FASCE, benefit of spironolactone for treating acne of adult female: study protocol for a randomized double-blind trial

Alexandra Poinas (alex_poinas@hotmail.com)
Centre Hospitalier Universitaire de Nantes https://orcid.org/0000-0003-4183-483X
Marie Lemoigne
Centre Hospitalier Universitaire de Nantes
Sarah Le Naour
Centre Hospitalier Universitaire de Nantes
Jean-Michel Nguyen
Centre Hospitalier Universitaire de Nantes
Solène Schirr-Bonnans
Centre Hospitalier Universitaire de Nantes
Valery-Pierre Riche
Centre Hospitalier Universitaire de Nantes
Florence Vrignaud
Centre Hospitalier Universitaire de Nantes
Laurent Machet
Centre Hospitalier Regional Universitaire de Tours
Jean-Paul Claudel
private practice
Marie-Thérèse Leccia
Centre Hospitalier Universitaire Grenoble Alpes
Ewa Hainaut
Centre Hospitalier Universitaire de Poitiers
Nathalie Beneton
Centre Hospitalier du Mans
Cécile Dert
Centre Hospitalier Universitaire de Nantes
Aurélie Boisrobert
Centre Hospitalier Universitaire de Nantes
Laurent Flet
Centre Hospitalier Universitaire de Nantes
Anne Chiffoleau

Centre Hospitalier Universitaire de Nantes
Stéphane Corvec
Centre Hospitalier Universitaire de Nantes
Amir Khammari
Centre Hospitalier Universitaire de Nantes
Brigitte Dréno
Centre Hospitalier Universitaire de Nantes

Study protocol

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Abstract

Background Acne vulgaris of adult woman has increased over the past 10 years; it affects currently 20 to 30% of adult women. The physiopathology of adult woman acne is distinguished from the teenager one essentially by 2 factors: hormonal one with a peripheral hyperandrogeny coupled with an hypersensibility of cutaneous androgens receptors and an inflammatory one linked with Cutibacterium acnes. On a therapeutic plan, in female acne, four types of systemic treatment, approved in this indication are: cyclines which are problematic for the bacterial resistance; zinc salts which target only the inflammatory lesions and are less effective as cycline; antiandrogens, with acetate of cyproterone associated with risks of phlebitis and pulmonary embolism and recently meningioma. The last alternative is represented by isotretinoin but the use in women of childbearing potential is binding because of the teratogen risks and in addition, peripheral hyperandrogenia represents an identified risk of relapse. In this context, the spironolactone could represent an interesting alternative. It blocks the 5-alpha-reductase receptors at sebaceous gland and inhibits LH production at the pituitary level. It has not isotretinoin constraints, does not lead to bacterial resistance and targets the peripheral hyperandrogenia. Currently, very few studies have been performed on a weak number of patients. They showed that at low doses (lower than 200mg/day), spironolactone can be effective against acne.

Methods: In that context, it seemed clearly interesting to perform the first double-blind randomized study spironolactone vs cyclines, which remains the moderate acne reference treatment and to demonstrate the superiority of spironolactone's efficacy in order to establish it as an alternative way to cyclines.

Discussion: Acne's treatment frequently used in female acne is systemic antibiotics with many courses as it is a chronic inflammatory disease. In the context of recent WHO revelation about serious, worldwide threat to public health about antibiotic resistance, this trial could permit to give to the physician another alternative in adult female acne before using isotretinoin whose management is more complex. Trial registration : On ClinicalTrials.gov, registration number NCT03334682, first published on 7 November, 2017. Recruitment is still ongoing. Keywords : acne vulgaris, spironolactone, cycline

Introduction

Background and rationale{6a}

To understand exactly what acne vulgaris is, we must begin below the skin's surface deep in the hair follicle. The follicle, which is lined with skin cells, contains sebaceous glands that produce oil (sebum). Normally the skin cells that line the follicle are shed and brought to the skin's surface by the sebum and are then washed away. However, when the cells stick together instead of shedding, they form a plug or blockage. A clogged pore is a commonly used term for a plugged follicle. Beneath the plug, a sac is formed (known as a microcomedone) that contains dead skin cells and oil. Bacteria (*Cutibacterium acnes*) grow freely in this environment, feeding on the dead skin cells and oil for fuel. As the sac continues to grow, either a whitehead (known as a closed comedone), or a blackhead (open comedone)

forms. In more serious cases, the sac will become larger spurred on by the cells that the body sends into the sac to fight the infection, inflammation will result; and a bump (papule or pustule), painful nodule or cyst will develop.

Though it becomes less common in adulthood than in adolescence, nearly half of people in their twenties and thirties continue to have acne. About 4% continue to have difficulties into their forties[1].

Acne vulgaris of adult woman has increased over the past 10 years; it affects currently 15% to 50% of adult women depending on the studies[2–4].

Acne in adult women is now a well-known entity considered as different from adolescent acne[5,6]. In the literature, it most often involves women aged 25 years or over. A recent study isolated two distinct clinical presentations: (a) the first one, closed to teenager acne, with diffuse acne lesions over the face including hyperseborrhea, retentional lesions (mainly closed comedone) and superficial inflammatory lesions; (b) the second one, is always mild to moderate acne located at the inferior third of the face (mandibular location), with mainly few deep inflammatory chronic cysts[7].

The physiopathology of adult woman acne is characterized by mainly two specific factors:

1- The hormonal factor suggested by the premenstrual flare up of acne lesions in more than 60% of adult women[2,8] and by the efficacy of anti-androgens and contraception of 4th generation (non androgenic progestin).

The androgen level in blood, previously investigated in the population of adult women with acne, shows abnormalities are between 7.6% [7] to 86% [9,10], according the studies. This strong difference can be explained by the different profiles of female acne included in the trials. Indeed, some studies included females with endocrine illnesses associated with hirsutism, irregular cycles and acne. In one study, serum sex-hormone binding globulin (SHBG) values correlated negatively with acne severity, possibly via an increased level of free testosterone [11]. On the contrary, 3 other studies did not show any link between androgen level and acne severity [9,12,13]. When comparing adult female acne versus control population, a higher level of dehydroepiandrosterone (DHEAS)[10,12], delta-4 androstendione[10], dihydrotestosterone (DHT)[13], free testosterone[10,13] has been noted. Eventually, DHEAS, DHT and IGF-1 serum levels correlated positively with acne lesions counts in female acne [14].

However, in the majority of adult female, where acne is the alone clinical sign (no other clinical sign of hyperandrogenia), no abnormal hormone profiles are present. Two of the main hypotheses discussed today are either a hypersensitivity of androgens receptors identified in sebocytes and keratinocytes or an hyperactivity of enzymes metabolizing androgens in these cells: the term of peripheral hyperandrogenia is proposed.

