Statistical analysis plan	STAR PHRC 2015	Hôpitaux de Toulouse

Statistical Analysis Plan

STAR

Administrative information

Study title	Comparison of two strategies of glucocorticoid withdrawal in rheumatoid arthritis patients in low disease activity or remission
Acronym	STAR
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Research promoter Promoter number	Toulouse University Hospital 15 7824 01
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ABBREVIATIONS

PR
RA
FLARE
HAQ
RAID
DAS
LDA
GC
AUC
AIC
DMARD
COPD
AIDS
VS
CRP

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THE STATISTICAL ANALYSIS PLAN AND TECHNICAL CONSIDERATIONS

The statistical analysis plan (SAP) aims to outline the different statistical methods that will be used to meet the objectives of the study as well as all of the analyzes that will be carried out as part of the final analysis. If necessary, the methods for constructing and imputation of variables will be presented.

The statistical analysis plan is carried out before freezing the database and must be approved by the biostatistician, the methodologist and the principal investigator before implementing the statistical analyses.

The statistical analyzes will be carried out blind to the group the patients belong to (the groups under study will be identified by the letter A or B), using STATA version 18 software (StataCorp, College Station, TX, USA). Unblinding will only be carried out after submission of the statistical analysis report.

Any deviation from this statistical analysis plan must be the subject of an amendment to this document and must be signed by the biostatistician, the methodologist and the principal investigator.

GENERAL CONSIDERATIONS ON THE STUDY RESULTING FROM THE PROTOCOL

1) Rationale of the study

According to the 2013 update of the European League Against Rheumatisms (EULAR) recommendations for the management of rheumatoid arthritis (RA), glucocorticoid (GC) withdrawal should be considered in patients reaching a target of remission or low disease activity to prevent or minimize the adverse effects of long-term GC therapy. While GCs are widely used in RA and GC withdrawal exposes RA patients to flare, joint destruction, withdrawal syndrome and adrenal insufficiency, there is an unmet need for an effective and safe GC withdrawal strategy to decrease these risks and increase the rate of effective GC withdrawal. Hydrocortisone replacement therapy has been proposed as a potential strategy to decrease the risk of GC withdrawal syndrome and adrenal insufficiency in patients subject to long-term GC therapy. We hypothesise that this strategy, which has never been investigated in RA, may increase the probability of GC withdrawal and decrease the risk of adverse events in RA patients who are candidates for GC withdrawal.

2) Study Design

This study is a national multicenter double-blind parallel arm, phase IV, controlled 1:1 randomized trial of superiority comparing two strategies of GC withdrawal in patients in remission or low disease activity:

- **Group 1**: tapering prednisone using a pre-defined schedule and hydrocortisone placebo (GC tapering group).
- **Group 2**: replacing prednisone with hydrocortisone and a prednisone placebo with a predefined schedule for tapering the prednisone placebo (hydrocortisone replacement group).

Randomization will be performed if DAS28 is lower than 3.2 after one month of a stable dose of prednisone 5 mg/day, and will be stratified on the center and the length of the GC duration before the beginning of the study.

3) Primary Objective

To compare a prednisone tapering strategy to a hydrocortisone replacement strategy on the success rate of prednisone and hydrocortisone withdrawal at one year in RA patients in low disease activity or remission.

4) Secondary Objectives

1. To compare the proportion of patients who could withdraw from prednisone whatever the additional hydrocortisone associated treatment.
2. To compare the proportion of patients with acute adrenal insufficiency at one year between the two groups.
3. To compare the proportion of patients with biological adrenal insufficiency at one year between the two groups.
4. To compare proportion of patients needing extra prednisone to control flares.
5. To compare the proportion of patients with intra-articular injections.
6. To compare the proportion of patients who have at least one flare confirmed by the investigator during the protocol.
7. To compare the area under the curve of the means of the FLARE at one year with a self-assessment questionnaire.
8. To compare the proportion of patients in DAS28 remission and in DAS28 low disease activity at 7 and 12 months between the groups.
9. To compare the medians of HAQ at 4, 7 months and 1 year between the groups.
10. To compare the medians of RAID at 4, 7 months and 1 year between the groups.
11. To compare the medians of the EQ-5D at 4, 7 months and 1 year between groups.
12. To compare the medians of the FACIT-F at 4, 7 months and 1 year between groups.
13. To compare the proportion of patients with “serious” adverse events at 1 year between the groups.

5) Study Population

a. Inclusion Criteria

- Patients aged ≥ 18 years.
- Fulfilling the 2010 ACR/EULAR criteria for RA.
- Treated with a stable dose of sDMARDs or bDMARDs for at least 3 months.
- Who have been treated with prednisone or prednisolone for at least 6 months.
- With a stable dose of prednisone or prednisolone of 5mg/day for at least 3 months.
- With a DAS28 ≤3.2 for at least 3 months.
- Patients with health insurance.
- Patients who have signed a written informed consent form.

b. Non-inclusion Criteria

- Any chronic condition that would need long term corticoid use (e.g. chronic lung diseases).
- Evidence of a flare within the last 3 months.
- Evidence of an allergy or intolerance to hydrocortisone or prednisone.
- Chronic idiopathic, or autoimmune clinical adrenal insufficiency.
- GC joint injections within the last 3 months or scheduled in the next 3 months.
- Any GC intake expected more than >5mg/day within the next 12 months (i.e.
- administration with rituximab, multiple sclerosis requiring frequent GC infusions,...).
- Any disease with GC contraindication.
- Association with sultopride and with live vaccines.
- Significant trauma or major surgery within the 3 months prior to the baseline visit.
- Scheduled surgery in the next 12 months.
- Fibromyalgia.
- Foreseeable poor compliance with the strategy.
- Patient with any condition that would prevent participation in the study and completion of
- the study procedures, including language limitation.
- Alcohol and/or drug misuse as determined by the investigator.
- Pregnancy or breastfeeding.
- Patient is not willing to sign the informed consent.
- Juridical Protection

c. Exclusion criteria

- DAS28>3.2 after one month of a stable dose of prednisone 5 mg/day.

6) Randomization

A randomization liste has been established by the Unité de soutien Méthodologique à la Recherche (USMR) at Toulouse University Hospital before the start of the study. The number of patients allocated in the two strategy groups has been balanced with a 1:1 ratio. The randomization was stratified on the center and on the GC duration before the beginning of the study (more or less than 2 years). In each stratum, a design based on randomized blocks of 2 patients was applied, according to the 1:1 ratio. The randomization list was provided electronically. A document describing the randomization procedure has been kept confidentially by Toulouse USMR. The person in charge of the randomization at the USMR will not be implicated in the study analyses.

