorigenic potential

There was no evidence of a mutagenic effect. There was no evidence of clinically relevant tumorigenic potential of spironolactone in a long-term rat study.

Reproductive toxicity

Feminizing effects on the external genitalia were observed in male offspring during gestation of exposed rats at daily doses of about 160 mg / kg body weight. Endocrine disorders in both sexes (changes in hormone concentrations in plasma) were found at about 80 mg / kg, prostate weight reduction in male pups at 40 mg / kg. Studies in rats and mice have shown no evidence of teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate, Microcrystalline Cellulose, Carboxymethyl Starch Sodium (Type A) (Ph. Eur.), Corn Starch, Talc, Copovidone, Sodium Dodecyl Sulfate, Colloidal Silica, Magnesium Stearate (Ph. Eur.)

6.2 Incompatibilities

None known so far.

6.3 Shelf life

5 years

6.4 Special precautions for storage

These medicines do not require any special storage conditions.

6.5 Nature and contents of container

PVC-Alu blister

Pack of 20 tablets

Pack of 50 tablets

Pack of 100 tablets

HDPE bottle pack * with 100 tablets

* for use on more than one patient

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Ratiopharm GmbH

Graf-Arco-Str. 3

89079 Ulm

Germany

8. MARKETING AUTHORISATION NUMBER(S)

Spironolactone-ratiopharm® 50 mg tablets 2351.01.00

Spironolactone-ratiopharm® 100 mg tablets 763.00.00

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Spironolactone-ratiopharm® 50 mg tablets

Date of approval: 2 July 1982

Date of last renewal of approval: 24 May 2002

Spironolactone-ratiopharm® 100 mg tablets

Date of approval: 12 October 1979

Date of last renewal of approval: 13 September 2004

10. DATE OF REVISION OF THE TEXT

January 2016

11. LEGAL CLASSIFICATION

Prescription only medicine.

21 APPENDIX 2 ASSESSMENT OF THE IMP RISK CATEGORY

Study title: Spironolactone for Adult Female Acne (SAFA)	
EudraCT: 2018-003630-33	
Risks associated with trial IMP ☒ Type A = comparable to the risk of standard medical care ☐ Type B = Somewhat higher than the risk of standard medical care ☐ Type C = markedly higher than the risk of standard medical care	This Trial has been categorised as Type A. Although the IMP is being used outside its licensed indication, there is extensive clinical experience with the product for acne and no reason to suspect a different safety profile in the trial population. **Clinical justification for risk adaptation** 1) Spironolactone is a potassium-sparing diuretic, which has been widely used for many years in other health conditions, such as hypertension and heart failure and the safety profile is well known. 2) Trial dose of 50 - 100mg spironolcatone is considered a low dose. 3) Spironolactone has been used off-license in female acne for over 30 years due to its antiandrogenic properties and US Guidelines suggest it has a role to play in the management of female acne therapy (Zaenglein et al. J Am Acad Dermatol 2016;74(5):945-73 e33). 4) The trial population is a much younger population than would be taking spironolactone within its licensed indication. Consequently, they are likely to have cardiovascular and renal systems which are in a better condition, and with fewer comorbidities, than most patients receiving the drug for its licenced indication. 5) Spironolactone is defined by the FDA as a category C drug (**Risk not ruled out:** Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). Feminisation of the male foetus is said to occur in the last trimester of pregnancy (Zaenglein et al. 2016). 6) Concerns have been raised about teratogenicity of spironolactone but risk of harm to the foetus is not thought to be high, and is likely to be lower than for other oral treatments for acne, such as tetracycline antibiotics, co-cyprindiol and significantly lower than with oral isotretinoin (Zaenglein et al. 2016).

IMP	Body system	Hazard	Likelihood (L, M, H)	Mitigation	Comments
Spironolactone	Metabolic	Hyperkalemia	L	Blood serum potassium and kidney function (eGFR) tested at baseline	US Guidelines state ongoing monitoring of blood potassium in young, healthy women with normal kidney function is not necessary (Zaenglein 2016).

	Reproductive	Pregnancy	L	Women of child-bearing potential (WOCBP) at risk of pregnancy must have a negative urine or serum pregnancy test at baseline	Using the CTFG decision tree, WOCBP at risk of pregnancy taking part in SAFA must use their usual hormonal or barrier method of contraception for the first 6 months of the study (i.e. until study treatment has stopped) and for at least 4 weeks (approximately one menstrual cycle) afterwards. The trial will exclude women who are pregnant or breastfeeding, and those not consenting to the above precautions.