2- A chronic activation of Innate Immunity of the skin in link with the presence of resistant *C. acnes* strains in the pilosebaceous follicle. Indeed, in the great majority of adult women with acne for many

years, frequent prescriptions of topical antibiotics (erythromycin, clindamycin) induce the development of *C. acnes* and *Staphylococcus* resistant strains.

At the therapeutic level, four types of systemic treatment are approved in acne[15] .

- Cyclines which can induce modifications of cutaneous microbiome and bacterial resistance with risk of non-clinical response[16].
- Zinc salts which target only the inflammatory lesions and were shown to be less effective than cyclines[17].
- Antiandrogens, such as acetate of cyproterone which are associated with risks of phlebitis pulmonary embolism, hypertriglyceridemia and hypercholesterolemia
- Isotretinoin which is a teratogenic drug obliging to a strict use of contraception, with monthly control of pregnancy test, cholesterol, triglycerides, and liver enzymes. It could be also associated with depression in some patients. In addition, even if the risk of relapse is low after isotretinoin course (less than 20%), it has been shown higher in women with hyperandrogenia [18]. Thus, even if isotretinoin by inducing apoptosis of sebaceous glands is the most effective drug in acne, its use remains not always easy, with contra indications.

Of note, the direct cost of acne in the United States is estimated to exceed $1 billion per year, with $100 million spent on over-the-counter products[19]. Despite this high cost, 81% of women reports failures with systemic antibiotics, and failures with isotretinoin range from 15 to 30%[20].

In this context, the spironolactone can represent an interesting alternative. It blocks the 5-alpha-reductase receptors at sebaceous gland and inhibits LH production at the pituitary level [21]. It is not submitted to the isotretinoin constraints, does not lead to bacterial resistance and targets the peripheral hyperandrogenism.

Currently, 10 randomized controlled trials (RCT) have been performed with a low number of female acne patients[22]. Between 10 to 66 female patients with acne were treated by spironolactone. These ten RCTs included 16 comparisons of spironolactone versus placebo or active treatment and all these trials were considered high risk of bias (inter alia selection, detection and/or reporting bias). The interest in acne is that low dosages of spironolactone appear to induce clinical response in acne: 50 to 200 mg per day (with one study using spironolactone at the dose of 100 mg per day but 16 days per month [23]). The endpoint varied between studies but was most frequently the lesions count [24–26]. In all the studies published, spironolactone was effective on acne lesions located on the face[27] and/or on the back[28–30]. In the largest study published until now, Shaw *et al.* treated 85 women with spironolactone 50 to 100 mg/day either as single-drug therapy or as an adjunctive treatment in an open study. They reported a complete response on acne lesions in one third of the cases, a marked improvement in another third and a partial improvement in the last third of patients[8] . Notably, all these studies were performed in an open setting with no control group. The tolerance was excellent. The most frequent adverse events are fatigue and menstrual irregularities, but they are always grade 1 with no need of treatment interruption.

In that context:

- where some opened trials indicate that spironolactone is effective in female acne, and could represent an interesting alternative to systemic treatments as antibiotics or isotretinoin,
- where no randomized trials comparing spironolactone versus cycline, which remains the reference treatment for moderate acne, have been performed,
- where no labelling for acne exists for spironolactone,

it appears of particular interest to perform the first double-blind randomized study comparing spironolactone versus cycline. The objective is to demonstrate the superiority of spironolactone's efficacy in adult female acne in order to establish it as an alternative therapy to cycline that could be prescribed by the dermatologist with the advantage to be not expensive.

Originality and innovative aspects of FASCE trial

In spite of numerous scientific references about the efficacy of the spironolactone on adult women' acne, never a randomized clinical trial has been performed to demonstrate its efficacy in comparison to the treatment usually used.

Furthermore, acne's treatment frequently used in this indication is an antibiotic treatment; and WHO recently reveals serious, worldwide threat to public health about antibiotic resistance (WHO First Global on antibiotic resistance -30 April 2014[31]).

To find an effective and cheap treatment without antibiotics parts is important; the pathology is not lethal but it affects at least 15% of the adult population and it causes a serious handicap in daily life with societal impact. This trial could permit to give to the dermatologist another alternative to systemic antibiotics before prescribing isotretinoin whose management is more complex.

Another original aspect of this study is the use of specific evaluation scales that are more accurate for adult women acne.

Until today, several grading system have been described [32] : more than 25 methods of assessing acne severity and more than 19 methods for counting lesions are available. In 1997, for example, Doshi, Zaheer and Stiller devised a global acne grading system (GAGS)[33]. This system divides the face, chest and back into 6 areas (forehead, each cheek, nose, chin and chest and back) and assigns a factor of 1, 2 or 3 to each area, based on size.

Currently, the commonly used scale for acne, in France and in Europe, is Global Evaluation Assessment (GEA)[34]or ECLA (Echelle de Cotation des Lésions d'Acné) [35] proposed by our team. However, they were designed for adolescents with acne, and are focused on the lesions located on the face.

As detailed above, adult women have frequently lesions on the mandibular region, explaining that the use of standard scales in this population could underestimate their lesions. Recently, our new scoring tool

AFAST (Adult Female Acne Scoring Tool) has been proposed for this goal [36].

AFAST scale is composed of the GEA scale to assess acne on the face and of a second scale developed to assess acne on the mandibular zone. This is a very important issue as in these zones, only very few inflammatory lesions, limited to the mandibular region are observed [7]. Thus, the use of currently available scales considering the whole face to assess the severity of acne underestimate the severity of this type of acne in scoring it most of the time as mild and sometimes as moderate. In addition, AFAST permits modulating results from acne grading on the full face (GEA - Score 1) with that of the mandibular and submandibular zone (Score 2), hence conditions the choice of the best adapted treatment approach.

- Score1: The GEA, as we quoted, is a validated acne assessment scale[34]. It was based on the global assessment described by Thiboutot *et al*[37].
- Score 2: this score exclusively assesses acne on an area from the left and right mandibular zone to the upper edge of the trunk [36].

The use if this scoring tool will allow us to precisely evaluate the effect of spironolactone in the context of adult female acne.

To conclude, spironolactone has no official labelling for acne making its prescription not easy for the dermatologist in their office and thus this randomized trial could have an impact on daily practice.

This clinical randomized trial will be stratified on the patient's contraception.

Indeed, as we quoted, another option in the arsenal of hormonal treatments is oral contraceptives (OCs), which acts largely by suppressing ovarian androgen production. Pills combining both an estrogen and progestin are used for acne, as progestin-only and contraceptive implants may exacerbate the condition[38].