7) Sample size calculation

This is a two-arm parallel group randomized controlled trial of superiority comparing the success rate of GC withdrawal between two strategies. Patients will be randomized into two groups:

- Group 1: “GC tapering group”: patient will taper prednisone until withdrawal.
- Group 2: “Hydrocortisone replacement group”: patient will stop prednisone and replace it with hydrocortisone 20 mg/day for 3 months then 10 mg/day for 3 months then discontinue hydrocortisone.

The hypothesis has been formulated that in the tapering group, the proportion of patients who would withdraw GC (success) would be about 30% (1).
We assume that replacing prednisone with hydrocortisone, which is considered as a safe regimen in GC withdrawal (2), could increase the success rate to 60% in the intervention group.

Given these hypotheses, 42 patients will be necessary for assessing a significant difference between groups, with a 5% type 1 error rate, an 80% power and a two-sided comparison. Given that we anticipate a 20% rate of patients lost to follow-up, the study will include 102 randomized patients (51 in each group). It is expected that about 20% of patients will not fulfil the inclusion criteria at the M1 Randomization visit. Thus, about 122 patients need to be included at M0 to provide 102 randomized patients at M1.

8) Endpoints

a. Primary endpoint

The primary endpoint is the proportion of patients who could withdraw from prednisone and hydrocortisone (success rate) in each group at the end of the study (12 months).
The withdrawal strategy will be considered a failure for:

- Patients who still receive oral prednisone and/or hydrocortisone at the end of the study.
- Patients who received more than two intra-articular or peri-articular injections during the whole study to treat a synovitis a bursitis or a tenosynovitis related to the RA.
- Patients who received more than two GC short therapies during the whole study.
- Patients who had clinical or biological signs of adrenal insufficiency that led to taking hydrocortisone until the end of the protocol.
- Patients who received more than two weeks of GC for a reason other than their disease.

The investigator at each center will record this variable at the end visit, blinded to the randomization arm.
An intention-to-treat analysis will be performed. All patients lost to follow-up will be analyzed as a failure to the strategy.
This outcome will be easy to collect, blinded, and does not need to be validated by an independent committee.

b. Secondary endpoints

1. Proportion of patients who could only withdraw from prednisone, even if much additional hydrocortisone was prescribed. If the patient could withdraw from prednisone even when still receiving hydrocortisone for a biological adrenal insufficiency for example, this will be considered success.

2. Proportion of patients with acute adrenal insufficiency at one year.

An acute adrenal insufficiency will be suspected in the following cases:

- Abnormal fatigue.
- Digestive disorders including nausea, diarrhea and abdominal pains.
- Myalgia.
- Psychiatric disorders and confusion.
- Dehydration.
- Unexplained fever.
- Weight loss.
- Hypotension.
- Biological abnormality such as hyponatremia, hyperkaliemia, renal salt loss and hypoglycemia.

If an acute adrenal insufficiency is suspected, an extra visit will be performed in emergency and if the acute adrenal insufficiency is confirmed, the patient will be hospitalized to be treated at the choice of the investigator. If the serum cortisol dosage confirms clinical adrenal insufficiency, an open hydrocortisone therapy by hydrocortisone 20mg/d will be started and an appointment with the endocrinologist will be made. If the serum dosage does not confirm adrenal insufficiency, hydrocortisone will be stopped and other causes of the symptoms will be investigated. If no severe concomitant disease is found, the patient will be able to go back to her/his step of the protocol.
All clinical adrenal insufficiency reports will be reviewed by an independent committee to decide whether, according to the report, the diagnosis of clinical adrenal insufficiency can be validated and recorded for the study. This will be declared as a serious adverse event.
It is expected that less than 1% of patients in this study will experience clinical adrenal insufficiency.

3. Proportion of patients with biological adrenal insufficiency.

Two blood tests will be scheduled with a Synacthène® test at 4 and 7 months. A pathological Synacthène® test will be diagnosed if one hour after Synacthène®, serum cortisol is below 200 ng/mL or 600 nmol/L, or 20 µg/100 ml. In case of abnormal test at the latest Synacthène® test another Synacthène® test will be realized at M12.

4. Proportion of patients who needed a short rescue GC treatment during the protocol.

5. Proportion of patients who needed a GC intra-articular or peri-articular injection during the protocol related to the RA.

6. Proportion of patients with a flare confirmed by the clinician. In case of symptoms of flare, the patient will have an extra visit at her/his center. For DAS28 >3.2, a flare will be confirmed. A flare will be also diagnosed if the DAS28 is >3.2 at any scheduled visits.

7. The area under the curves of the self-administered Flare Assessment in Rheumatoid Arthritis (FLARE) questionnaire. FLARE is an approved self-assessment questionnaire that will be completed at each visit and in case of FLARE at home by the patient. The results are expressed as continuous data. The area under the curve of all the questionnaires will be the variable analyzed.

8. Proportion of patients in remission and low disease activity at 7 months and one year.

Patients with DAS28 <2.6 will be considered in remission, patients with DAS28 between 2.6 and 3.2 will be considered in LDA.

9. Functional impairment assessed by the Health Assessment Questionnaire (HAQ) at baseline, 4, 7 months and one year.

The HAQ will be calculated at baseline, 4, 7 months and one year and is expressed as continuous data.

10. Patient reported Outcomes assessed by the Rheumatoid Arthritis Impact of Disease (RAID) questionnaire at baseline, 4, 7 months and 1 year.

The RAID questionnaire will be calculated at baseline, 4, 7 and 12 months and is expressed as continuous data.

11. The EuroQol 5-dimensional descriptive system (EQ-5D) will be completed at baseline, 4, 7 and 12 months. The EQ-5D questionnaire will be calculated at baseline, 4, 7 and 12 months and is expressed as continuous data.

12. The Functional Assessment of Chronic Illness Therapy - Fatigue Scale (FACIT-F): the FACIT- F questionnaire explores the fatigue reported by the patient. It will be completed at baseline, 4, 7 months and 12 months. It will be expressed as continuous data.

13. Proportion of patients with at least a serious adverse event over one year.

POPULATION

1) Intention-to-treat population (ITT)

The intention-to-treat (ITT) population consists of all randomized patients, that is, all patients who were randomly assigned to one or the other arm of the study. (Prednisone taper group/Hydrocortisone replacement group).
Analyzes by treatment arm carried out on the ITT population will be conducted on the basis of the "intention to treat" principle, i.e. patients will be analyzed in their randomization group (including in the event of 'treatment allocation error).

