CONFIDENTIEL

CHU Hôpitaux de Rouen

MP3

Methotrexate alone or methotrexate + prednisone low dose in alopecia areata totalis or universalis : results of a 2-step double blind randomized controlled trial

MP3 trial

Version n° 5.0 du 3 avril 2014

PROTOCOLE DE RECHERCHE BIOMEDICALE
2011/121/HP
Etude multicentrique

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VERSION n° 5.0 du 3 avril 2014 :

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I. SYNOPSIS

Title	Methotrexate alone or methotrexate + prednisone low dose in alopecia areata totalis or universalis : resultst of a 2-step double blind randomized controlled trial
Principal Investigator - Coordinator	Prof. Pascal JOLY - Clinique Dermatologique - CHU de Rouen - 1 rue de Germont 76031 ROUEN cedex
Classification	Biomedical interventionnal research
Sponsor	Direction de la Recherche et de l'Innovation - CHU de Rouen - 1 rue de Germont - 76031 Rouen Cedex
Type of trial	Double blind multicenter randomized superiority study comparing 2 arms and 2 phases of treatment for a total duration of 12 months. Randomisation stratified by blocks and centralized
Inclusion criteriae	Patient with severe alopecia areata defined as : 1. AA totalis or universalis involving the totality of the scalp area and potentially the all body surface. 2.chronic course defined as AA without hair regrowth for at least 6 months despite topical and oral treatments including phototherapy PUVA or UBV, topical corticosteroids (clobetasol propionate), minoxidil, IV pulse of methyl prednisolone excluding methotrexate. Whatever previous treatments were used a wash out period of 2 months is needed before the end of the last treatment and study entry.
Study objectives	Main objective : proportion of complete or almost complete >90% hair regrowth (HR) without relapse for the study duration (until month 12) using methotrexate as compared with placebo. Secondary objectives : 1. Assessing the usefullness of secondary addition of a low dose of corticosteroid in combinaion with methotrexate in patients who have not obtained a HR >25% after 6 months of treatment with methotrexate alone. 2. Assessing the usefullness of continuing a treatment with methotrexate alone beyond 6 months in patients who have not obtained a HR >25% after 6 months of treatment with methotrexate alone. 3. Assessing the HR obtained with methotrexate alone or in combination with a low dose of CS treatment in patients who do not achieved a HR with the placebo. 4. Assessing the evolution of patients' quality of life during the study 5. Assessing the tolerance of the different therapeutics regimens.
Inclusion criteria	1- age ≥ 18 ans, < 70 ans, 2- Informed consent 3- patient with a severe AA defined as 3.1 totalis or universalis involving the all scalp surface and potentially the all body surface. 3.2 chronic course of AA defined as : AA totalis o runiversalis without hair regrowth for at least 6 months despite topical and systemic treatments including phototherapy PUVA or UVB, topical application of superpotent corticosteroids (clobetasol propionate cream), topical minoxidil 5%, IV pulse CS excludind the previous use of methotrexate.

	4. for potential child bearing women a contraception is needed during the study and the year following methotrexate withdrawal. 5. for men participating in the study a contraception is needed during the study and for 5 months after methotrexate withdrawal. 6. a 2 month wash out period is needed between the end of the last systemic treatment used and study entry. 7. Updated vaccination
Exclusion criteria	-Pregnant of breastfeeding women -known hypersensitivity to one of the study products (methotrexate, prednisone) -HIV positive serology -active hepatitis B or C -any conventionnal immunosuppresive treatments such as cyclosporine, mycophénolate mofetil, cyclophosphamide, azathioprine) or any other systemic treatment potentially effective on alopecia areata during the 2 months before inclusion in the study. -uncontrolled cardiac arythmia -severe cardiac insuffisancy (class III ou IV, NYHA) -unstabled angina pectoris or ischemic cardiopathy including recent (<3months) myocardial infarction or post myocardial infacrtion cardiac insuffisancy ; -severe liver disorder or abnormal liver enzymes (transaminases and/or alcaline phosphatase higher than 2N) or any recent liver disease (<2years) which might predict a poor tolerance of methotrexate - intake of drugs known as potentially having a liver toxicity or interfering with the metabolism of methotrexate or which might potentially increase the blood toxicity of methotrexate. -alcohol consumption >60g per day -significant renal insuffisancy defined as a creatinine clearance < 50mL/min according to Cockcroft formula. -uncontrolled diabetes melitus (glycemia ≥ 2,5g/L and or HbA1C ≥ 8.5% before treatment) -recent gastric ulcer (<15 days) -any other condition which might contra indicate a CS treatment at an initial dosage of 0,3mg/kg/day -uncontrolled artiel hypertension -severe bacterial , viral or fungal infection or recent past history of severe infection having needed a hospital stay or the use of IV antibiotics during the 4 weeks before study entry. -Evolutive neoplasia (excluding BCC) -past history of recent (<5years) neoplasia which could contra indicate the use of methotrexate -unconsenting patient -primary or secondary immunodeficiency -administration of a live vaccine during the 4 weeks befort study entry -patients having already being treated with methotrexate for their AA (in order no to select poor responders to methotrexate) - poor general condition defined as Karnofsky index <50% -severe chronic lung obstructive disease (FEV <50% or grade II dyspnea) -severe mental impairment -symptomatic osteoporosis -blood abnormalities (Hb <10g/dL and/or leucocytes <3000/mm3 and/or platelets<100000/mm3) -albuminemia <25g/L -patient under legal protection

outcome criteria P 3	**Main outcome criteria** Proportion of patients with a complete or almost complete HR of terminal hair at Month-12 as assessed on 4 photos (top back, left and right side of the scalp) examined by four international experts. Complete or almost complete HR is defined as the reappearance of terminal hair on a scalp area greater or equal to 90% (SALT score ≤10). All patients who did not achieve a rate of HR of >25% at Month-6 and had to be re-randomized to receive methotrexate + prednisone or placebo from Month-6 to Month-12 will be analyzed as treatment failure for the primary endpoint, even if they secondarily achieve complete HR at Month12 **Secondary outcomes** Secondary endpoints are 1. Global regrowth assessment (GRA) which will be evaluated at Month-12 by four international experts, study investigators and patients themselves, and classified in 7 categories: no regrowth, regrowth of non-terminal hair fuzz, or regrowth of terminal hair corresponding to a SALT score of ≤25%, SALT >25% and ≤50%, SALT >50% and ≤75%, SALT >75 and ≤ 90%, and complete or almost complete regrowth (SALT >90%); 2. Relapse rate. Relapse is defined as the occurrence of 3 or more new patches of >2cm, or a disseminated relapse during the study (under treatment) in patients who initially achieved > 25% HR, (whatever the initial treatment was) ; 3. evolution of quality of life as evaluated by the Dermatology Life Quality Index (DLQI), Skindex and the Scalpdex 4. Treatment tolerance. 5. Concordance in the assessment of GRA between patients, investigators and experts. Secondary endpoints will be evaluated in both: 1- patients who receive methotrexate or placebo for 12 months without being re-randomized at Month-6 2 patients initially assigned to the placebo or methotrexate group who will be re-randomized at Month-6 to receive either methotrexate + prednisone or methotrexate + placebo of prednisone.
Study procedures	Two step double blind randomized multicenter study including 2 arms and 2 phases of treatments for a total duration of 12 months. During a first phase (6 months) patients will be randomized to receive either oral methotrexate 20 or 25mg/week depending on patients' weight or a placebo of methotrexate. Patients who will achieve a ≥25 hair regrowth at month 5 will continue the same treatment (methotrexate or placebo) until the end of the study at month 12. Patients who will not achieve hair regowrth or will achieve a minimal hair regrowth (<25%) at the M5 evaluation will continue the same treatment until M6 and will then be re-randomized (without unblinding of the initial randomization) to receive (from M6 to M12) methotrexate (20 to 25mg per week depending on patients' weight) combined with oral prednisone (20mg/day from M6 to M9 and then 15mg/day from M9 to M12) or methotrexate combined with a placebo of prednisone. NB : Hair regrowth will be assessed at month 5 in order to have time to send photos to the experts, then receive their evaluation of HR which will potentially trigger the re randomization of the patient and the delivery of the therapeutic units to the different sites to start the second phase of treatment at month 6.