Other processes in place to mitigate risks to participant safety

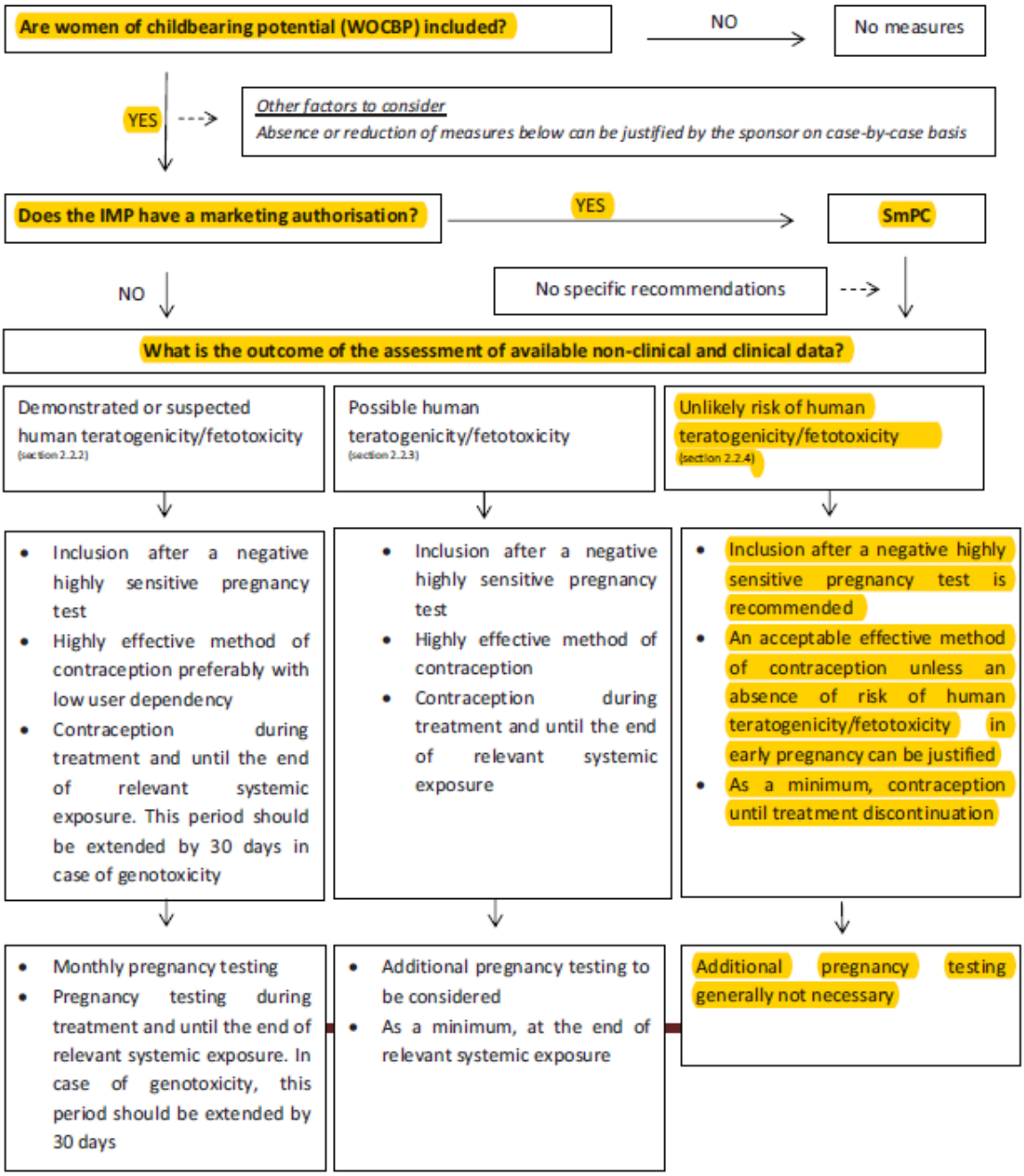
- The blood results will be monitored centrally. The trial manager will be contacted if a participant's results are above the Upper Limit of Normal (for potassium) and below 60ml/min/1.73m2 (for eGFR/kidney function) and instructed to contact the Research Nurse (RN) at site to ensure the RN has contacted the participant and told them to stop taking their study drug.
  Please note: This IMP would be prescribed within the same consultation a patient attended in normal care.
- Adverse reactions of special interest (ARSI) are being recorded for up/down dosing purposes and have been specified based on previous studies of spironolactone.
- Case Report Forms will collect information about severity and duration of any ARs to inform safety monitoring. Clinicians would ask about duration and severity of any side effects as standard practice.
- Serious Adverse Events will be collected, and reviewed monthly by the Trial Management Group and annually (if not biannually) by the independent Data Monitoring and Ethics Committee.
- Participants will start on 1 tablet (50mg spironolactone) for the first 6 weeks of the trial. In both arms dose escalation will be offered at 6 weeks, increasing to 2 tablets (100mg) if the participant is tolerating any side effects.
  The reason for dose escalation is to minimise the risk of side effects from spironolactone, which can cause gastro-intestinal disturbances, dizziness, gynaecomastia and menstrual disturbances, particularly at higher doses. The choice of spironolactone dosage was based on responses by dermatologists to a survey carried out by the UK Dermatology Clinical Trials Network, and is in line with US guidelines.
- Participants will carry a trial card with 24 hour emergency site contact details and will be instructed to contact their study clinician as soon as possible if they are concerned about any side effects.
- The trial card has details of the 24 hour emergency unblinding service available for healthcare professionals to contact if unblinding becomes necessary.
- The trial will exclude women currently taking:

- Potassium-sparing diuretic (spironolactone) – taking more spironolactone may cause more adverse reactions.
- ACE inhibitor (captopril, enalapril, fosinopril, lisinopril, perindopril, ramipril) – may upset blood chemistry by causing a very high potassium level
- Angiotensin receptor blockers (ARBs; candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan) - may upset blood chemistry by causing a very high potassium level
- Digoxin - spironolactone may decrease the kidneys' ability to remove digoxin from the body, causing a slow or irregular heartbeat.

Clinical Trial Facilitation Group
CTFG

Decision Trees - Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials

Women of Childbearing Potential (WOCBP)



Page 12: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

22 SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes
05-NOV-2018 v1	First version
20-NOV-2018 v2	Section 4.2: APPROACHING PARTICIPANTS; summary details about social media campaign removed at the request of Sponsor
04-JAN-2019 v3	• Section 3.2 RATIONALE FOR DOSE REGIMEN OF SPIRONOLACTONE added at the request of the MHRA • 'Women of childbearing potential at risk of pregnancy must be willing to use their usual hormonal or barrier method of contraception for the first 6 months of the study' **Changed to**: 'Women of childbearing potential at risk of pregnancy must be willing to use their usual hormonal or barrier method of contraception for the first 6 months of the study (whilst taking the study IMP) and for at least 4 weeks (approximately one menstrual cycle) afterwards' In all appropriate sections of the protocol
08-MAR-2019 v4	• Added exclusion criterion to exclude women who have 'ever taken spironolactone', because duration of effect of spironolactone is unknown. • Added detailed description of the social media advertising campaign in section 4.2: APPROACHING PARTICIPANTS, at the request of Sponsor
25-JUN-2019 v5	• Second paragraph of Section 4.8 REGISTRATION/RANDOMISATION PROCEDURES corrected to clarify that TENALEA will generate the Patient Identification Number and manage drug distribution.
01-NOV-2019 v6	• Update to social media advertising campaign • Blood test results removed from 4.5 ELIGIBILITY CRITERIA and added to 4.6 STOPPING CRITERIA, for clarity. • 4.8 SCREEN FAILURES section updated in line with new stopping criteria • INCLUSION CRITERIA specify 'acne vulgaris' • 5.6 PROHIBITED THERAPIES updated to explain that 'Participants who develop incidental infections in the first 12 weeks of the study and are prescribed more than 2 weeks of continuous antibiotics which could also be prescribed for the management of acne will be excluded.'
16-MAR-2020 v7	• Wording added to allow the week 6 and week 12 visits to be conducted remotely, if needed in light of covid-19 contingency planning.
12-MAY-2020 v8	• Changed wording for follow-up ("… up to 52 weeks" instead of "… at 52-weeks") • Changed wording for follow-up data analysis • Added that participant's contact details (postal address only) will be shared with SCTU and stored securely
16-DEC-2020 v9	• Wording added to allow for the study IMP at baseline to be posted/delivered directly to the participants • Wording added to allow for participants to send in photos of their acne as part of their baseline

08-MAR-2021 v10	• Changed wording regarding reduction of sample size to 398 participants • Wording added with details for process for pregnancy reporting based on SCTU internal Standard Operation Procedure (SOP) • Details added how informed consent forms and questionnaires should be shared with SCTU • Updated trial manager name and details • Update to updated SCTU CTIMP protocol template (FORM5036)