The former pills (of 1st and 2nd generation) contain a progestogen, derived of the so-called androgenic testosterone (levonorgestrel or norethisterone), with effects close to male hormone and which can therefore aggravate the acne. The progestogen prevails over the estrogen and this pill has a progestational climate and favors the acne at women who are subject to it.

On the other hand, when the progestogen belongs to the 3rd generation (gestodene, norgestrel or desogestrel), i.e. not androgenic, the estrogen asserts itself, and the pill climate is estrogenic which is wished in case of acne but the effect is more often suspensive, with relapse after stopping treatment.

For the pills of 4th generation, an anti-androgenic progestogen has been chosen (and not only, not-androgenic) which neutralizes the androgens.

Nevertheless, because of thrombosis risks, the French Regulatory Authorities (ANSM) advised physicians, in December 2012, to favor systematically the pills of 2nd generation in first intention.

Female patients included in our trial, unless in case of surgery sterilization or early menopause will be women of childbearing potential. They will be included if they have an effective contraception; mechanical contraception or abstinence will not be accepted.

Stratification will be done on 4 arms following the acne effect foreseen by the contraception:

1st arm: Implant, generation I and II of OCs or progesterone intrauterine device and other kind of hormonal contraception (vaginal ring, patch, injection …)

2nd arm: Copper intrauterine device (IUD) (hormone-free contraception)

3rd arm: Generation III and IV of OCs

4th arm: No contraception (surgery sterilization or menopause)

Objectives {7}

The primary objective was to demonstrate the superiority of spironolactone's efficacy in adult female acne compared to the doxycycline (reference treatment).

The secondary objectives are

the comparison between the two arms, of:

- The safety (clinical and biological) up to 12 months of follow-up
- The percentage of patients having AFAST score 1 (GEA) at 0 or 1 at 2, 4 ,6, 9 and 12 months
- The percentage of patients having AFAST score 2 (mandibular) at 0 or 1 at 2, 4 ,6, 9 and 12 months
- Complete remission, at 2, 4, 6, 9 and 12 months
- The Quality of Life at 2, 4, 6, 9 and 12 months between the two arms

and

- Comparison of *acnes, Malassezia and S. epidermidis, aureus* at D0 (baseline), and 4 months in each arm and between the 2 arms
- Comparison of inflammatory lesions of the face at D0 (baseline) and 2, 4, 6, 9 and 12 months in each arm and between the 2 arms
- Comparison of retentional lesions of the face at D0 (baseline) and 2, 4, 6, 9 and 12 months in each arm and between the 2 arms
- Comparison of the number of face lesions between D0 (baseline) and 2, 4, 6, 9 and 12 months in each arm and between the 2 arms

- Comparison of the trunk lesions (Factor F2 of ECLA) between D0 and 2, 4, 6, 9 and 12 months in each arm and between the 2 arms
- Comparison of the percentage of patients' relapse between the 2 arms at M4 and M6
- Comparison of the percentage of reappearance of 10% and more of inflammatory lesions between the 2 arms at M6
- Cost-effectiveness analysis (economic efficiency analysis) of spironolactone versus doxycycline at 6 months

Trial design {8}

Our study is a randomized double blind trial during the first 6 months (timeline for primary objective), and open during the last 6 months of follow-up. The female patients will be randomized either in the acne routine care arm *i.e.* cycline (Doxycycline 100 mg/day during 3 months followed by placebo during 3 months) or in the experimental drug (Spironolactone 150 mg/day during 12 months).

Blindness will be removed for all patients after 6 months evaluation - once the primary endpoint is measured-, whatever the result, to limit the constraints for the patients in the doxycycline arm. Indeed, if blindness was maintained, patients in the doxycycline arm would have to take a placebo during up to 6 months, in addition to the 3 months already taken. The objective of the last 6 months follow-up is to assess the maintenance of each treatment's efficacy during this time.

Methods: Participants, Interventions And Outcomes

Study setting {9}

Patients will be recruited by dermatology department of several French reference centres, including study centres from Western France belonging to IDGO, Dermatological Institute of the Western Region, supported by GIRCI GO. The investigation centers are the dermatological department of the University Hospital of Nantes, Brest, Le Mans, Grenoble and Tours, the regional hospital of La Rochelle and a private dermatologist of Tours.

Eligibility criteria {10}

It is commonly admitted that acne affecting female patients under 20, is considered as "adolescent female acne". Since this protocol concerns adult female acne, the recruited patients will be women aged at least 20 years.

These patients will have acne vulgaris with at least 10 inflammatory lesions and no more than 3 nodules.

The eligibility criteria are shown in table 1

Who will take informed consent {26a}

Before proceeding with any examination related to the research, the investigator obtains the patient's freely given, FASCE's informed consent, in writing.

Model consent form and other related documentation given to participants and authorized surrogates {32}

The Supplementary Material file contains the French informed consent form that the patient signs prior to the inclusion in the trial (version 2, updated July 1, 2017)

Additional consent provisions for collections and use of participant data and biological specimens {26b}

Biological samples for bacteria strain will be collected, stored and kept if the patient signed the biocollection informed consent. This biocollection and consent procedure have been registered under number DC-2011-1399 to French Ethic Committee: CPP Ouest IV.

Interventions

Explanation for the choice of comparators {6b}

As we already quoted, although acne is not an infectious disease, oral antibiotics have remained a mainstay of treatment over the last 40 years. The anti-inflammatory properties of oral antibiotics, particularly cyclines are efficacious in treating inflammatory acne[39,40]

All the guidelines: French[41]**, European**[42] **and American**[43] **recommend thus the cycline for first treatment but limited to a treatment period of 3 months to minimize the development of bacterial resistance. This is why the treatment duration of the comparator arm we choose, is doxycycline 100mg/day during 3 months.**

The guidelines specify also that monotherapy with systemic antibiotic is not recommended. Concomitant topical therapy with for example benzoyl peroxide should be used with systemic antibiotics and for maintenance after completion of systemic antibiotic therapy. In the two arms, patients will receive this topical therapy.

The primary objective is efficacy of doxycycline or spironolactone seen at M4 and/or M6. To avoid results bias and because our experience shows that between M4- M6, maximum efficacy is seen for cycline, the best rate of success between M4 and M6 will be chosen for the primary endpoint.

For the spironolactone, after only 3 months of treatment, the response of acne to spironolactone may not be optimal[22]. A retrospective trial made by Burcke and Cunliffe observed an average reduction of acne optimal at month 6 [24].

In conclusion, in order not to bias the study in either direction, on the primary objective the efficacy of the two treatments will be measured at 4 and 6 months in each arm and the best results of the two arms will be compared (Figure 1).

At the end of M6 visit, after the clinical evaluation, the unblinding data will be broken. Patients with complete or partial remission will continue the trial. Failed patients will drop out the trial and be treated by the investigators according to their usual practice. The same will be done at M9 visit: failed patients will drop out the trial and will be treated by the investigators according to their usual practice.