Number of patients to include	90 patients
Number of sites	**13** sites in France

Statistical analysis P 3	The statistical hypothesis corresponds to a proportion of complete or almost complete HR at M12 of 30% in the methotrexate arm and 5% in the placebo arm. Accordind to this hypothesis, the number of patients to include is 78 patients for a statisical power of 80% and an alpha risk of 5%. Taking into account some patients who will be lost to follow up 90 patients will be included. The number of patients achieving a >90% HR (SALT ≤10) at Month-12 while receiving the same treatment assigned at the initial randomization will be compared between the two treatment groups using Fisher's exact test.
Study schedule	inclusion period : 24 months duration of treatment : 12 months number of visits at the study sites per patient : 9 visits + 1 visit in relapsing patients.

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III. OBJECTIVES OF THE RESEARCH

III.1. PRIMARY OBJECTIVES

The primary objective of the study is to evaluate the efficacy of methotrexate in achieving sustained complete or almost-complete (≥90%) hair regrowth, 12 months after initiation of treatment, compared to placebo.

III.2. SECONDARY OBJECTIVES

The secondary objectives are:

1) To evaluate the usefulness of the secondary addition of a low dose of systemic corticosteroid in combination with methotrexate in patients who have not achieved hair regrowth, or have achieved only poor hair regrowth after 6 months of treatment with methotrexate alone.

2) To evaluate the usefulness of extending methotrexate treatment beyond 6 months in patients who have no HR , or who have only achieved weak HR after 6 months of treatment with methotrexate alone (late HR)

3) To evaluate the rate of HR obtained with methotrexate alone or methotrexate combined with low levels of systemic corticosteroids in patients who did not achieve a HR with placebo.

4) To evaluate the quality of life of patients during treatment

5) To evaluate the tolerance of these different therapeutic regimens

IV. STUDY DESIGN

IV.1. PRIMARY AND SECONDARY EVALUATION CRITERIA

IV.1.1. Primary endpoint

The primary endpoint will be the rate of patients achieving complete or near-complete regrowth of terminal hair 12 months after initiation of methotrexate versus placebo, while receiving the same treatment for the duration of the study from initial randomization. All patients who have had their treatment changed at the M6 assessment and who have not received the same treatment during the 2 study periods (M0 to M6 and M6 to M12) will be considered as failure for the primary endpoint, even if significant hair regrowth is achieved with the 2nd sequence.

Complete or near-complete hair regrowth" is defined as the reappearance of terminal hair (not just fine fuzz) on an area greater than or equal to 90% of the scalp. This criterion

(complete or almost complete hair regrowth) is recommended by the International Alopecia Areata Foundation in its "alopecia areata investigational assessment guidelines".

The evaluation of the primary endpoint will be performed by a panel of 4 dermatologists with expertise in hair disorders , who will not participate in the study as investigators, and will evaluate the HR in a blinded manner of the treatment arm, on a series of 4 photos of the scalp (top, back, left side, right side). In case of disagreement between the 4 experts, a vote will be taken.

NB: *Despite the double-blind design of the study, the evaluation of regrowth at 6 months (> or < 25%) and the evaluation of the primary endpoint will be performed by an evaluation committee of 4 experts (and not by the investigator), because blood abnormalities (methotrexate-related macrocytosis, prednisone-related leukocytosis) or possible digestive disorders relatively frequent with methotrexate (nausea) could biase an evaluation performed by the investigator*

This evaluation by a panel of experts was recommended by the experts who reviewed the first version of the protocol. This methodology of assessment on photographs examined by experts has already been used and has shown its reliability in several therapeutic trials in androgenetic alopecia.

IV.1.2. Secondary endpoints

1) Global Regrowth Assesment (GRA) 12 months on a 7-criteria scale:

- complete or almost complete hair regrowth (greater than or equal to 90%),
- major regrowth (greater than or equal to 75%)
- moderate regrowth (≥50% and <75%),
- partial regrowth (<50% and ≥25%),
- minimal regrowth (<25%)
- regrowth of only one hair
- no regrowth

This evaluation will be performed jointly by:

- 4 independent experts (based on the four photographs taken by the investigators

In case of discordance in the evaluation of the experts, the rating retained will be that proposed by 2 of the 3 first responding experts),

- the investigators,
- the patients.

The concordance between these assessments will be evaluated by a concordance test.

A meeting of investigators will be organized to train the investigators in this semi-quantitative evaluation, to homogenize their evaluation as much as possible.

This evaluation of hair regrowth at month 6 and month12 will allow to determine :

A - <u>In patients initially randomized in the methotrexate arm and considered as "non-responder or poor responder" at M6</u>:

- the rate of “late” hair regrowth achieved by extending methotrexate alone beyond 6 months.
- the rate of hair regrowth obtained by adding a low dose of systemic corticosteroid therapy to methotrexate.

B - In patients initially randomized in the placebo arm and considered as "non-responder or poor responder" at M6

- the proportion of HR obtained with each of the 2 treatment regimens proposed during the second randomization (MTX alone and MTX + prednisone)
- the proportion of HR in patients secondarily randomized in the MTX arm (after placebo failure) will be compared to that in patients initially randomized to receive methotrexate (during the first part of the study).

2) Relapse Rate

Relapse is defined as the occurrence of at least 3 new patches with a diameter ≥2 cm, or diffuse relapse in patients who achieved complete or almost -complete hair regrowth.

3) Quality of Life

Patients' quality of life will be assessed at M0, M3, M6, M9, and M12 using the DLQI , skindex France questionnaires. These questionnaires are well validated in the literature, easy to fill in, and well accepted by the patients. They are particularly suitable for measuring quality of life in patients with chronic inflammatory dermatosis.
A quality of life questionnaire specific to scalp diseases (Scalpdex) will also be used.

5) Tolerance

Defined as the occurrence of adverse events and serious adverse events which will be recorded according to the WHO classification. This evaluation will be carried out at all the visits planned in the protocol.

These evaluation criteria will make possible the assessment of the proportion of complete or almost complete regrowth under treatment (which is a very hard evaluation criterion that has practically never been used in studies to date, but which is the most clinically relevant because it corresponds to the patients' expectations).
On the other hand, they will make it possible to evaluate the maintenance of the benefit of the treatment in the medium term, as well as the evolution of the quality of life of the patients, which are two criteria considered indispensable and which have been recommended by the International Alopecia Areata Foundation in its "alopecia areata investigational assessment guidelines"

IV.2. RESEARCH DESIGN

This study is a multicenter (involving 13 French centers), prospective, randomized, double-blind, superiority study (central randomization by blocks of variable size). This study is designed to compare the efficacy of methotrexate versus placebo in patients with severe alopecia areata with secondary treatment of methotrexate + prednisone.

IV.3. DESCRIPTION OF RANDOMIZATION AND BLINDING

IV.3.1. Randomization

The study will be performed in 2 parallel groups. Patients with severe AA who meet the inclusion criteria, without any exclusion criteria and who have given their consent, may be included in the study.

Patients will be randomly assigned to one of two groups at baseline

Group A: Methotrexate

Group B: Placebo

The master randomization list to randomize patients at inclusion will be established by the biostatistician of Professor Jacques Benichou's Biostatistics Unit before the start of the trial. Randomization will be centralized and stratified by center using balanced blocks whose size will depend on the recruitment envisaged in each center. The numbers in each treatment group are balanced with a 1:1 ratio. The randomization will be done at the time of inclusion after notification to the DRCI of the Rouen University Hospital (CHU de Rouen - Hôpitaux de Rouen - 1 rue de Germont 76031 ROUEN cedex - Telephone: 0232888265 - Fax: 0232888287 - E mail: Delegation.Recherche@chu-rouen.fr) thanks to an inclusion fax. This document will be returned by the sponsor to the investigator, by fax, specifying the inclusion number and the result of the randomization (inclusion in the methotrexate arm or in the Placebo arm). A document specifying the randomization procedure is kept confidential by the Biostatistics Unit, the DRCI and the PUI of the Chu de Rouen, and they will ensure that the investigators are kept blinded to the allocated treatment.