2) Per Protocol Population (PP)

The Per Protocol population will be composed of all subjects from the ITT population having no major deviations from the protocol.

Major deviations from the protocol considered will be as follows:

- Non-compliance with an eligibility criterion,
- Major deviation regarding the administration schedule of the treatments under study:
  - treatment reversal
  - In particular, continuation of prednisone in the hydrocortisone replacement group.
- Subjects who have received glucocorticoid treatment prescribed for an indication other than RA for more than two weeks ,
- Endpoint not determined at the end of the study.

The reasons for excluding the population per protocol will be listed and described in a table.

Patients presenting errors in taking the levels of the treatments under study at M4 [CRF p45] and M7 [CRF p70] were listed and presented to the investigators blinded to the randomization group and therefore to the treatment consumed. The principal investigators then decided, patient by patient, based on the number of capsules consumed per level [Derived variable] and comments from the investigative teams in order to define whether this was a reason for excluding the per population. protocol.
The summary tables (tables 1 and 2) are presented in the appendix to this SAP.

3) Population for safety analysis

The population for the safety analysis will be composed of all subjects included in the study (having given consent to participate and having been randomized), having taken at least one dose of treatment.
Subjects will be analyzed in the treatment group actually received (notably in the event of a batch allocation error).

VARIABLES OF INTEREST

No.	VARIABLE NAME	DERIVATIONS
1	**Age at inclusion date** (in years)	From the variables "Date of birth" [*CRFp9*] and "Date of inclusion visit" [*CRFp9*], we will calculate the number of days, divided by 365.25 to obtain a duration in years. We can convert this duration into months if necessary.
2	**Duration of illness** at inclusion (in years)	From the variables "Date of RA diagnosis" [*CRFp9*] and "Date of inclusion visit" [*CRFp9*], we will calculate the number of days, divided by 365.25 to obtain a duration in years. We can convert this duration into months if necessary.
3	**Duration of remission** (in years)	From the variable " *Duration of illness (in months)* " [*Derived variable*] we will subtract the number of months collected by: "How long has the patient been in remission/low activity level?" » [*CRFp10*]. This will allow us to obtain the duration in years with active disease. We can convert this duration into months if necessary.
4	**Duration of smoking cessation** (years)	From the variable " *if Weaned, date of definitive weaning* " [CRF p13] and "Date of inclusion visit" [*CRFp9*], we will calculate the number of days elapsed between these two dates, divided by 30.4375 to obtain a duration in months. We can convert this duration into years if necessary. This variable will take the value "missing" if " *if Weaned, date of definitive weaning* " [CRF p13] is coded missing.
5	**Tobacco consumption** (No/Yes, weaned patient/Yes, current)	From the variable " *Tobacco consumption* " (yes/no) and the weaning variable (ongoing/withdrawn) [CRF p13]. The " *Tobacco consumption* " variable will take the value: " Not if : • " *Tobacco consumption* " = No "Yes, weaned" if: • " *Tobacco consumption* " = Yes • AND "weaning" = Weaned "Yes, current" if: • " *Tobacco consumption* " = Yes • AND "weaning" = In progress
6	**BMI at inclusion**	From the variables: " *Weight* " [CRF p15] and " *Height* " [CRF p15], the variable " *BMI at inclusion* " will take the following value: $$IMC = \frac{poids\ (kg)}{taille^2(cm)}$$ THE " *BMI* " variables to M4 / M7 / M9 / M12 will be defined on the same model from the " *Weight* " variables [CRF p15, 23, 47, 72, 97, 114] and the " *Height* " variable [CRF p15] .

No.	VARIABLE NAME	DERIVATIONS
7	**Presence of high blood pressure** (yes/no)	From the variables: " *SBP* " and " *PAD* " [CRF p15], the variable " *Presence of Arterial Hypertension* " will take the value: " If yes : • SBP ≥ 140 mmHg • AND/OR DBP ≥ 90 mmHg " Not if : • SBP < 140 mmHg • AND PAD < 90 mmHg THE " *Presence of Arterial Hypertension* " variables at M4 / M7 / M9 / M12 will be defined on the same model from the " *SBP* " and " *PAD* " variables [CRF p15, 23, 47, 72, 97, 114] .

8	**Charlson score at baseline**	The Charlson score will be calculated as defined below:
		
		• " *History of clinical myocardial infarction* " [CRF p14] = Yes then add 1 to the score
		• " *History of decompensation of heart failure* " [CRF p14] = Yes then add 1 to the score
		• " *Obliterative arteriopathy of the lower limbs* " [CRF p14] = Yes then add 1 to the score
		• " *History of stroke (ischemic or hemorrhagic)* " [CRF p14] = Yes then add 1 to the score
		• " *Dementia* " [CRF p14] = Yes then add 1 to score 1
		• " *COPD* " [CRF p14] = Yes then add 1 to the score
		
		• " *History of peptic ulcer* " [CRF p14] = Yes then add 1 to the score
		• " *Hepatic pathology* " [CRF p14] = Yes
		  o AND " *Severity* " = Mild then add 1 to the score
		• " *History of diabetes* " [CRF p14] = Yes
		  o AND " *Complication* " = Not complicated so add 1 to the score
		• " *History of diabetes* " [CRF p14] = Yes
		  o AND " *Complication* " = Complicated then add 2 to the score
		• " *Hemiplegia* " [CRF p14] = Yes then add 2 to the score
		• " *Moderate (clearance < 60mL/min) to severe renal impairment (clearance <30mL/min)* " = Yes then add 2 to the score
		• " *History of solid cancer* " [CRF p14] = Yes
		  o AND " *Type* " = localized then add 2 to the score
		• " *History of Leukemia* » [CRF p14] = Yes then add 2 to the score
		• " *History of Lymphoma* " [CRF p14] = Yes then add 2 to the score
		• " *Hepatic pathology* " [CRF p14] = Yes
		  o AND " *Severity* " = Moderate to Severe then add 3 to the score
		• "AIDS" [CRF p14] = Yes then add 6 to the score
		
		• *Age* " variable [Derived variable] takes the value:
		  o [50 – 60[add 1 to the score