Interventions description {11a}

The study being double-blinded, the study treatment, the comparator and its placebo, will be managed by the pharmacist of the coordinating centre, CHU Nantes.

The orally dose of 150 mg of spironolactone, once a day during all the trial has been chosen as a result of literature and our experience.

Dispensation will be made at each protocol visit (i.e. every two months during 12 months).

The efficacy of spironolactone has been established by several studies showing improvement, with lesion reductions ranging from 50 to 100 percent in women treated for acne [44]. In most of these studies, the dosage range used was 100 to 200mg daily, with response noted over approximately three months[44].

For the comparator, as the French Guidelines for acne treatment recommended [41], the doxycycline treatment for acne vulgaris will be 100mg during 3 months, administered once a day.

From M4 to M6, a placebo will be administered to the patient.

Dispensation will be made at each protocol visit (i.e. every two months during 6 months).

The two treatments will be taken by oral route. As the antibiotics must be taken during a meal, and to retain the double-blind way of our trial, the patient of the 2 arms should take their treatment during a meal. The treatment should be taken with a full glass of water and the patient should remain in the upright position for at least one hour.

Monotherapy with systemic antibiotic is not recommended [43]. Concomitant topical therapy with for example benzoyl peroxide 5% should be used with systemic antibiotics and for maintenance after completion of systemic antibiotic therapy. In the two arms, patients will have this topical therapy.

All the schedule of the trial is shown figure 2

Criteria for discontinuing or modifying allocated interventions {11b}

No dose adjustment is required by the protocol. However, in case of hyperkaliemia, the treatment by spironolactone will be adjusted.

The patient must stop using the product and seek emergency medical attention immediately if she develops signs and symptoms of a serious hypersensitivity reaction such as throat tightness, difficulty to breath, feeling faint, swelling of the eyes, face, lips, or tongue.

Also she must stop using the product if she develops hives or itching of the face or body.

Strategies to improve adherence to interventions {11c}

FASCE will assess compliance using return tablet count. At M2, M4, M6, M9 and M12 visit, the patient return the empty study drug units and the investigator, or a member of his team will count them.

Relevant concomitant care permitted or prohibited during the trial {11d}

Due to spironolactone, anything that can induce hyperkalemia is forbidden: sparing potassium diuretics, potassium supplementation and drugs like ACE inhibitors, angiotensin II antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), heparin and low molecular weight heparin, ciclosporin, tacrolimus and trimethoprim.

Lithium is also not recommended in this trial. Concurrent use of lithium and spironolactone may result in increased lithium concentrations and lithium toxicity due to decreased lithium excretion. So, the monitoring of lithium plasmatic concentration will be reinforced.

Provisions for post-trial care {30}

At the end of the clinical research, the patient will be followed by her dermatologist and will benefit from the usual care of her disease.

The sponsor takes out an insurance policy covering the financial consequences of its civil liability in compliance with the regulations.

Outcomes {12}

The primary endpoint corresponding to treatment's efficacy is determined by the rate of success in each arm.

This rate of success (or relapse) is defined by a decrease of both AFAST scores 1 and 2:

1°) AFAST score 1 (corresponding to GEA score): decrease of at least 2 grades compared to baseline or to grade 0 if the baseline was at 1

and

2°) AFAST score 2 (mandibular score): decrease to grade 1 if baseline was > 1 or to grade 0 if the baseline was at 1

AFAST score 1 (also called GEA) assesses the comedones (open and closed), the non-inflammatory lesions, the papules and pustules and the nodules. The stage is defined according to a global evaluation of severity of acne and ranges from Grade 0 (no acne) to Grade 5 (the worse situation). AFAST score 2 assesses acne on an area from the left and right mandibular zone to the upper edge of the trunk and ranges from Grade 0 (no acne) to Grade 3 (the worse situation).

For the secondary endpoints:

- Number and type of Adverse Event (AE) and Serious Adverse Events (SAE) up to 12 months of follow-up and abnormal values of ionogram (Sodium, Potassium, Chlore and Calcium) at 0,2 4 and 9 months

- Number of patients with AFAST score 1 (GEA) at 0 or 1, at M2, M4, M6, M9 and M12
- Number of patients with AFAST score 2 (Mandibular) at 0 or 1, at M2, M4, M6, M9 and M12
- Number of patients with both AFAST score 1 and AFAST score 2 at 0 or 1, at M2, M4, M6, M9 and M12
- Quality of life questionnaire EQ-5D and index of quality of life in Acne (CADI) at M2, M4, M6, M9 and M12;
- Bacterial and parasital sampling at D0 and M4. Presence *of P. acnes, M. Furfur and S. epidermidis, aureus* will be searched
- Number of inflammatory lesions of the face at D0 (baseline) M2, M4, M6 M9 and M12
- Number of retentional lesions of the face at D0 (baseline) M2, M4, M6 M9 and M12
- Number of face lesions at D0 (baseline) M2, M4, M6 M9 and M12
- Number of trunk lesions (Factor F2 of ECLA) at D0 (baseline) M2, M4, M6 M9 and M12
- Number of patients with relapse at M4 and M6.

The definition of relapse is the same as primary endpoint:

1°) AFAST score 1 (GEA score): increase of 2 points versus score of previous visit, in case of success

Or

2°) AFAST score 2 (mandibular score): increase of 1 point versus score of previous visit, in case of success

- Number of patients with a reappearance of 10% and more of inflammatory lesions at M6
- Incremental cost-effectiveness ratio (cost per Quality-Adjusted Life-Year, QALY) of the comparison between the spironolactone and cycline at 6 months. Criteria for the calculation of the cost-effectiveness ratio are detailed in the Methods for additional analyses' paragraph.

Participant timeline {13}

The maximum duration of treatment per patient correspond to 12 months, and the recruitment period to 41 months.

Sample size {14}

For sample size estimation purposes, the targeted difference in the percentage of success is 70% in the experimental arm compared to 50% of success in the control arm, indicating a relative increase of success equal to 40%. Assuming a Type I error rate of 5% and at least 80% power, the sample size required is at least 91 subjects per group. To take into account possibility of lost to follow-up, 10% (9 subjects) will be added in each group. Finally, approximately 200 subjects will be randomized to the two arms in a 1:1 ratio.

Recruitment {15}

Acne vulgaris is a common pathology. Some centers like Nantes have a one-day consultation devoted to acne. A feasibility study performed in each centre showed that between 8 and 15 patients could be included per year, making these recruitments targets achievable.

Assignment of interventions: allocation

Sequence generation {16a} and Concealment mechanisms {16b}

This balanced block randomization is computer-generated. Subjects are randomized into blocks as the allocation progresses, a block being a subgroup of predetermined size within which there is a random allocation of patients. The software used for the randomization is SAS version 9.4.