The treatment must be started within one week after randomization.

A second randomization list for patients with minimal or no regrowth (<25% regrowth) at M5, will be established by the biostatistician of Professor Jacques Benichou's Biostatistics Unit before the trial started.

The randomization will be centralized and stratified by center using balanced blocks whose size will depend on the recruitment envisaged in each center. The numbers in each treatment group are thus balanced with a 1:1 ratio. The request for a new randomization,

during the M6 visits and for patients with minimal or no regrowth, will be made by sending a second randomization fax to the promoter (DRI of the Rouen hospital) at 02 32 88 82 65. This document will be returned by the promoter to the investigator, by fax, specifying the result of the randomization (inclusion in the methotrexate + Placébo arm or in the methotrexate + Prednisone arm). A document specifying the randomization procedure is kept confidential by the Biostatistics Unit, the DRCI and the PUI of the Chu de Rouen, and they will ensure that the investigators are blinded to the allocated treatment.

IV.3.2. Insu removal procedure

The treatment periods for the initial randomization phase, upon inclusion, as well as for the randomization phase at M6 for patients with minimal or no hair regrowth (<25% regrowth) are double-blind. Blinding will be maintained until final data analysis.
The treatment code (the nature of the treatment) assigned to each patient will be kept by the promoter (Rouen University Hospital), the biostatistical unit of Prof. Jacques Benichou and the central pharmacy of Rouen University Hospital in the form of 2 treatment assignment lists. One list was for the initial randomization phase, at inclusion, and a second list for the randomization phase at M6.
In case of absolute necessity of unblinding, i.e. in an emergency situation, in case of adverse events requiring the knowledge of the treatment assigned to the patient for his management, the investigator will have to contact by phone the coordinating investigator of the trial before any lifting of the treatment code.

Coordinating investigator :
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In case of knowledge of the treatment, the reason and the date of information as well as the signature of the investigator must appear on the observation book and that of the coordinating investigator on the list of allocation of the corresponding treatments, held by the promoter (Rouen University Hospital), the biostatistical unit of Pr Jacques Benichou and the central pharmacy of Rouen Hospital.

Any patient for whom unblinding has been performed will no longer be able to receive treatments tested in the study.

V. SELECTION OF RESEARCH SUBJECTS

V.1. INCLUSION CRITERIA

Criteria 1, 2, 3 and 5 are cumulative. Criterion 4 concerns only women of childbearing age.

11- age ≥ 18 years, < 70 years,
2- patient having been informed and having given consent,
3- patient with severe alopecia defined as:
3.1- "AT or AU defined clinically by the existence of a diffuse, non-scarring alopecia of the entire scalp and possibly of all body hair, including eyelashes, eyebrows.
3-2 Chronic alopecia defined as having evolved without HR for at least 6 months, despite topical and systemic previous treatments (including phototherapy (PUVA or UVB), applications of superpotent CS (such as clobetasol propionate: cream or dermoval gel), applications of minoxidil 5%, or IV pulse of corticosteroids, excluding methotrexate, and oral corticosteroids (drugs tested in the trial). Regardless of the treatment previously tried, a washout period of 2 months will be required between the end of the last treatment previously tried and inclusion in the study.
3- for women of childbearing age, effective contraception (IUD, estrogen-progestin contraception....) will be required during treatment and for one year after stopping treatment,
4- up-to-date vaccination status. Investigators should check the vaccination status of eligible patients and follow national recommendations for adult vaccination schedules, with a 28-day delay between any vaccination and the first administration of any of the study treatments.

NB: The inclusion criteria have been modified based on the recommendations of the experts who reviewed the previous project: i) to focus on the most severe patients (for whom no alternative therapy exists), including only chronic AT or AU (since IV corticosteroid pulses have some efficacy in acute types of AA). ii) only including patients in whom previous treatments have failed so that the analysis does not have to be stratified (neither on the basis of acute or chronic nature, nor on the basis of spontaneous or resistant evolution to previous treatment at the time of inclusion).

V.2 NON INCLUSION CRITERIA

- Pregnant of breastfeeding women
-known hypersensitivity to one of the study products (methotrexate, prednisone)
-HIV positive serology
-active hepatitis B or C

-any conventionnal immunosuppresive treatments such as cyclosporine, mycophénolate mofetil, cyclophosphamide, azathioprine) or any other systemic treatment potentially effective on alopecia areata during the 2 months before inclusion in the study.

-uncontrolled cardiac arythmia

-severe cardiac insuffisancy (class III ou IV, NYHA)

-unstabled angina pectoris or ischemic cardiopathy including recent (<3months) myocardial infarction or post myocardial infacrtion cardiac insuffisancy ;

-severe liver disorder or abnormal liver enzymes (transaminases and/or alcaline phosphatase higher than 2N) or any recent liver disease (<2years) which might predict a poor tolerance of methotrexate

- intake of drugs known as potentially having a liver toxicity or interfering with the metabolism of methotrexate or which might potentially increase the blood toxicity of methotrexate.

-alcohol consumption >60g per day

-significant renal insuffisancy defined as a creatinine clearance < 50mL/min according to Cockcroft formula.

-uncontrolled diabetes melitus (glycemia ≥ 2,5g/L and or HbA1C ≥ 8.5% before treatment)

-recent gastric ulcer (<15 days)

-any other condition which might contra indicate a CS treatment at an initial dosage of 0,3mg/kg/day

-uncontrolled artiel hypertension

-severe bacterial , viral or fungal infection or recent past history of severe infection having needed a hospital stay or the use of IV antibiotics during the 4 weeks before study entry.

-Evolutive neoplasia (excluding BCC)

-past history of recent (<5years) neoplasia which could contra indicate the use of methotrexate

-unconsenting patient

-primary or secondary immunodeficiency

-administration of a live vaccine during the 4 weeks befort study entry

-patients having already being treated with methotrexate for their AA (in order no to select poor responders to methotrexate)

- poor general condition defined as Karnofsky index <50%

-severe chronic lung obstructive disease (FEV <50% or grade II dyspnea)

-severe mental impairment

-symptomatic osteoporosis

-blood abnormalities (Hb <10g/dL and/or leucocytes <3000/mm3 and/or platelets<100000/mm3)

-albuminemia <25g/L

-patient under legal protection

V.2. RECRUITMENT PROCEDURE

Recruitment will be carried out by the 13 dermatology departments participating in the trial and usually managing this type of AA. Patients with severe AA (as defined in chapter "Inclusion criteria") who meet the inclusion criteria and who do not meet any non-inclusion criteria may be included in the study. Once the diagnosis has been made and the inclusion and non-inclusion criteria have been verified, the patient will be informed about the study and then asked to give consent after a period of reflection and time to answer these questions. Then, the randomisation will be done with the DRCI of the Rouen University Hospital

VI. RESEARCH TREATMENT

VI.1. DESCRIPTION OF THE EXPERIMENTAL DRUGS

VI.1.1. Randomisation at inclusion

VIII.1.1.1. Methotrexate

Patients weighing 50 kg or more will receive a weekly dose of 25 mg methotrexate on a fixed day per week (ten 2.5 mg tablets). Patients weighing less than 50 kilograms will receive a methotrexate dose of 20 mg on a fixed day per week (eight 2.5 mg tablets). Methotrexate will be started at a dose of two tablets (5 mg) on the first dose (first week), and then in the absence of haematological and/or hepatic abnormalities at the Day 7 visit (haemoglobin ≥ 10 g/l, leukocytes ≥ 3000/mm3, platelets ≥ 100,000/mm3, GOT and GTP < 2.5 the upper laboratory standard) at a dose of four tablets (10 mg) on the second dose (second week) irrespective of weight. If no haematological and/or hepatic abnormalities will be detected at Day 14, methotrexate will then be administered at a dose of 20 to 25 mg (depending on patient's weight) once a week for 6 months or 12 months depending on the randomisation arm.

Two folic acid tablets (10 mg) will be routinely prescribed the day after the methotrexate is taken.