No.	VARIABLE NAME	DERIVATIONS
		○ [60 – 70[add 2 to the score ○ [70 – 80[add 3 to the score ○ [80 – 90[add 4 to the score ○ [90 – 100[add 5 to the score
9	**History of Synthetic DMARD use** (yes/no)	From the table *History of disease-modifying treatment, taken for RA* and the variable " *Has the patient already taken disease-modifying treatment for RA?"* » [*CRFp11*], we will create a binary variable from the consumption of synthetic DMARDs (Methotrexate; Leflunomide; Hydroxychloroquine; Sulfasalazine). The " *Synthetic DMARD consumption history* **" variable** will take the value: " If yes : • "Has the patient already taken disease-modifying treatment for RA ? » = Yes AND • at least 1 synthetic DMARDS is consumed (Methotrexate; Leflunomide; Hydroxychloroquine; Sulfasalazine) " No " if : • "Has the patient already taken disease-modifying treatment for RA ? » = No OR • "Has the patient already taken disease-modifying treatment for RA ? » = Yes • AND the patient does not consume any of the treatments mentioned (Methotrexate; Leflunomide; Hydroxychloroquine; Sulfasalazine)
10	**Number of Synthetic DMARDs** previously consumed	From the table *History of background treatment, taken for RA* and the variable " *Has the patient already taken disease-modifying treatment for RA?"* » [*CRFp11*], we will create a discrete quantitative variable from the number of synthetic DMARD treatments (Methotrexate; Leflunomide; Hydroxychloroquine; Sulfasalazine) consumed. The value of this variable will correspond to the sum of all synthetic DMARDs consumed. It will take the value 0 if : • "Has the patient already taken disease-modifying treatment for RA ? » = Yes ○ AND the patient does not consume any of the treatments mentioned (Methotrexate; Leflunomide; Hydroxychloroquine; Sulfasalazine)
11	**History of Biological DMARD consumption** (yes/no)	• From the table *History of disease-modifying treatment, taken for RA* and the variable " *Has the patient already taken disease-modifying treatment for RA?"* » [*CRFp11*], we will create a binary variable from the consumption of biological DMARDs (Etanercept; Adalimumab; Infliximab; Certolizumab pegol; Golimumab; Abatacept; Tocilizumab; Anakinra;

No.	VARIABLE NAME	DERIVATIONS
		Tofaticinib; Bariticinib; Rituximab; sarilumab; upadacitinib ; filgotinib)). The variable " *History of biological DMARD consumption* **"** will take the value: " If yes : • "Has the patient already taken disease-modifying treatment for RA ? » = Yes AND • at least 1 biological DMARDS is consumed (Etanercept; Adalimumab; Infliximab; Certolizumab pegol; Golimumab; Abatacept; Tocilizumab; Anakinra; Tofaticinib; Bariticinib; Rituximab; sarilumab; upadacitinib; filgotinib) " No " if : • "Has the patient already taken disease-modifying treatment for RA ? » = No OR • "Has the patient already taken disease-modifying treatment for RA ? » = Yes • AND the patient does not consume any of the treatments mentioned (Etanercept; Adalimumab; Infliximab; Certolizumab pegol; Golimumab; Abatacept; Tocilizumab; Anakinra; Tofaticinib; Bariticinib; Rituximab; sarilumab; upadacitinib; filgotinib)
12	**Number of Biological DMARDs** previously consumed	From the table *Background treatment history, taken for RA* , [*CRFp11*], we will create a discrete quantitative variable from the number of synthetic DMARD treatments (Etanercept; Adalimumab; Infliximab; Certolizumab pegol; Golimumab; Abatacept; Tocilizumab; Anakinra ; Tofaticinib; Rituximab; upadacitinib; The value of this variable will correspond to the sum of all synthetic DMARDs consumed. It will take the value 0 if : • "Has the patient already taken disease-modifying treatment for RA ? » = Yes o AND the patient does not consume any of the treatments mentioned (Etanercept; Adalimumab; Infliximab; Certolizumab pegol; Golimumab; Abatacept; Tocilizumab; Anakinra; Tofaticinib; Bariticinib; Rituximab; sarilumab; upadacitinib; filgotinib)

No.	VARIABLE NAME	DERIVATIONS
13	**Consumption of synthetic DMARDs during the study** (yes/no)	From the variables " *Current consumption of synthetic DMARDs (yes/no) "* at M1 / M4 / M7 / M9 / M12 [Derived variable], the variable " *Consumption of synthetic DMARDs during the study"* will take the value: " If yes : • " *Current consumption of synthetic DMARDs "* at M1 = Yes OR • " *Current consumption of synthetic DMARDs "* at M4 = Yes OR • " *Current consumption of synthetic DMARDs "* at M7 = Yes OR • " *Current consumption of synthetic DMARDs "* at M9 = Yes OR • " *Current consumption of synthetic DMARDs "* at M12 = Yes " Not if : • " *Current consumption of synthetic DMARDs "* at M1 = No • AND " *Current consumption of synthetic DMARDs "* at M4 = No • AND " *Current consumption of synthetic DMARDs "* at M7 = No • AND " *Current consumption of synthetic DMARDs "* at M9 = No • AND " *Current consumption of synthetic DMARDs "* at M12 = No
14	**Consumption of biological DMARDs during the study** (yes/no)	From the variables " *Current consumption of biological DMARDs (yes/no) "* at M1 / M4 / M7 / M9 / M12 [Derived variable], the variable " *Consumption of biological DMARDs during the study"* will take the value: " If yes : • " *Current consumption of biological DMARDs "* at M1 = Yes OR • " *Current consumption of biological DMARDs "* at M4 = Yes OR • " *Current consumption of biological DMARDs "* at M7 = Yes OR • " *Current consumption of biological DMARDs "* at M9 = Yes OR • " *Current consumption of biological DMARDs "* at M12 = Yes