The randomization will be centralized and stratified based on the 4 groups of contraception following:

Strate 1: Implant, generation I and II of OCs or progesterone intrauterine device and other kind of hormonal contraception (vaginal ring, patch, injection …)

Strate 2: Copper intrauterine device (IUD) (hormone-free contraception)

Strate 3: Generation III and IV of OCs

Strate 4: No contraception (surgery sterilization or menopause)

Implementation {16c}

The randomization key is known to biostatistician and data managers, to make it impossible for the investigator to assign a particular position for the dressings. At the randomization visit (Day0) the investigator after checking the inclusion and non-inclusion criteria will validate the randomization on the eCRF. Drugs prescription for 2 months will be done (blinded spironolactone/doxycycline). In addition, a concomitant topical therapy, benzoyl peroxide 5%, will be given.

Assignment of interventions: Blinding

Who will be blinded {17a}

Our study is a randomized double blind trial during the first 6 months (timeline for primary objective), and open during the last 6 months of follow-up. The female patients will be randomized either in the acne routine care arm i.e. cycline (Doxycycline 100 mg/day during 3 months followed by placebo during 3 months) or in the experimental drug (Spironolactone 150 mg/day during 12 months).

Blindness will be removed for all patients after 6 months evaluation - once the primary endpoint is measured-, whatever the result, to limit the constraints for the patients in the doxycycline arm. Indeed, if blindness was maintained, patients in the doxycycline arm would have to take a placebo during up to 6 months, in addition to the 3 months already taken. The objective of the last 6 months follow-up is to assess the maintenance of each treatment's efficacy during this time.

Procedure for unblinding if needed {17b}

If unblinding, due to emergencies, is deemed to be necessary, the investigator should inform the sponsor.

The unblinding will be done via the eCRF thanks to a detailed procedure which will be given to each site. Each decoding will be tracked and classified in the investigator management file and the trial management file.

Data collection and management

Plans for assessment and collections of outcomes - description of the parameters for evaluating efficacy {18a}

The first endpoint is the new validated score for Adult Female acne: AFAST [36].

AFAST (for Adult Female Acne Scoring Tool) uses two independent scores: Score 1 corresponding to GEA grading for acne on the face[34], and Score 2 corresponding to the evaluation of the mandibular region. Scores are not added up.

For each patient, AFAST score 1 (GEA) and AFAST score 2 should be assessed by the same evaluator at each visit.

The other score we will use is ECLA. The evaluation chart of acne ECLA hurts have been finalized by 6 dermatologists (private and hospital practice) [35]. It is composed of 3 factors: Factor 1 (F1) counts the acne lesions on the face; Factor 2 (F2) counts the lesions acne on the trunk and Factor 3 (F3) counts the scars.

In this study, only the factor F2 will be used.

The factor F2 assesses the extensive character of acne lesions on 5 defined areas: cervical areas (F2N); chest areas (F2C); back area (F2B) and arm area (F2A) according to a qualitative scale 0=absent, 1=poor 2=medium 3=significant. It is completed by the count of the present nodules in each area..

With regard to the study questionnaires, we will use EQ-5D and Cardiff Acne disability Index (CADI). The EQ-5D questionnaire, validated in France [45], will be given at each visit to the patient to measure their quality of life. The EQ-5D consists of a questionnaire and a visual analogue scale. The questionnaire focuses on five dimensions: mobility, personal autonomy, current activities, pain/discomfort, and anxiety/depression. For each of these dimensions, three answers are possible (EQ-5D-3L), thus allowing for 243 health states.

The Cardiff Acne disability Index (CADI) is a disease-specific questionnaire measuring disability induced by acne[46]. It is a well-known acne disability measure and has been used in some studies to assess the burden of living with acne on a patient's experience of disability[47,48]. The questionnaire was developed as a multidimensional measure related to the impact of acne [49]. It is a 5-item scale; questions 1 and 2 address the psychological and social consequences of acne in general, question 3 is targeted at those with acne of the chest or back, question 4 enquires about the patients' psychological state and question 5 asks for the patients' (subjective) assessment of their current acne severity. The response to each question is scored from 0 to 3. CADI is validated by our team in French [50].

For the bacterial and parasital samples, they will be collected in nodulocystic and pustular skin of the included patients at D0 and M4, using an Eswab to be unloaded in an AMIES transport environment (1 mL). The analysis will be centralized at Nantes University hospital and performed by Dr Stéphane Corvec .

Plan to promote participant retention and complete {18b}

At the randomization visit, a patient's diary will be given to note their health resources consumption, medical compliance, concomitant treatments and AE. The visits will be made every 2 months up to M6 where the main objective is set. At each visit, the empty blister will be collected and counted. At each visit, the drugs will be prescribed for 2 months (blinded spironolactone/doxycycline and placebo + concomitant topical therapy). At the visit M2 (2 months after the randomization), the physician or a member of his team will have to be vigilant and tell the patient to carefully follow the order of treatments. Two envelopes will be given, one for M3 (blinded doxycycline or spironolactone) and one for M4 (blinded spironolactone or doxycycline's placebo).

Data management {19}

An electronic Case Report Form (eCRF) shall be drawn up for each subject. The identification of the subject will be performed using the first letter of the family name, the first letter of the first name, the center number and the inclusion number, supplemented by the month and year of birth. This code should be the only information featuring in the eCRF enabling a retrospective link with the patient.

The investigator shall also encode the patient data on any documents that may be in its possession (imaging, biology test reports, etc.) attached to the eCRF.

At the end of the study, database reconciliation is carried out between the CRF database and safety database. This reconciliation is performed before database locking. Similarly, an annual reconciliation is carried out when updating the Annual Safety Report (ASR).

Confidentiality {27}

Each patient's medical data shall only be provided to the sponsor or any person duly authorized by the sponsor, and, where applicable, to authorized health authorities, in confidential conditions.

The sponsor and the supervisory authorities may request direct access to medical records for the purposes of verification of the procedures and/or data in respect of the clinical trial, within the limits authorized by the legislation and regulations.

The data compiled during the trial may be processed electronically in compliance with CNIL (National Commission on Informatics and Liberty) requirements. The CNIL is an independent French administrative regulatory body whose mission is to ensure that data privacy law is applied to the collection, storage, and use of personal data.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

At the end of the study, biological samples resulting from sampling (bacteria strains) shall be kept in the case of further scientific benefit, naturally the subject's written consent should be collected.

The samples will be stored in the biocollection under the responsibility of Pr. Dréno. This biocollection and consent procedure have been registered under number DC-2011-1399 to French Ethic Committee: CPP Ouest IV.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The primary efficacy variable is the percentage of success defined in paragraph 2.1.2. The comparison between the two arms will be done using a Cochran–Mantel– Haenszel test controlling for class of contraception (4 strates).