VIII.1.1.2. Placebo

Eight to 10 methotrexate placebo tablets (depending on weight: 8 tablets if <50kg, 10 tablets if ≥ 50kg) will be administered one day per week, combined with 2 speciafoldine placebo tablets the day after.

Patients whose regrowth at M5 will have been assessed as ≥25% by the committee of experts will continue methotrexate or methotrexate placebo, from the 1st randomisation, until M12.

VI.1.2. Patients Re randomized at M6

Patients with minimal or no regrowth at M5 will be re-randomized (regardless of the original arm: methotrexate or placebo) WITHOUT unblinding of the initial treatment, to receive from M6 to M12:

VIII.1.2.1. Méthotrexate + Prednisone

- either methotrexate (20 to 25 mg/week depending on weight) + oral prednisone 20mg per day for 3 months then 15 mg per day for 3 months + two folic acid tablets (10mg) every week.

VIII.1.2.2. Méthotrexate + Placebo

- either methotrexate (20 to 25 mg/week depending on weight) + an equivalent number of prednisone placebo tablets +two folic acid tablets (10mg) per week.

VI.2. WHAT TO DO IN THE EVENT OF A RELAPSE IN PATIENTS WHO HAVE ACHIEVED REGROWTH

VI.2.1. Definition of regrowth

Relapse is defined as: i) the reappearance of one or more new patches of at least 2 cm in diameter or ii) the occurrence of a more diffuse relapse of hair over the entire scalp in a patient who has achieved complete or near-complete regrowth after treatment.

VI.2.2. Course of action

In order to keep the blinding until the end of the study, no adaptation of the doses of the products studied (methotrexate, prednisone) will be authorised.
The extension of our original study showed the difference in significance of localised relapses (which are frequent under treatment, particularly when the prednisone dose is progressively tapered in patients receiving combined treatment, and which do not interfere with the maintenance of an aesthetically correct hair regrowth), compared with diffuse relapses, which can be considered as treatment failure.

- Patients with plaque-type relapses can be treated with topical corticosteroid therapy (clobetasol propionate cream) one application/day not to exceeding 20 grams per week.

- Patients with diffuse relapseswill be considered as treatment failure (it is indeed exceptional that a diffuse relapse can be controlled by the addition of topical CS alone.

VI.3. DOSAGE ADJUSTMENT OF THE STUDY DRUGS

VI.3.1. Methotrexate dose adjustment

The weekly dosage of methotrexate (or its placebo) will be adjusted according to the following circumstances

1) Development of renal failure :

Renal function (creatinine, Cockroft clearance) should be assessed monthly.

If clearance decreases below 30 ml/min on at least two evaluations (including a second evaluation performed two-weeks after the first result), methotrexate or placebo should be discontinued. However, the patient should be evaluated until the end of the trial.

If it drops below 50 ml/min: reduce the weekly dose of methotrexate or placebo by one tablet (i.e. 2.5 mg methotrexate) and recheck blood creatinine and clearance twice a month

2) Change in weight:

If weight falls below 50 kg, reduce the weekly dose of methotrexate or placebo from 10 tablets to 8 tablets (i.e. a reduction from 25 to 20 mg of methotrexate).

3) Introduction of any of the following drugs:

ketoconazole, penicillin, VKA, phenytoin, retinoid, thiazide diuretic and any other drug that may potentiate toxicity: reduce the weekly dosage of methotrexate or placebo by 1 tablet (i.e. a reduction of 2.5mg of methotrexate).

4) Development of digestive disorders (nausea, vomiting).

In patients with digestive symptoms, digestive exams must be carried out according to the investigator's judgement. Symptomatic treatment may be undertaken (anti-emetic drugs). If the digestive p symptoms persist despite these measures, investigator may reduce the dosage of methotrexate or placebo depending on the evolution of the digestive problems.

5) Onset of febrile infection (pneumonia, upper urinary tract infection etc)

Methotrexate or placebo will be discontinued and then restarted one week after return to apyrexia at the same dosage as before the infection occurred.

6) Occurrence of a non-febrile infection (lower urinary tract infection, skin infection etc)

Methotrexate or placebo should be continued at the same dosage with daily monitoring of body temperature until the infection is resolved.

7) Development of liver toxicity

7A - Increase in one or more enzymes (SGPT, SGOT, gamma GT) >5 N: discontinue methotrexate or placebo and monitor liver biology weekly:

- if regression to < 3 N : restart methotrexate or placebo at the initial dose reduced by 5 mg/week and maintain biweekly liver biology monitoring until the end of the study,
- if the figures do not regress to < 3N after at least 4 weeks of stopping methotrexate or its placebo, the patient will be withdrawn from the study.

7B - Increase in one or more enzymes between 3 and 5 N: do not stop methotrexate or its placebo, but check the liver biology 15 days later:

- if abnormalities persist: reduce the dosage of methotrexate or placebo by 2 tablets (equivalent to 5 mg/week of methotrexate), and maintain bi-monthly monitoring of liver biology until the end of the study,
- if the abnormalities regress: continue methotrexate or placebo at the same dosage and maintain fortnightly monitoring of liver biology until the end of the study.

7C - In the event of a second episode of liver toxicity (increase in one or more enzymes to at least 3 N for no obvious reason other than methotrexate: discontinue methotrexate or placebo permanently. The patient is withdrawn from the study.

8) Development of haematological toxicity

- If Hb < 10 g/dl or white blood cells < 3000/mm3 or platelets < 100,000/mm3 : discontinue methotrexate or placebo and check BCC weekly.
- in case of partial or complete regression of abnormalities: restart methotrexate or placebo at the initial dosage reduced by 2 tablets (equivalent to 5 mg/week of methotrexate), and maintain fortnightly monitoring of CBC until the end of the study;
- in case of recurrence of haematological toxicity: permanent discontinuation of methotrexate or its placebo. The patient is withdrawn from the study.
- if no regression of abnormalities after at least 4 weeks of discontinuation of methotrexate or its placebo: definitive discontinuation of methotrexate or its placebo.

The patient is withdrawn from the study.

Any change in methotrexate or placebo dosage should be clearly noted in the case report form, along with the reason for the change.

VI.3.2. Prednisone dose adjustment

In the event of grade III or IV side effects (notably weight gain ≥7 kilos, uncontrolled diabetes becoming insulin-requiring, uncontrolled hypertension, etc.), the dosage of Prednisone or its placebo will be reduced from 20mg to 15mg per day. In case of persistence of this side effect, a further decrease of prednisone or its placebo will be left to the discretion of the investigating physician who will judge according to the patient's clinical condition and biological examinations.

VI.4. PATIENT OUTCOME AT THE END OF THE STUDY

The investigators will be free to decide whether or not to continue methotrexate treatment (alone or combined with prednisone) after the end of the study.
However, continuation of this prescription would be off labelled and the sponsor cannot be held responsible for any side effects that may occur after the end of the study.

VI.5. ASSOCIATED TREATMENTS PROHIBITED IN THE PROTOCOL

The following treatments are prohibited during the trial
- immunosuppressive drugs such as ciclosporine, mycophenolate mofetil, cyclophosphamide, azathioprine,
- aspirin (analgesic doses), NSAIDs, trimethoprim (see monograph on methotrexate).
- any live vaccine during the trial until one month after the end of treatment),
- as well as any other treatment that could potentially be effective on AA (puvatherapy, UVB, local immunotherapy, biologics , intravenous immunoglobulins, etc.), except for low doses of topical corticosteroids in patients with plaque type relapsing AA (see paragraph VII.2- What to do in the event of relapse, page 27).

VI.6. AUTHORIZED TREATMENTS

These adjuvants treatments will be proposed routinely in patients who will be re randomized at month 6 (and who can potentiallty receive corticosteroids from month 6 to M12):

- normo caloric diet, low in fast sugars, high in protein,
- salt-free diet (2 g salt/day),
- calcium 1 g/day, vitamin D 200 IU/day (Orocal D3 : 2cp/d or Cacit D3 : 1cp/d)
- biphosphonate (actonel35 ® or Fosamax 70 ® 1cp/week: only in postmenopausal women

- gastric protection by proton pump inhibitor (not systematic, only in case of gastric pain),

VII. CONDUCT OF THE RESEARCH

Patients will be recruited over a period of 24 months and followed for a period of 12 months.