No.	VARIABLE NAME	DERIVATIONS
		" Not if : • " *Current consumption of biological DMARDs* " at M1 = No • AND " *Current consumption of biological DMARDs* " at M4 = No • AND " *Current consumption of biological DMARDs* " at M7 = No • AND " *Current consumption of biological DMARDs* " at M9 = No • AND " *Current consumption of biological DMARDs* " at M12 = No
15	**Consumption of Methotrexate during the study** (yes/no)	From the variables " *Consumption of Methotrexate (yes/no)* " at M1 / M4 / M7 / M9 / M12 [Derived Variable], the variable " *Consumption of Methotrexate during the study* " will take the value: " If yes : • " *Methotrexate consumption* " at M1 = Yes OR • " *Methotrexate consumption* " at M4 = Yes OR • " *Methotrexate consumption* " at M7 = Yes OR • " *Methotrexate consumption* " at M9 = Yes OR • " *Methotrexate consumption* " at M12 = Yes " Not if : • " *Methotrexate consumption* " at M1 = No • AND " *Methotrexate consumption* " at M4 = No • AND " *Methotrexate consumption* " at M7 = No • AND " *Methotrexate consumption* " at M9 = No • AND " *Methotrexate consumption* " at M12 = No THE variables " *Consumption of […] during the study (yes/no)* " will be defined on the same model from the variables " *Consumption of […] (yes/no)* **"** at M1 / M4 / M7 / M9 / M12 [Derived variable] for the following treatments: Methotrexate, Leflunomide, Hydroxychloroquine, Sulfasalazine, Etanercept, Adalimumab, Infliximab, Certolizumab pegol, Golimumab, Abatacept, Rituximab, Tocilizumab, Anakinra, Tofaticinib, Bariticinib.
16	**Duration of treatment currently received** (in months)	From the variables " *Date of start of the basic treatment currently received* " [*CRFp13*] and "Date of the inclusion visit" [*CRFp9*], we will calculate the number of days elapsed between these two dates, divided by 30.4375 to obtain a duration in years.

No.	VARIABLE NAME	DERIVATIONS
17	**Current consumption of synthetic DMARDs** at M1/M4/M7/M9/M12 (Yes No)	From the table in Appendix 2 [CRF p158 – p164], the variables "DCI" and "Visit", the variable " *Current DMARD consumption synthetic to M1* " will take the value: " If yes : • INN = Methotrexate OR Leflunomide OR Hydroxychloroquine OR Sulfasalazine AND • Visit = M1 "No" if these conditions are not met. THE variables " *Current DMARD consumption synthetic (yes/no)* " to M4 / M7 / M9 / M12 will be defined on the same model from the variables collected in Table Appendix 2 [CRF p158 – p164] using the " *Visit" variable.*
18	**Number of synthetic DMARDs currently consumed** at M1 / M4 / M7 / M9 / M12	From the variables " *Current DMARD consumption synthetic DMARDs* " to M1, the variable " *Number of synthetic DMARDs currently consumed* to M1" will take the value: The value of this variable will correspond to the sum of the different synthetic DMARDs consumed at M1. THE variables " *Number of synthetic DMARDs currently consumed* " at M1 / M4 / M7 / M9 / will be defined on the same model from the variables collected in the table Appendix 2 [CRF p158 – p164] using the variable " *Visit"* .
19	**Current consumption of biological DMARDs** at M1 / M4 / M7 / M9 / M12 (yes/no)	From the table in Appendix 2 [CRF p158 – p164], the variables "DCI" and "Visit", the variable " *Current DMARD consumption organic to M1* " will take the value: " If yes : • INN = Etanercept OR Adalimumab OR Infliximab OR Certolizumab pegol OR Golimumab OR Abatacept OR Tocilizumab OR Anakinra OR Tofaticinib OR Bariticinib OR Rituximab OR sarilumab OR upadacitinib OR filgotinib AND • Visit = M1 "No" if these conditions are not met. THE variables " *Current DMARD consumption biological (yes/no)* " to M4 / M7 / M9 / M12 will be defined on the same model based on the variables collected in Table Appendix 2 [CRF p158 – p164] using the variable " *Visit".*
20	**Number of biological DMARDs currently consumed** at M1 / M4 / M7 / M9 / M12	From the variables " *Current DMARD consumption biological* " to M1, the variable " *Number of biological DMARDs currently consumed* to M1" will take the value: The value of this variable will correspond to the sum of the different *biological DMARDs* consumed at M1.

No.	VARIABLE NAME	DERIVATIONS
		THE variables " *Number of biological DMARDs currently consumed"* at M1 / M4 / M7 / M9 / will be defined on the same model from the variables collected in table Appendix 2 [CRF p158 – p164] using the variable " *Visit"* .
2 1	**Methotrexate consumption** at M1 / M4 / M7 / M9 / M12 (yes/no)	From the table in Appendix 2 [CRF p158 – p164], the variables "DCI" and "Visit", the variable " *Consumption of Methotrexate at M1"* will take the value: " If yes : • DCI = Methotrexate AND • Visit = M1 "No" if these conditions are not met. THE " *Consumption of […] (yes/no)"* variables at M4 / M7 / M9 / M12 will be defined on the same model from the variables collected in table Appendix 2 [CRF p158 – p164] for the following treatments: Methotrexate, Leflunomide, Hydroxychloroquine, Sulfasalazine, Etanercept, Adalimumab, Infliximab, Certolizumab pegol, Golimumab, Abatacept, Rituximab, Tocilizumab, Anakinra, Tofaticinib, Bariticinib.
23	**Duration of treatment with prednisone at 5 mg/day** (month)	From the variables " *Date since the patient received 5 mg/day of prednisone equivalent"* [*CRFp13*] and "Date of the inclusion visit" [*CRFp9*], we will calculate the number of days elapsed between these two dates, divided by 30.4375 to obtain a duration in months.
24	**Consumption of Prednisone 5 mg/day** at inclusion (yes/no)	From the variable " *Name of corticosteroid currently received : Prednisone (Princeps/generic) "*, the variable *Consumption of Prednisone 5mg/d at inclusion (yes/no)* will take the value: " If yes : • *Name of corticosteroid currently received : Prednisone = Princeps* OR • *Name of corticosteroid currently received : Prednisone = Generic* " Not if : • *Name of corticosteroid currently received : Prednisone* = missing
25	**Consumption of Prednisolone 5mg/day** at inclusion (yes/no)	From the variable " *Name of corticosteroid currently received : Prednisone (Princeps/generic) "*, the *Prednisolone Consumption variable 5mg/day on inclusion (yes/no)* will take the value: " If yes : • *Name of corticosteroid currently received : Prednisolone = Principles* OR