The ITT modified will be applied. That implies that all randomized patients will be included in the final analysis, minus those who did not reach the inclusion criteria after randomization and those who never began their treatment.

All secondary objectives are expressed as a percentage or a status at a fixed time of follow-up. General Linear Mixed models will be planned to take into account the repeated measurements collected on the same subject during their follow-up.

Cox model with time dependent covariates can also be used for secondary objectives for which a status is considered. Significance will be set at 5% in a bilateral situation.

For the cost-effectiveness analysis, 95% confidence intervals for differential (between arms) costs and QALYs and for the incremental cost-effectiveness ratio will be estimated using the non-parametric bootstrap estimation procedure.

Interim analyses {21b}

No interim analysis will be performed and no early stopping rule for futility will be proposed.

Methods for additional analyses (e.g. subgroup analyses) {20b}

An economic evaluation taking the form of a cost-effectiveness analysis (CEA) will be conducted to compare the efficiency of spironolactone to cycline treatment.

The analysis will be conducted from the societal perspective, which means that costs to hospitals, to the National Health Insurance System and to patients will be considered, over a 6 months' time horizon, to be consistent with the primary endpoint. The main judgment criterion will be the Incremental Cost-Effectiveness Ratio defined as a Cost per Quality-Adjusted Life-Year (QALY) gained. To estimate QALYs, patients will be asked to fill in the EuroQol EQ-5D health-related quality of life questionnaire.

For the estimation of costs, resources consumed will be recorded prospectively in a patients' diary on a period of 6 months following the start of the treatment. The main resources to be collected are presented in the following table.

Ambulatory care
· Medication
· Ambulatory physician visits
· Dermocosmetic care

Unit costs will be estimated using conventional tariffs from the French National Health Insurance System to value ambulatory care consumption.

Costs in each arm will be estimated by multiplying the amount of each type of resources consumed by their corresponding unit monetary value.

In CEA, the outcomes of an intervention are evaluated in terms of Quality-Adjusted Life-Years (QALYs). QALYs are a numerical composite measure that encompasses information about the length of life and the health-related quality-of-life. They are computed by weighting each year by a corresponding quality of life factor usually ranging from 0 (death) to 1 (perfect health). Quality of life weights will be obtained by asking patients to answer to the EuroQol EQ-5D quality of life questionnaire at the baseline and at 2, 4, and 6 months from the baseline. The difference in QALYs between the two arms of the study will be calculated by using an area under the curve analysis, with linear interpolation of utility scores between measurement time points.

EQ-5D will be submitted also at 9 and 12 months to evaluate quality of life until M12, as a secondary objective, independently from the cost-effective analysis.

The Incremental Cost-Effectiveness Ratio (ICER, see below) comparing the spironolactone and the cycline arms will be analysed via a non-parametric bootstrap approach to produce estimated confidence intervals at 95% over the mean ICER.

$$ICER = [Costs_{Spironolactone} - Costs_{Cycline}] / [QALYs_{Spironolactone} - QALYs_{Cycline}]$$

Cost-effectiveness of spironolactone will be assessed according a willingness to pay of 50 000 euros. The probability of cost-effectiveness will also be assessed with several willingness to pay thresholds and will be represented in an acceptability curve. A sensitivity analysis will be performed in order to assess robustness of the ICER result.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

All subjects receive the assigned study treatment until unacceptable toxicity, death, lost to follow-up, withdrawal of consent, or termination of the study by the sponsor, in accordance with local standard of care.

Unacceptable toxicity and death will be considered as failure for the primary criteria analysis. Lost to follow-up, missing data for the primary criteria and early termination of the study by the sponsor will be also considered as failure by the intent-to-treat modified (ITTm) and not replaced.

Patients who did not reach the inclusion criteria after randomization and those who never began their treatment will be replaced.

For the clinical secondary criteria analysis, patients with missing data will be withdrawn. Missing data in cost-effectiveness analysis will be imputed according the relevant method, depending on the type of missing data.

If a patient is released from the study (e.g. in the event of Adverse Reactions (AR) preventing the continuation of the study), her data will not be collected, except for safety data (follow-up of AR or onset

of AR associated with the experimental treatment, based on pharmacokinetics data).

Plans to give access to the full protocol, participant level-data and statistical code {31c}

According to French law, the results of the study will be published on the website of the regulatory authority. But the data-sharing is prohibited by the General Data Protection Regulation European law.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

It has been possible to carry out the protocol and the trial thanks to an Executive Committee which includes a Scientific Committee and a Steering Committee. The Scientific Committee was created and coordinated by Prof. B. Dreno. Its membership comprises, biostatistician and methodologist, the study coordinator, the health economist and the project manager of the clinical investigation center (CIC1413). The Steering Committee is composed of the members of the Scientific Committee with the addition of the data management team, the nurse study who coordinates assistance for patient inclusion in the other centers, and the monitoring Clinical Research Assistant (CRA). The sponsor project manager coordinates this committee and drafts the “FASCE newsletter” which provides, among other things, the latest news on patient inclusion, amendments to the protocol, etc.

Composition of the data monitoring, its role and reporting structure {21a}

The Data and Safety Monitoring Committee “DSMC” is an advisory committee responsible for reviewing the safety of a clinical trial for the sponsor and the coordinator of the study.

Its members, well-versed in the field of clinical trials (pathology and methodology), are not involved in the study. They are appointed for the duration of the study and undertake to take part and observe data confidentiality. The members of the DSMC are selected collectively by the coordinator, Prof. B. Dreno and the sponsor.

The DSMC is solicited at least once a year for safety analysis: the members receive the annual safety report and may be additionally consulted if a SUSAR or SAR involves a specific analytical problem or in the event of doubt on any risk/benefit questioning arising in the course of the study.

Adverse event reporting and harms {22}

Side effects reported in clinical trial and case series with spironolactone and management of acne in adult females [22]:

The most common side effect in both the clinical trials and case series was menstrual irregularities: 38/264 (14.4%) in the clinical trials and 216/543 (39.8%) in the case series. No side effect, apart from menstrual disturbances, had an incidence above 5% in the Randomized Clinical Trials or case series. Uncommon side effects (0.1–1.0%) were postural hypotension, depression, diarrhea, muscle pain,

increased appetite, drowsiness, rashes/drug eruptions, chloasma-like skin pigmentation, polydipsia, weakness, edema of the legs, change in libido, and palpitations. No women were reported to have elevated levels of potassium and a recent multicenter study in 974 women [51] concluded that routine monitoring of serum potassium in healthy women taking spironolactone for acne is not necessary.

Some investigators mentioned that certain side effects were considered beneficial: breast enlargement, reduced symptoms of premenstrual syndrome, and less greasy skin and hair.