VII.1. RESEARCH SCHEDULE

VII.1.1. Screening visit

The screening visit will explain to the patients the modalities of participation in the study, collect their consent and perform the biological and radiographic examinations needed for inclusion.

VII.1.2. Inclusion visit (M0)

This visit will collect clinical (including quality of life questionnaires) and biological parameters. It will allow to take photographs, to make sure that the inclusion and exclusion criteria are observed , to collect the patient's written consent, to perform a skin biopsy of the scalp (ancillary study), and to make the randomization request.

- Clinical evaluation (temperature, cardiac frequency , blood pressure, weight).
- Past history and associated disorders .
- current treatments.
- negative pregnancy test for women of childbearing age

Patients randomized to the methotrexate arm or the placebo arm will start their treatment orally.

VII.1.3. Visit M1

- Assessment of treatment tolerance (clinical examination [weight, blood pressure, temperature, digestive tolerance] + standard biological tests - see paragraph above).

VII.1.4. Visit M2

- Tolerance of the treatment (clinical and biological examinations)
- Pregnancy test for women of childbearing age

VII.1.5. Visit M3

- Treatment tolerance (clinical and biological examinations)
- Quality of life questionnaires.

VII.1.6. Visit M5

- Photographs of the scalp (top, back, left and right side)

Assessment of HR (≥ or < 25%) by blind experts

- Treatment tolerance (clinical and biological examinations)

VII.1.7. Visit M6

- -Global RegrowthAssessment (GRA)
- Quality of life questionnaires.
- Treatment tolerance.

At this M6 evaluation, patients who have not achieved a therapeutic response at M5 (no regrowth or regrowth of less than 25% of the scalp area as assessed by the panel of experts) will be re-randomized (without removing the blind on the initial randomization arm) to receive either methotrexate 20 or 25mg/week + prednisone 20mg/day for 3 months (M6 to M9), then 15 mg/day for the next 3 months (M9 to M12), or methotrexate 20 to 25mg/week + prednisone placebo from M6 to M12.

-Pregnancy test for women of childbearing age

VII.1.8. Visit M9

- Tolerance.
- Quality of life questionnaires.

-Pregnancy test for women of childbearing age

VII.1.9. Visit M12

- Photographs
- Evaluation of the primary endpoint by the panel of blind experts

-Global Regrowth Assessment (GRA)

- Quality of life questionnaires.

- Tolerance.

-Pregnancy test for women of childbearing age

At the end of this visit, male patients will be reminded that contraception (condom) remains necessary for at least 5 months after stopping treatment. Similarly, for women of childbearing age, they will be reminded that effective contraception (IUD, oestrogenic contraception....) remains necessary for one year after stopping treatment.

VII.1.10. Monitoring of patients between inclusion and month 6.

Clinical and biological monitoring will be consistent with standard practice and will include monthly:

- clinical examination,
- Blood cell count
- SGOT, SGPT, gamma GT
- b HCG in women of childbearing age,

Every other month:

- creatinine level
- albuminemia

VII.1.11. Monitoring of patients staying in their initial randomisation group between M6 and M12

Clinical and biological monitoring will be consistent with standard practice and will include monthly:

- clinical examination,
- Blood cell count
- SGOT, SGPT, gamma GT
- b HCG in women of childbearing age,
- creatinine level

VII.1.12. Monitoring of patients re-randomised at the M6 assessment

(patients likely to receive methotrexate and prednisone)

Clinical and biological monitoring will be in accordance with standard practice and will include monthly :

- clinical examination,
- Blood cell count
- serum electrolytes
- glycelmia ,
- SGOT, SGPT, gamma GT
- b HCG in women of childbearing age,

Every other month:

- creatinine level
- albuminemia
- cholesterol triglycerides
-A bone densitometry will be performed only in case of symptomatic osteopenia appearing during the study

VII.2. TOLERANCE OF THE TREATMENT

At each evaluation, a detailed record of possible serious adverse events will be made.
These side effects will be graded from 1 to 4 according to the WHO classification.

VII.3. TREATMENT DURATION AND EVALUATION

8 visits are scheduled over the 12-month follow-up period.
The visits are scheduled as follows: pre-screening visit, inclusion visit, M1 visit, M2 visit, M3 visit, M6 visit, M9 visit, M12 visit.
An additional visit (V relapse) may be scheduled on request in relapsing patients, in order to adapt the treatment (see paragraph XI-2: Adaptation of prednisone doses).

VIII. SAFETY ASSESSMENT

VIII.1. DEFINITIONS

VIII.1.1. Adverse events (AE)

(Article R1123-39 of the Public Health Code)
An adverse event is any harmful manifestation occurring in a person who participate in a biomedical research, whether or not this manifestation is related to the research or to the product on which this research is based.

Adverse reaction
An adverse drug reaction is a noxious and unintended response to an investigational drug/device/procedure.

VIII.1.2. Serious adverse event or reaction

(Article R1123-39 of the Public Health Code)
A serious adverse event or reaction is one that :
- results in death,
- or which endangers the life of the person who is the subject of the research,
- or which results in a significant or lasting disability or handicap,
- or that requires hospitalization or prolongation of hospitalization,
- or results in a congenital anomaly or malformation,
- or any other event deemed medically significant by the investigator.

Some circumstances requiring hospitalization do not fall under the "hospitalization/extended hospitalization" severity criterion, including:
- Hospitalization as per the protocol,
- hospitalization for medical or surgical treatment scheduled before inclusion
- Hospitalization of less than 24 hours.

VIII.1.3. Unexpected adverse event

An unexpected event is any adverse effect of the investigational drug/device/procedure whose nature, severity or course is not consistent with the information provided in the reference document (Summary of Product Characteristics, Investigator's Brochure, instruction or use leaflet for CE marked devices, protocol).

VIII.1.4. New safety event

A new event means, in particular, any new safety data arising during the trial:
- Likely to affect the safety of the patient,
- May lead to a reassessment of the benefit/risk ratio of the trial,
- Sufficient to consider changes in the conduct of the research, or in the research documents

VIII.2. RESPONSABILITIES OF THE INVESTIGATOR

The investigator assesses each adverse event in terms of its seriousness.

VIII.2.1. Collection of adverse events

The investigator vollects the AE in the AE form located in the appendix of the observation book.

VIII.2.2. Notification of adverse events to the sponsor

The investigator must notify the sponsor without delay, from the day he/she becomes aware of them, of all serious adverse events occurring in the trial.
This initial notification should be in the form of a written report and should be followed, if necessary, by additional detailed written report(s).
The investigator should document the event to the best of his/her ability and provide a medical diagnosis.

The notification is sent by fax to the sponsor using the serious adverse event report form located in the appendix of the observation booklet, dated and signed, to:

CHU-Hôpitaux de Rouen, Direction de la Recherche et de l'Innovation,
1 rue de Germont
76031 Rouen Cedex 1

Tel : 02 32 88 82 65

Fax : 02 32 88 82 87

Copies of laboratory results or reports of examinations or hospitalization relating to the SAE, including relevant negative results, must be attached to this form, without omitting to make these documents anonymous.

The investigator should ensure that relevant follow-up information is provided to the sponsor as soon as it becomes available.

The investigator should follow the patient who has experienced an SAE until resolution, stabilization at a level acceptable to the investigator, or return to baseline, even if the patient has been discharged from the trial, and should inform the sponsor of the progress of the serious adverse events.

VIII.2.3. Assessment of the intensity of adverse events

The investigator is asked to evaluate the intensity of the adverse events observed in the research participant and to report it in the observation booklet, either with the help of a grading scale for adverse events annexed to the protocol (e.g. the NCI-CTC classification for cancer trials), or by more general terms such as

Mild : does not interfere with usual daily activity

Moderate : partial limitation of usual daily activity

Severe : limitation of usual daily activity

VIII.2.4. Assessment of causality

The investigator should assess the causal relationship of the adverse events with the investigational drug(s)/device(s)/procedure(s), the comparator(s), any associated treatment(s) and the research.