No.	VARIABLE NAME	DERIVATIONS
		• *Name of corticosteroid currently received : Prednisolone = Generic* " Not if : • *Name of corticosteroid currently received : Prednisolone* = missing
26	**Consumption of Methylprednisolone 4 mg/day** at inclusion (yes/no)	From the variable " *Name of corticosteroid currently received : Prednisone (Princeps/generic) "*, the variable *Consumption of Methylprednisolone* **4** *mg/d at inclusion (yes/no)* will take the value: " If yes : • *Name of corticosteroid currently received : Methylprednisolone = Principles* OR • *Name of corticosteroid currently received : Methylprednisolone = Generic* " Not if : • *Name of corticosteroid currently received : Methylprednisolone* = missing
27	**Number of temporary stops**	From the table listing prednisone treatment discontinuations [CRF p20], this variable will correspond to the count of the number of lines with: • " *a start date of the temporary shutdown "* not missing • OR *a non-missing "temporary shutdown end date "*.
28	**Number of dose modifications**	From the table listing the modification of prednisone treatment dose [CRF p20], this variable will correspond to the count of the number of lines with: • A non-missing " *Dosage "* • OR a non-missing " *dose change start date "* • OR a non-missing " *dose change end date "*.
29	**Vitamin D supplementation** (Yes No)	From the variables " *Vitamin-calcium supplementation (yes/no) "* and " *If yes, Complete: (Vitamin D / Calcium)* » [*CRFp15*], we define 2 modalities: • " If yes : ○ " *Vitamin-calcium supplementation?* » = yes ▪ AND " *If yes, Complete "* = Vitamin D • " Not if : ○ " *Vitamin-calcium supplementation?* » = no ○ OR if " *Vitamin-calcium supplementation?* » = yes ▪ AND " *If yes, Complete "* = Calcium • "Missing" if: ○ " *Vitamin-calcium supplementation?* » = missing ○ OR if " *Vitamin-calcium supplementation?* » = yes ▪ AND " *If yes, Complete "* = Missing

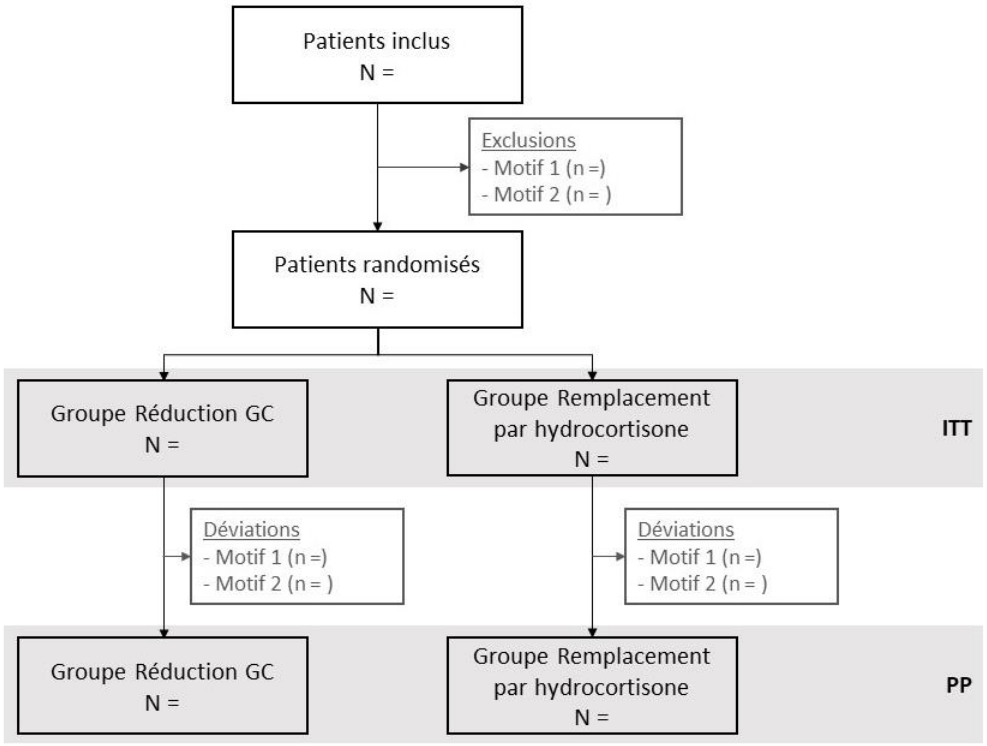
No.	VARIABLE NAME	DERIVATIONS
30	**Calcium Supplementation** (Yes No)	From the variables " *Vitamin-calcium supplementation (yes/no)* " and " *If yes, Complete: (Vitamin D / Calcium)* » [*CRFp15*], we define 2 modalities: • " If yes : o " *Vitamin-calcium supplementation?* » = yes ▪ AND " *If yes, Complete* " = Calcium • " Not if : o " *Vitamin-calcium supplementation?* » = no o OR if " *Vitamin-calcium supplementation?* » = yes ▪ AND " *If yes, Complete* " = Vitamin D • "Missing" if: o " *Vitamin-calcium supplementation?* » = missing o OR if " *Vitamin-calcium supplementation?* » = yes ▪ AND " *If yes, Complete* " = Missing
31	**Vitamin D and calcium supplementation** (Yes No)	From the variables " *Vitamin-calcium supplementation (yes/no)* " and " *If yes, Complete: (Vitamin D / Calcium)* » [*CRFp15*], we define 2 modalities: • " If yes : o " *Vitamin-calcium supplementation?* » = yes ▪ AND " *If yes, Complete* " = Vitamin D ▪ AND " *If yes, Complete* " = Calcium • " Not if : o " *Vitamin-calcium supplementation?* » = no • "Missing" if: o " *Vitamin-calcium supplementation?* » = missing o OR if " *Vitamin-calcium supplementation?* » = yes ▪ AND " *If yes, Complete* " = Missing
32	**Rheumatoid factors** (positive negative)	From the value of the Rheumatoid Factors [*CRFp17*] and "The Laboratory positivity threshold " [*CRFp17*], we define 2 modalities: • "Positive" if: o The value in IU/L of Rheumatoid Factor is greater than or equal to the Laboratory positivity threshold in IU/L • "Negative" if: o "The value in IU/L of Rheumatoid Factor is lower than the Laboratory positivity threshold in IU/L • "Missing" if: o The value in IU/L of Rheumatoid Factor is missing