Cyclines's most frequent adverse reactions are photosensitization, gastrointestinal disorders, including gastric or oesophageal pain, nausea/vomiting.

Any adverse event, whether expected or unexpected, serious or not, must be real-time collected in the study eCRF.

All SAEs whether expected or unexpected, must be reported immediately (from the day of the investigator becoming aware of the event) to the sponsor through the eCRF.

The information mentioned on this form and on joined documents must be complete, accurate, clear (no abbreviation…) and coded.

Pregnancy, overdose, misuse, medication errors or potential medication errors, quality defects should be notified by the investigator to the sponsor even if there is no adverse reaction associated.

Frequency and plans for auditing trial conduct {23}

An inspection or audit may take place as part of this study, performed by the sponsor or/and by the regulatory authorities. Inspectors will check the documents, logistics, records and any other resources that the authorities consider to be associated with the clinical trial and that may be located at the trial site itself.

Plans for seeking research ethics committee/institutional review board (REC/IRB) approval {24}

This clinical study was submitted and approved by the southwest Ethical Review Board (Comité de Protection des Personnes Sud-Ouest et Outre-mer III) on October 3, 2017.

Plans for communicating important protocol amendments to relevant parties (e;g; trial participants, ethical committees) {25}

The amended protocol should be a dated, updated version. If necessary, the information form and consent form should be amended.

The updated protocol is at version 8 on 26 november 2019.

All the submissions/declarations were made by the Sponsor Department at CHU Nantes to the French regulatory authority (ANSM) and the southwest Ethical Review Board (Comité de Protection des

Personnes Sud-Ouest et Outre-mer III)

Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators {29}

The investigators will share the entirety of the final trial dataset,

Disseminations plans {31a}

The trial results will be published in international dermatological, medical and scientific journals and presented at national and international conferences.

Authorship eligibility guidelines and any intended use of professional writers {31b}

The investigators will follow the rules and guidelines of the International Committee for Medical Journal Editors (ICMJE) [52]. In practice, the Scientific Committee will be among the authors of the publication, as will the investigators who have included the most patients in the trial. The trial sponsor and the French Ministry of Health, which provided the grant, must be cited in the publication.

Discussion

Although it is prescribed for more than 30 years in USA as acne treatment in women, spironolactone has no official labelling for acne anywhere in the world, making its prescription not easy for dermatologists. Thus, if we demonstrate the superiority of spironolactone versus cycline in the treatment of adult women acne, our randomized trial could have an impact on daily practice, leading the dermatologist to prescribe this treatment to the patients with a guarantee of an acceptable benefit/risk balance.

Moreover, beyond the demonstration of the superiority of spironolactone versus cycline in the treatment of adult women acne, several collective benefits of this FASCE trial can be envisaged.

Firstly, this treatment will improve greatly the quality of life of these patients. This will have real social and economic impacts given the substantial social and economic costs of acne vulgaris care. For example, in the United States, acne vulgaris is responsible for more than 5 million physician visits [53].

Secondly, as we stated above, the World Health Organisation worried about the excessive use of antiobiotics [31]. This study, if the results are conclusive, will allow the physicians to choose spironolactone instead of antibiotics. This saving in antibiotic prescriptions will contribute to reduce the occurrence of antibiotic resistance.

Thirdly, spironolactone can be an alternative to isotretinoin in female that is of a particular interest for two reasons: firstly, isotretinoin is associated with a strict program of contraception often difficult to follow for the patients, secondly the peripheral hyperandrogenia that is frequent in adult female does not well response to isotretinoin with frequent relapses.

In view of all the potential benefits and impacts of this study, its results are eagerly awaited by dermatologists, and in particular by private dermatologists, who see these adult patients suffering from acne in their offices.

Trial Status

This trial is still ongoing; patient inclusion is not yet complete.

The updated protocol is at version 8 on 26 november 2019.

The first patient was included on 31 january 2018

Recruitment by the investigating centres is planned to continue until 30, June 30 2021

Abbreviations

ACE	Angiotensin-converting-enzyme
AFAST	Adult Female Adult Scoring Tool
AMH	Anti Mullerian Hormone
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
ASR	Annual Safety Report
CADI	Cardiff Acne disability Index
CRA	Clinical Research Associate (monitor)
CNIL	Commission Nationale de l'Informatique et des Libertés
CRF	Case Report Form
DHEAS	Dehydroepiandrosterone
DHT	Dihydrotestosterone
ECLA	Echelle de cotation des Lésions d'Acné
eCRF	Electronic Case Report Form
GAGS	Global Acne Grading System

GCP	Good Clinical Practice
GEA	Global Evaluation Assessment
IGF 1	Insulin-like Growth factor1
IUD	IntraUterine Device
LH	Luteinizing hormone
NSAID	Non steroidal anti-inflammatory drug
OC	Oral Contraceptive
RCT	Randomized controlled trial
SAE	Serious Adverse Event
WHO	World Health Organisation

Declarations

Ethics Approval and Consent to Participate

All patients participating in the study are given oral and written information about this trial and sign the informed consent form.

An independent ethical review board, the Comité de Protection des Personnes Sud-Ouest et Outre-mer III, issued a favourable opinion for this clinical trial and gave its approval on 03 October, 2017.

Consent for publication

Not applicable

Availability of data and materials

Data sharing is not applicable to this paper as no datasets were generated or analysed during the current study.

The data from the completed trial will not be shared and will only be transmitted to the sponsor. Data collected during the test may be processed electronically, in accordance with the requirements of the CNIL (compliance with reference methodology MR001).

DECLARATION OF Competing interestS

The authors declare that they have no competing interests. This study is considered to be externally funded as Prof. Dreno has been awarded government funding (via a funding body).

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This grant is allocated following peer review. The research projects selected by this call for tenders must contribute to medical progress and the improvement of the health care system. The experts' comments have been taken into account in the final protocol submitted to the regulatory authorities. The funding body will be mentioned in the acknowledgements as having funded the research but does not get involved in the study, analysis or interpretation of the data.

Authors’ contribution

AP writes the manuscript. AK, BD, SSB, VPR, FV, AC and JMN assisted with the drafting of the manuscript. AP, BD, AK, BD, SSB, VPR, FV, AC, LF, ML, SLN, SC and JMN designed the trial. BD, AP, JMN, VPR, AC, LF wrote the protocol and/or the file for the experimental drug and assisted with the drafting of the manuscript. CD coordinated the submission of the protocol and the follow-up of (1) the Health Ministry’s tender and (2) the regulatory authorities and coordinates the trial. JMN wrote the methodological/statistical analyses in the protocol. VPR and SSB wrote the health economic analyses, ML, SLN, LM, JPC, MTL, EH, NB, AB, BD participates in patient enrolment and follow-up. AC assists with pharmacovigilance for the trial.