VIII.2.5. Expected serious adverse events

The potential risks or complications related to the study drugs or to the research procedures are

- related to Methotrexate (Cytolytic and cholestatic hepatitis, anemia, neutropenia, thrombocytopenia, lymphopenia, pulmonary fibrosis, hypersensitivity pneumonitis, serious infection)
- related to Prednisone (hypertension, diabetes, heart failure, stroke, severe infection, hypokalemia)

VIII.2.6. Reporting period

Any serious AE must be reported if it occurs for a research participant:
- From the date of signing consent,
- During the entire duration of the participant's follow-up in the trial,
- Up to 12 months after the end of the trial for the research participant

VIII.2.7. Special cases

Serious events subject to immediate reporting:

All -serious adverse events and/or abnormal test results, defined in the protocol as critical to the evaluation of the safety of the clinical trial subjects, should be reported promptly to the sponsor by the investigator.

In the context of this trial, Serious Events subject to immediate reporting:

- On blood count, anemia ≤ 10.5G/l, neutropenia 1200, lymphopenia 1200 and thrombocytopenia 120000.
- On liver function tests, SGOT >1.5N, SGPT>1.5N, and GT>1.5N.

VIII.2.8. Pregnancy

If a woman becomes pregnant during the course of the trial, the pregnancy must be reported to the sponsor using the specific form in the appendix of the case report form.

The investigator must follow the patient until the pregnancy is terminated or terminated and notify the sponsor of the outcome.

If the outcome of the pregnancy falls within the definition of serious adverse events (spontaneous abortion with hospitalization, fetal death, congenital anomaly, etc.), the investigator must follow the procedure for reporting severe adverse events.

VIII.3. RESPONSABILITIES OF THE SPONSOR

The promotor keeps a detailed record of all AE reportes to him by the investigator(s).

VIII.3.1. Reporting of serious unexpected adverse events

The sponsor should assess the causal relationship between the serious adverse event and the investigational medicinal product(s), comparator(s), any associated treatment(s), and the research.

All adverse events for which the investigator or sponsor believes that a causal relationship with the investigational drug can reasonably be considered are considered suspected adverse events.

The sponsor assesses whether the adverse reaction is expected or unexpected, based on the reference document.

The sponsor reports all suspected serious and unexpected adverse reactions to the relevant health authorities and the relevant Ethics Committee:

- In the case of a serious adverse reaction resulting in death or life-threatening, without delay and at the latest within 7 days from the day the sponsor becomes aware of it; additional relevant information is transmitted within a further 8 days.
- In the other cases of serious adverse reaction, at the latest within 15 days of the day on which the sponsor became aware of it; additional relevant information is transmitted within a further 8 days.

A concomitant report to the EMA (European Medicines Agency) is made in the European pharmacovigilance database Eudravigilance.

VIII.3.2. Reporting of safety developments

The sponsor also declares without delay to the competent health authorities and to the relevant Ethics Committees any new safety fact.

VIII.3.3. Informing the investigators

The sponsor transmits to the investigators concerned any information likely to affect the safety of individuals.

VIII.3.4. Annual safety report and semi annual listing

Once a year, the sponsor sends a safety report to the competent Health Authorities and the relevant Ethics Committees.

Every six months, the sponsor sends the competent Health Authorities and the Ethics Committees concerned a list of suspected serious unexpected adverse reactions that have occurred in the research outside the national territory or that have occurred in other research that it is conducting in France with the same drug.

VIII.4. STEERING COMMITTEE

It will be made up of the clinical initiators of the project (Professor Pascal JOLY, Professor Olivier CHOSIDOW, Doctor Pascal REYGAGNE, Doctor Philippe ASSOULY), the

biostatistician in charge of the project (Professor Jacques BENICHOU), and a representative of the promoter (CHU of Rouen)

It will define the general organization and the progress of the research and will coordinate the information.

It will initially determine the methodology and will decide during the course of the research what to do in unforeseen cases, and will monitor the progress of the research, particularly in terms of tolerance and adverse events.

VIII.5. INDEPENDENT MONITORING COMMITTEES

The treatments used are proven since they have been commonly used for more than 30 years. Therefore, no unexpected adverse events related to the treatments are expected. Therefore, a monitoring committee was not considered necessary.

VIII.6. COLLEGE OF EXTERNAL REVIEWERS

A panel of external reviewers, including clinicians not participating in the study as investigators, will be formed to evaluate the primary endpoint and one of the secondary endpoints.

The evaluation of the primary endpoint will be performed by this panel of evaluators composed of 4 dermatologists with expertise in scalp pathology, who are not participating in the study as investigators. They will evaluate the regrowth of the treatment arm on a series of 4 photographic views of the scalp (top, back, left side, right side). In case of disagreement between the 4 experts, a vote will be taken.

The evaluation of one of the secondary criteria corresponding to the Global Regrowth Assessment (GRA) at 12 months will be carried out jointly by this committee of 4 independent experts (based on the 4 photographs taken by the investigating physician (in case of disagreement in the evaluation of the 4 experts, the rating will be the one proposed by 3 of the 4 experts).

IX. STATISTICS

IX.1.1. Calculation of the number of patients

The assumptions made are as follows:

-1 The rate of complete or almost complete HR obtained with methotrexate is supposed to be 30%.

-2 The rate of complete or almost complete HR obtained with placebo is supposed to be 05%.

These assumptions seem reasonable in light of the literature and tend to minimize the difference that can be expected in order not to be overly optimistic and to avoid

underpowering the study. Thus, the hypothesis taken for the placebo group is a high hypothesis since no regrowth should be observed in the placebo group in patients with chronic (>6 months) AT or AU despite previous local and systemic treatments. Conversely, the assumption made regarding methotrexate is a low assumption compared with the literature, considering that the results of retrospective studies are often overestimated.

In view of these assumptions, the number of patients required to demonstrate a difference between the two treatment groups with a power of 80% (b = 20%) for Fisher's exact test (comparison of two proportions) at a 5% risk of first kind a in two-sided formulation, is 39 patients per group, i.e. 78 patients in total:
Taking into account the possibility of a few patients lost to follow-up (4 patients for a 5% loss of follow-up rate, 8 patients for a 10% loss of follow-up rate), 90 patients will be included.

IX.1.2. Statisticals analysis strategy and data collection

Statistical data management

The research data will be collected using the CRF. The data will be centralized in the Biostatistics Department of the Rouen University Hospital (Inserm Unit U657, Professor Jacques BENICHOU). The analysis will be conducted in intention to treat (primary analysis) and per protocol (secondary analysis) in accordance with the recommendations in force.
Patients lost to follow-up will be included in the intention-to-treat analysis and systematically considered as failure regardless of the arm.
Given the relatively small number of patients to be included in the trial, an interim analysis is not planned.
The final analysis will be conducted at the end of the 90 enrollments, after the last patient has completed the entire follow-up.

IX.1.3. Justification of the tests and statistical methods

All analyses will be performed with SAS software (version 9 or higher, SAS Institute, Cary, North Carolina, USA) and LogXact software (version 7 or higher, Cytel Software Corporation, Cambridge, Massachusets, USA).

Description of the data

At inclusion, patient characteristics will be described using the usual descriptive parameters: mean, standard deviation, median, interquartile range, and range for quantitative variables; frequencies and cumulative frequencies (if applicable) for qualitative variables. This

description will be done globally as well as for each of the two randomized groups (placebo and methotrexate).

Primary endpoint

The primary endpoint is a dichotomous endpoint describing the success or failure of complete regrowth: success is defined as complete or near-complete regrowth at one year over at least 90% of the scalp following at least partial regrowth over at least 25% of the scalp at six months. This means that patients with no regrowth or less than 25% scalp regrowth at six months will be considered failures regardless of their outcome at one year following the second randomization.

Fisher's exact test will be used to compare the proportions of patients with complete or near-complete regrowth in the two arms (placebo or methotrexate). In addition, an adjusted comparison will be performed using the exact logistic regression model with complete regrowth (success, failure) as the dependent variable and the treatment group and variables appearing to be prognostic of complete regrowth as the dependent variables such as age, sex, weight, duration of progression, or association with a pathology.