No.	VARIABLE NAME	DERIVATIONS
33	**Anti-CPP2** (positive negative)	From the value of Anti-CPP2 [*CRFp17*] and "Laboratory positivity threshold " [*CRFp17*], we define 2 modalities: • "Positive" if: o The value in IU/L of Anti-CPP2 is greater than or equal to the Laboratory positivity threshold in IU/L • "Negative" if: o "The value in IU/L of Anti-CPP2 is lower than the Laboratory's positivity threshold in IU/L • "Missing" if: o The value in IU/L of Anti-CPP2 is missing
34	**Collection of consent** (yes/no)	From the variable *Date of signing of free and informed consent* [CRF p9], the variable "Collection of consent" will take the value: " If yes : • Consent signature date = not missing " Not if : • Consent signature date = missing
35	**Number of prednisone capsules consumed** per level at M4 and M7	From the variables *Prednisone bottle: Number of units reported* and *Prednisone bottle: Number of units given during the previous visit* , the variable " **Number of prednisone capsules consumed at level 1** " will take the value: Corresponding to the subtraction between: The *number of units given* and the *number of units reported* at level 1 [CRF p 45 and 90] The variables **Number of prednisone capsules consumed at level 2/3/4/5/6** and **Number of hydrocortisone consumed at level 1/2/3/4/5/6** will be derived using the same methods.
36	**Total number of prednisone capsules consumed** at M4 and M7	From the variables *Number of prednisone capsules consumed at level 1 / 2 / 3, the variable "* **Total number of capsules consumed** at M4" will correspond to the sum of all the variables mentioned (i.e. the sum of the number of capsules consumed at level 1, 2 and 3). **Total Number** variable **of prednisone capsules consumed** at M7 will be derived using the same methods using the variables *Number of prednisone capsules consumed at level 1/2/3* . Variables **Total number of hydrocortisone capsules consumed** at M4 and **Total number of hydrocortisone capsules consumed** at M7 will be derived using the same methods.
37	**Patient with pathological Synacthen test** at M4 / M7 / M9 / M12 / VA1 / VA2 (yes/no)	Given the significant number of concordance problems between the variable " *Cortisol 60 minutes after stimulation with 0.25 mg of Synacthen®* " and the binary variable " *Is the Synacthen test considered pathological?* ", we have chosen to derive a variable which will allow us to reclassify patients with a pathological test or not, depending on the quantitative value of the variable " *Cortisol 60 minutes after stimulation with 0.25 mg of Synacthene®* ". This variable will be derived as follows:

No.	VARIABLE NAME	DERIVATIONS
		From the *Cortisol variables 60 minutes after stimulation with 0.25 mg of Synacthène® in µg/100mL* at M4 / M7 / M9 / M12 / VA1 and VA2 [CRF p60, p85, p102, p127, p144, p155], the variable " **Patient with pathological Synacthen test** (yes/no) » [CRF p61, p86, p103, p128, p145, p156], will take the value: " If yes : • the value of the variable: Cortisol 60 minutes after stimulation with 0.25 mg of Synacthène® in µg/100mL is strictly less than 20 µg/100mL. " Not if : • the value of the variable: Cortisol 60 minutes after stimulation with 0.25 mg of Synacthène® in µg/100mL is greater than or equal to 20 µg/100mL. variables **with pathological Synacthen test** at M7 / M9 / M12 / VA1 / VA2 to M4 will be derived according to the same methods. Due to concordance problems, for the analysis we will base ourselves on this derived variable and not on the CRF variable" [CRF p61, p86, p103, p128, p145, p156].
39	**Additional visit 1 carried out** (yes/no)	From the variable *Date of visit* for VA1 [CRF p135], the variable " **Additional visit 1 carried out** " will take the value: " If yes : • The date of the visit is not missing " Not if : • No if the visit date is missing The variable **Additional visit 2 carried out** (yes/no) will be derived using the same methods from the variable *Date of visit* for VA1 [CRF p146]
40	**Follow-up duration** (months)	From the variables " *Date of inclusion visit* " [*CRFp9*] and "Date of end of study" [*CRFp157*], we will calculate the number of days elapsed between these two dates, divided by 30.4375 to obtain a duration in months .

DATA ANALYSIS AT INCLUSION

1) Flowchart



2) Descriptive analyses : descriptive tables at inclusion

A descriptive analysis of the explanatory variables will be carried out before any other analysis. Descriptive characteristics of patients included in this study will be described for the entire population and by strategy group separately.
The study data will be summarized in descriptive tables. These will contain a column for each type of strategy (A/B). The total number of subjects, including missing observations, will be indicated at the top of each column. The analysis population will be systematically specified in the title of the table.

For continuous variables, the dispersion and central tendency parameters will be used:

- the standard deviation and the mean for Gaussian distributions,
- the interquartile range and the median otherwise.

For categorical variables, the descriptive analysis will be carried out using the numbers and frequencies for each observed modality.

Baseline patient characteristics will be described for the entire ITT population, overall and by randomization group. They will also be described for the PP population if there is a difference in numbers between the ITT and PP population greater than 10%.

Example tables for quantitative variables

	Total (N =…)		**Strategy A (N =…)**		**Strategy B (N =...)**	
	Avg	DS	Avg	DS	Avg	DS
	Med	IIQ	Med	IIQ	Med	IIQ
Variable 1*						
Variable 2**						

***** Gaussian distribution variable summarized as mean (Avg), standard deviation (SD)
** Non-Gaussian distribution variable summarized as median (Med), interquartile range [IIQ]
N: total number of subjects (with and without missing data on the variable studied)
n : number of subjects in a given modality of the variable studied

Example Table for Categorical Variables

	Total (N =…)		**Strategy A (N =…)**		**Strategy B (N =…)**	
	not	%	not	%	not	%
Variable A						
Modality 1			not	%	not	%
Modality 2			not	%	not	%

N: total number of subjects (with and without missing data on the variable studied)
n : number of subjects in a given modality of the variable studied

Listing of descriptive tables at inclusion

Characteristics of patients at inclusion (ITT population)

- Gender (Male/Female) [CRF p9]
- Age at inclusion (years) [Derived variable]
- Duration of illness (years) [Derived variable]
- Duration of disease in remission/low activity level (months) [CRF p10]

Consumption of alcohol and tobacco:

- Alcohol consumption (yes/no) [CRF p13]
  - Daily consumption (glasses/day) [CRF p13]
- Tobacco consumption (yes/no) [CRF p13]
  - If yes: specify (in progress/withdrawn) [CRF p13]
  - Number of packages/years [CRF p13]
  - Duration of smoking cessation (months) [Derived variable]
- Tobacco consumption (no/yes, patient weaned/yes, current) [Derived variable]

- Corticosteroid therapy before inclusion (≤ 2 years / > 2 years) [CRF p 19]