All authors read and approved the final manuscript.

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Table 1

Inclusion Criteria	Non-inclusion Criteria
· Female patient ≥ 20 years old	· Patient affected by active /progressive diseases, as infections including Hidradenitis suppurativa, cancers, or endocrine syndrome (*eg polycystic ovary syndrome),* Addison's disease)
· Patient with acne, with at least 10 inflammatory lesions and no more than 3 nodules (GEA score between 2 and 4)	· Patient affected by Rosacea (folliculitis)
• Patient who already had one cycline course for her acne treatment with a 3 months* wash out or who never had any cycline	• Patient with contra-indication to the use of one of the investigational products or auxiliary : o Patient with intolerance or hypersensitivity to cyclin's, spironolactone or to any ingredient present in associated benzoyl peroxide gel o Patient with significant impairment of renal excretory function, acute or chronic renal failure, anuria. o Patient with life-threatening or very severe hepatic impairment. (grade III or IV)
· Patient having signed an informed consent	• Patient with hyperkalaemia or strongly requiring potassium-sparing diuretics (eg amiloride, canrenoate, eplerenone, triamterene), or treated continuously with ACE inhibitors, angiotensin II antagonist, NSAIDs, heparin and molecular weight heparin, ciclosporin and tacrolimus, or treated with lithium.
· Absence of use of oral antibiotics and Zinc salts in the last 30 days	· Patient requiring topical isotretinoin or who stopped this drug since less than 2 weeks
· Absence of use of topical antibiotics in the last 15 days	· Association with potassium salts except in case of hypokalemia
· Absence of use of systemic isotretinoin and antiandrogens in the last 6 months (but antiandrogens used as contraceptive are authorized)	· Patient previously treated with spironolactone
· Absence of microphysiotherapy in the last 15 days	· Pregnant woman or likely to become pregnant or nursing and refusing to use an effective contraceptive method
· Women of child-bearing age under contraception since 3 months (oral contraception, implant, IUD or other kind of hormonal contraception).	· Patient participating in another interventional clinical trial
· Patients with social security	· Patient under guardianship or trusteeship

Table 1 : the inclusion and non-inclusion criteria of FASCE trial File name = Supplementary Material File Title = Informed consent form Description: The informed consent form given to each patient (French version)

Figures

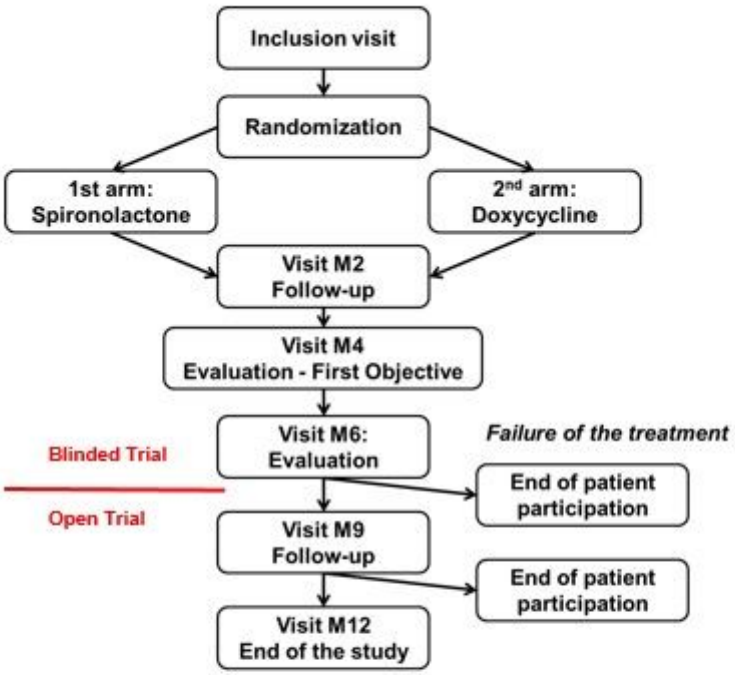
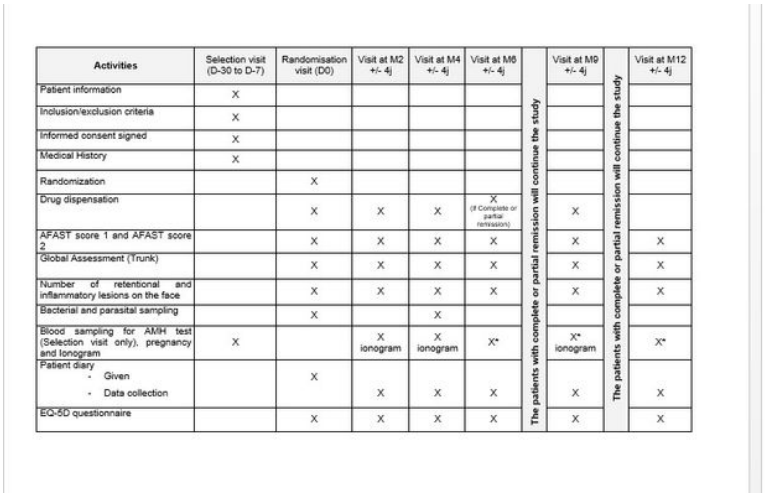


Figure 1

Study diagram



Activities	Selection visit (D-30 to D-7)	Randomisation visit (D0)	Visit at M2 +/- 4j	Visit at M4 +/- 4j	Visit at M6 +/- 4j	The patients with complete or partial remission will continue the study	Visit at M9 +/- 4j	The patients with complete or partial remission will continue the study	Visit at M12 +/- 4j
Patient information	X								
Inclusion/exclusion criteria	X								
Informed consent signed	X								
Medical History	X								
Randomization		X							
Drug dispensation		X	X	X	X (If Complete or partial remission)		X		
AFAST score 1 and AFAST score 2		X	X	X	X		X		X
Global Assessment (Trunk)		X	X	X	X		X		X
Number of retentional and inflammatory lesions on the face		X	X	X	X		X		X
Bacterial and parasital sampling		X		X					
Blood sampling for AMH test (Selection visit only), pregnancy and Ionogram	X		X ionogram	X ionogram	X*		X* ionogram		X*
Patient diary - Given - Data collection		X	X	X	X		X		X
EQ-5D questionnaire		X	X	X	X		X		X
CADI questionnaire		X	X	X	X		X		X
Adverse events			X	X	X		X		X
Concomitant treatments	X	X	X	X	X		X		X

* Pregnancy test if end of treatment

Figure 2

Study schedule

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdministrativeInformation.docx
- resultatsphrc2016mel2.xlsx
- Supplementarymaterialfile.docx