In order to base the analysis on the maximum number of patients, patients lost to follow-up will be considered as no complete regrowth in the main analysis. In a sensitivity analysis, the hypothesis of maximum bias on lost to follow-up will be tested by considering them as non-complete regrowths (failures of complete regrowth) in the group giving the most favorable results and as complete regrowths (successes) in the group giving the least favorable results.

Secondary endpoints

-Overall assessment of HR at 12 months

Comparisons between the two arms will be made with Fisher's exact test for 6-month outcomes for the following dichotomous criteria as defined by the expert committee assessment:

- complete or near-complete HR (greater than or equal to 90%) versus less than 90% regrowth,
- major regrowth (greater than or equal to 75%), versus regrowth of less than 75%,
- medium regrowth (≥50% and <75%), or major regrowth versus less than 50% regrowth,
- partial regrowth (<50% and ≥25%) medium or major, versus regrowth of less than 25%,
- regrowth of any degree vs. regrowth of only a fuzz or no regrowth;

A significance level adjustment will be considered to account for the multiplicity of comparisons (Bonferroni or alternative method).

For the results at one year, the two arms will be compared by Fisher's test by modifying the primary criterion as follows: a success will be defined as regrowth on at least 25% of the scalp at six months associated with a major regrowth (instead of complete or almost complete) at one year. We will also consider a medium or major regrowth at one year and finally a partial, medium or major regrowth at one year. In addition, a polytomous criterion will be considered with the following mutually exclusive modalities (with the extended Fisher test for comparison of the two arms): at least 25% regrowth at six months and complete or near-complete regrowth at one year; at least 25% regrowth at six months and major but not complete or near-complete regrowth at one year; at least 25% regrowth at six months and moderate regrowth at one year; at least 25% regrowth at six months and partial regrowth at one year.

The Fisher test will be used for comparisons of the proportions of complete or near-complete regrowth corresponding to the second randomizations: methotrexate + placebo arm versus methotrexate + prednisone arm separately in patients initially randomized to the placebo arm and to the methotrexate arm.

Agreement between clinical scores assessed at M12 by the investigator, the expert panel, and the patient will be investigated using the crude agreement rate and the kappa coefficient, estimated pointwise and by 95% confidence interval with a test against the null value for the estimated kappa coefficient.

Quality of life.

The overall quality of life score at each follow-up visit will be obtained by summing the integer scores (from 1 to 5) obtained for each question (see questionnaires in Appendix 2).
The completion rates of these scores will be described and compared according to the treatment arm at each follow-up visit and the mechanism governing the missing or not of the score will be studied and classified according to the method of Diggle and Rubins in one of the three modalities: MCAR, MAR, MNAR.

The mean numbers of missing scores will be described using means by patient subgroups and compared by analyses of variance at inclusion and analyses of variance for repeated measures for all measurement times.

If the missing data are non-random, i.e., related to the patient's clinical status (death, recurrence, patient-specific clinical status) and the last observed quality of life value, the analysis methods will need to take these into account.

The quality of life scores will be described at each time point and compared between the treatment arms both at inclusion and longitudinally throughout the follow-up using mixed models of analysis of variance for repeated measures. This modelling will have to take into account non-random missing data processes and will rely in particular on the following imputation methods

Simple imputations for sensitivity analyses:

Imputation by the mean of the observed quality of life scores, these means being calculated in the whole population, and/or at specific measurement times, and/or according to similar clinical characteristics of the patients, and/or according to the treatment arm (depending on the missing data process retained).

Imputation by an extreme quality of life score. This method can be used when the missing data are due to a negative event such as death, progression, etc.
An estimate of the time to deterioration of the quality of life scores below a predefined threshold will be made using the Kaplan-Meier method for each treatment arm. These times will be compared between arms using a Log Rank test.

Tolerance

The proportions of patients with adverse events on the one hand and serious adverse events on the other hand will be compared between the treatment arms by Fisher's exact test.
These tests will be complemented by a comparison of the number of adverse events (total or serious) per patient by the non-parametric Mann-Whitney test.

X. LOST TO FOLLOW UP ; NON COMPLIANCE WITH THE PROTOCOL

Patients lost to follow-up should remain exceptional, as should non-compliance with the protocol. They will be accounted for and must remain below 5% of the number of patients included.

XI. PATIENTS WHO HAVE FAILED THE PROTOCOL

A patient will be declared "failed" for the primary endpoint

- if he/she does not obtain complete or almost complete hair regrowth at M12 while taking the same treatment during the 2 phases of the trial
- if he/she changes treatment at the M6 evaluation due to lack of regrowth or regrowth < 25%, and therefore do not receive the same treatment during the 2 phases of the trial
- if he/she experience a severe side effect which needs discontinuation of treatment tested in the trial.
- if he/she is lost to follow-up

Any patient declared to have failed treatment must continue to be followed up and the logbook filled in until the end of the study (except for patients lost to follow-up).

XII. DURATION OF THE STUDY

Considering the inclusion capacity of our group of investigators (3 patients per center per year for the 13 centers of Rouen, Clermont-Ferrand, Lille, Amiens, Bordeaux, Nantes, Lyon, Reims, Limoge, Marseille, Henri Mondor, Tours, Grenoble, and 14 patients per year for the Sabouraud center for the treatment of scalp pathologies of the Saint Louis hospital), an inclusion period of 2 years seems sufficient to include the 90 patients of the study.

XIII. FINAL REPORT OF THE RESEARCH

The final report of the research will be written in collaboration by the coordinator and the biostatistician for this research. This report will be submitted to each of the investigators for their opinion. Once a consensus has been reached, the final version must be endorsed by the signature of each investigator and sent to the sponsor as soon as possible after the research is completed. A report written according to the reference plan of the competent authority must be sent to the competent authority and to the CPP within one year after the end of the research, understood as the last follow-up visit of the last subject included. This period is reduced to 90 days in the case of premature termination of the research.

XIV. FEASIBILITY OF THE STUDY

Feasibility was excellent:

1) the design of the study was established by Pr P Joly and Pr O Chosidow, who have each designed and conducted numerous therapeutic trials, 3 of which have been published in the New England Journal of Medicine ;

2) the investigators are experienced in therapeutic trials and have participated in numerous randomized studies;

3) Dr. Reygagne and Dr. Assouly are directors of the Sabouraud Center for the treatment of scalp pathologies at the Saint Louis Hospital. They have international expertise in the field of hair disorders , as well as a very large recruitment of patients with severe alopecia areata.

XV.EXPECTED RESULTS

This study should make it possible to evaluate, with a high level of proof, whether methotrexate is an effective medium-term treatment for severe peladic disease, one of the dermatological diseases with the greatest impact on the quality of life of patients, in contrast with an orphan therapeutic research. This study should also make it possible to determine the possible interest of the secondary addition of low-dose general corticosteroid therapy in patients who have not obtained HR after 6 months of treatment with methotrexate alone.

XVI.RIGHT OF ACCESS TO SOURCE DATE AND DOCUMENTS

The sponsor is responsible for obtaining the agreement of all parties involved in the research to ensure direct access at all research sites to source data, source documents and reports for the purpose of quality control and audit by the sponsor.

Investigators will make documents and individual data strictly necessary for monitoring, quality control and auditing of biomedical research available to persons having access to these documents in accordance with the regulatory and legislative provisions in force.

Source data is defined as any original document that can be used to prove the existence or accuracy of data recorded during the trial (list the type of source document required for the research).

In accordance with applicable laws and regulations, individuals with direct access to the source data should take all necessary precautions to ensure the confidentiality of information about the trial drug/device/procedure to the individuals involved. These persons, like the investigators, are subject to professional secrecy.

In accordance with the legislative provisions in force (articles L.1121-3 and R.5121-13 of the public health code), persons with direct access to the source data will take all necessary precautions to ensure the confidentiality of information relating to the experimental drugs/devices/procedures, to the research, to the persons involved, and in particular with regard to their identity and to the results obtained. These persons, as well as the investigators themselves, are subject to professional secrecy.

During the biomedical research or at its conclusion, the data collected on the persons involved and transmitted to the sponsor by the investigators (or any other specialist) will be made anonymous. Under no circumstances should the names of the persons concerned or their addresses appear in clear text.

The anonymity of the subjects will be ensured by a 7-character alphanumeric code including the center number, the randomization number of the patient and his initials (first letter of the name and first letter of the first name) on all the necessary documents, or by deletion by appropriate means of the nominative data on the copies of the source documents, intended for the documentation of the research

The sponsor will ensure that each person who takes part in the research has given written consent for access to individual data concerning him or her and strictly necessary for the quality control of the research.

XVII. QUALITY CONTROL AND ASSURANCE

XVII.1. DATA COLLECTION GUIDELINES

All information required by the protocol must be recorded in the paper observation books and an explanation must be given for any missing data. Data should be collected as they are obtained, and transcribed into these notebooks in a neat and legible manner.

Erroneous data found in the observation books should be clearly crossed out and the new data should be copied next to the crossed out information, accompanied by the initials, date and, if necessary, a justification by the investigator or the authorized person who made the correction.

XVII.2. CONTROL OF DATA QUALITY

The Study coordinator, mandated by the sponsor, will regularly visit each study center during

- at the start of the trial,
- during the course of the trial according to the rhythm of the inclusions,
- at the end of the trial.

The Study coordinator will have to ensure that the rights and safety of the subjects are respected, that the data and information transmitted are reliable, of high quality and traceable, and that the study is conducted in accordance with the protocol, the GCP and the regulatory and legislative framework in force.

The purpose of the visits will therefore be to verify and validate the following data in 100% of the observation books

- eligibility of included patients: compliance with inclusion and non-inclusion criteria
- compliance with the procedures for informing patients and collecting their consent

- compliance with the specific procedures of the protocol, the trial schedule, patient follow-up
- the quality of the data collected in the CRF: accurate, complete and consistent
- compliance with procedures for reporting adverse events and new developments
- proper management and traceability of study treatments/devices (visit to the pharmacy, storage and accounting of drugs/devices).

At the end of each visit, a standardized monitoring report will be drawn up by the CRA and reviewed by the sponsor.

XVII.3. AUDIT AND INSPECTION

An audit may be carried out at any time by persons mandated by the sponsor and independent of the research managers. The purpose of the audit is to ensure the quality of the research, the validity of its results and compliance with the law and regulations in force. Investigators agree to comply with the requirements of the sponsor and the Competent Authority with respect to an audit or inspection of the trial.

The audit may apply to all stages of the study, from the development of the protocol to the publication of the results and the classification of the data used or generated in the study.

XVIII. RETENTION AND ARCHIVING OF RESEARCH DATA

XVIII.1. SPONSOR

The sponsor and the investigators archive the essential documents and data relating to this research in accordance with Good Clinical Practice:

- for a period of 10 years following the end of the research (research involving cosmetic products),
- for a period of 15 years following the end of the research (research involving drugs/devices/procedures, medical devices or in vitro diagnostic medical devices or research not involving a product mentioned in article L.5311-1 of the public health code),
- for 30 years following the end of the research (research involving labile blood products, organs, tissues of human or animal origin or cell therapy preparations),
- for a period of 40 years following the end of the research (research involving blood-derived drugs/devices/procedures or medical devices incorporating a substance that may be considered a blood-derived drug/device/procedure),

XVIII.2. INVESTIGATOR

- The protocol and any amendments to the protocol
- Case report forms
- Source records of participants who have signed consent (Investigator)
- All other essential documents and correspondence related to the research

The investigator and the sponsor are responsible for the conservation and archiving of all these documents during the regulatory archiving period.

No removal or destruction will be made without the sponsor's agreement. At the end of the regulatory archiving period, the sponsor will be consulted for destruction. All data, documents and reports may be subject to audit or inspection.

XIX. ETHICAL AND REGULATORY CONSIDERATIONS

The sponsor and the investigator(s) undertake that this research will be carried out in accordance with the French law n°2004-806 of August 9, 2004, as well as in accordance with the Good Clinical Practices (I.C.H. version 6 of July 2002 and decision of November 24, 2006) and the Helsinki declaration version of October 2008 (which can be found in its integral version on the website http://www.wma.net).

The research is conducted in accordance with this protocol. Except in emergency situations requiring the implementation of specific therapeutic procedures, the investigator(s) undertake(s) to comply with the protocol in all respects, in particular with regard to the collection of consent and the notification and follow-up of serious adverse events.

This research has received the favorable opinion of the Comité de Protection des Personnes (CPP), CPP NordOuest I and the authorization of the AFSSAPS.
The Rouen University Hospital, promoter of this research, has taken out a civil liability insurance policy with Gerling in accordance with the provisions of article L1121-10 of the public health code.
The data recorded during this research are subject to computerized processing in the name of the structure responsible for data processing in compliance with the law n°78-17 of January 6, 1978 relating to data processing, files and freedoms modified by the law 2004-801 of August 6, 2004.
This research falls within the framework of the "Reference Methodology" (MR-001) in application of the provisions of Article 54 paragraph 5 of the amended law of January 6, 1978 relating to information, files and freedoms.
This change was approved by a decision dated January 5, 2006. The name of the promoter has signed a commitment to comply with this "Reference Methodology".

- This research is registered in the European database EudraCT under the number 2012-001234-33) registration in accordance with art. L1121.15 of the public health code.

- This research is registered on the site http://clinicaltrials.gov/

The collection of biological samples carried out within the framework of this research was declared to the AFSSAPS at the same time as the request for authorization of the research. After the research, the conservation of the collection of biological samples will be declared to the minister in charge of research and to the director of the Regional Health Agency (and submitted to the CPP for an opinion if there is a change in the purpose of the research).

The directors of the hospitals participating in the trial will be informed of the research project to be carried out there before it is implemented.
The financing of this study is provided by Programme hospitalier de recherche clinique (PHRC) of the French Ministry of Health (N°2012-001234-33) and a grant from the French Society of Dermatology.

Amendment to the protocol
Any substantial modification, i.e. any modification likely to have a significant impact on the protection of individuals, on the conditions of validity and on the results of the research, on the quality and safety of the products tested, on the interpretation of the scientific documents

that support the conduct of the research or on the methods of conducting the research, is the subject of a written amendment that is submitted to the sponsor; the sponsor must obtain a favourable opinion from the CPP and an authorization from the AFSSAPS prior to its implementation.

Non-substantial amendments, i.e. those that do not have a significant impact on any aspect of the research, are communicated to the CPP for information purposes.

All amendments are validated by the sponsor, the coordinating investigator, and by all those involved in the research concerned by the modification, before submission to the CPP and to the AFSSAPS.

All amendments to the protocol must be brought to the attention of all the investigators participating in the research. The investigators undertake to respect the content.

Any amendment that modifies the management of patients or the benefits, risks and constraints of the research is the subject of a new information note and a new consent form, the collection of which follows the same procedure as that described above.

XX. RULES FOR PUBLICATION AND COMMUNICATION

The analysis of the results will be the subject of communications in congresses and publications.

The text of publications and communications will be discussed with all the investigators participating in the trial. The order of co-authorship will take into account the participation of the different investigators in the trial (number of subjects included and evaluable).

The following wording should be used:

The publication rules are as follows:

- Case where the publication involves only the CHU:

In French: Centre Hospitalier Universitaire (CHU) de Rouen, service or department identifier, Rouen, F-76031, France.

In English: Rouen University Hospital, service or department identifier, Rouen, F-76031, France.

- Case where the publication involves the University Hospital and the University:

In English: Rouen University Hospital, service or department identifier, Rouen, F-76031, France; Univ Rouen, F-76000, France.

- When the publication involves the University Hospital, the University and INSERM:

In English: Rouen University Hospital, service or department identifier, Rouen, F-76031, France; Univ Rouen, F-76000, France; Inserm, Uxxx, and/or CICxxx Rouen, F-76000, France.

In the case of a trial financed within the framework of a national PHRC, the authors must specify that their study was financed by the French Ministry of Health.

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In accordance with the law n°2002-303 of March 4, 2002, patients are informed, at their request, of the overall results of the research.

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