Visits made and reasons

- M4 visit carried out (yes/no) [CRF p43]
  - If no, specify the reason (listing) [CRF p43]
- M7 visit carried out (yes/no) [CRF p68]
  - If no, specify the reason (listing) [CRF p68]
- M9 visit carried out (yes/no) [CRF p93]
  - If no, specify the reason (listing) [CRF p93]
- M12 visit carried out (yes/no) [CRF p110]
  - If no, specify the reason (listing) [CRF p110]
- VA1 visit carried out (yes/no) [Derived variable]
  - Reason for additional visit:
  - Disease outbreak according to patient (yes/no) [CRF p135]
  - Disease outbreak according to doctor (yes/no) [CRF p135]
  - Adverse events (yes/no) [CRF p135]
  - Clinical signs suggestive of adrenal insufficiency [CRF p135]
  - Other (yes/no) [CRF p135]
- VA12 visit carried out (yes/no) [Derived variable]
  - Reason for additional visit:
  - Disease outbreak according to patient (yes/no) [CRF p146]
  - Disease outbreak according to doctor (yes/no) [CRF p146]
  - Adverse events (yes/no) [CRF p146]
  - Clinical signs suggestive of adrenal insufficiency [CRF p146]
  - Other (yes/no) [CRF p146]

Characteristic of the disease on the day of the inclusion visit, at M1, at M4

Doctor questionnaire at inclusion, M1

- Weight (kg) [CRF p15 , p23, p47]
- Size (cm) [CRF p15]
- Systolic blood pressure (mmHg) [CRF p15 , p23, p47]
- Diastolic blood pressure (mmHg) [CRF p15 , p23, p47]
- High blood pressure (yes/no) [Derived variable]

Elements of DAS28 at inclusion, M1

- DAS28 score [CRF p15 , p23, p47]
- Number of painful joints [CRF p15 , p23, p47]
- Number of swollen joints [CRF p15 , p23, p47]

- Overall assessment of the activity by the doctor (/ 10) [CRF p15 , p23, p47]

Patient questionnaire at inclusion, at M1, at M4

- Presence of nocturnal awakenings linked to pain (yes/no) [CRF p16 , p23, p48]
- Duration of joint stiffness in the morning (minutes) [CRF p16 , p23, p48]
- Pain (0 to 10) [CRF p16 , p23, p48]
- Overall assessment of disease activity (0 to 10) [CRF p16 , p23, p48]
- Fatigue (from 0 to 10) [CRF p16 , p23, p48]

Comorbidities associated with RA (ITT population)

- History of clinical myocardial infarction (yes/no) [CRF p1 4]
- History of decompensation of heart failure (yes/no) [CRF p1 4]
- Obliterating arteriopathy of the lower limbs (yes/no) [CRF p14]
- History of stroke (ischemic or hemorrhagic) (yes/no) [CRF p14]
- Dementia (yes/no) [CRF p14]
- COPD (yes/no) [CRF p14]
- History of peptic ulcer (yes/no) [CRF p14]
- History of diabetes (yes/no) [CRF p14]
    - Type of diabetes (Complicated/Uncomplicated) (yes/no) [CRF p14]
- Moderate to severe renal insufficiency (yes/no) [CRF p14]
- Hemiplegia (yes/no) [CRF p14]
- History of leukemia (yes/no) [CRF p14]
- History of lymphoma (yes/no) [CRF p14]
- History of solid cancer (yes/no) [CRF p14]
    - Solid cancer type (Localized/Metastatic) [CRF p14]
- Liver Pathology (yes/no) [CRF p14]
    - Severity of liver pathology (Mild/Moderate to severe) [CRF p14]
- AIDS (yes/no) [CRF p14]
- Osteoporosis (yes/no) [CRF p14]
    - Fracture osteoporosis (yes/no) [CRF p14]
        - Number of severe fractures (yes/no) [CRF p14]

  Osteoporosis treatment (Treated with anti-osteoporosis/Untreated) [CRF p14]
- Other comorbidity associated with RA
    - Precision: … (yes/no) [CRF p14]
- Charlson Score [Derived Variable]

History and pathologies associated with inclusion (ITT population)

- Presence of FR (yes/no) [CRF p9]
- Presence of ACPA (yes/no) [CRF p9]
- Presence of erosion (yes/no) [CRF p9]
- Presence of extra-articular signs (yes/no) [CRF p9]
- If yes, specify:
  - Cutaneous rheumatoid nodules (yes/no) [CRF p9]
  - Rheumatoid lung (yes/no) [CRF p9]
  - Eye damage related to RA (yes/no) [CRF p9]
  - Felty or pseudo-Felty syndrome (yes/no) [CRF p9]
  - Gougerot-Sjögren syndrome (yes/no) [CRF p9]
  - Amyloidosis (yes/no) [CRF p9]
  - Rheumatoid vasculitis (yes/no) [CRF p9]
  - Others, specify [CRF p9]
- History of orthopedic surgery related to RA (yes/no) [CRF p9]
- If yes, specify:
  - Number of surgical procedures [CRF p 10]
  - Nature of interventions [CRF p10]
- Presence of another inflammatory/autoimmune/dysimmune disease in addition to RA (yes/no) [CRF p 10]
- If yes, specify:
  - Number of associated dysimmune pathologies [CRF p 10]
  - Disease descriptions [CRF p10]

History of disease-modifying treatment for RA (ITT population)

History of disease-modifying treatment for RA

- Background treatment for RA (yes/no) [CRF p11]
- If yes, complete:
  - History of consumption of a synthetic DMARD (yes/no) [Derived variable]
  - Number of synthetic DMARDs previously consumed [Derived variable]
  - If yes, specify:
    - History of taking methotrexate (yes/no) [CRF p11]
      - Dosage (mg) [CRF p11]
      - Route of administration [CRF p11]
      - Number of sockets [CRF p11]
      - Taking frequency [CRF p11]
    - History of taking Leflunomide (yes/no) [CRF p11]
      - Dosage (mg) [CRF p11]
      - Route of administration [CRF p11]
      - Number of sockets [CRF p11]
      - Taking frequency [CRF p11]
    - History of taking Hydroxychloroquine (yes/no) [CRF p11]
      - Dosage (mg) [CRF p11]
      - Route of administration [CRF p11]
      - Number of sockets [CRF p11]
      - Taking frequency [CRF p11]
    - History of taking Sulfasalazine (yes/no) [CRF p11]
      - Dosage (mg) [CRF p11]
      - Route of administration [CRF p11]
      - Number of sockets [CRF p11]
      - Taking frequency [CRF p11]
    - History of taking another synthetic DMARD (yes/no) [Derived variable]
  - History of consumption of a biological DMARD (yes/no) [Derived variable]
  - Number of previously consumed biological DMARDs [Derived variable]
  - If yes, specify:
    - History of taking Etanercept (yes/no) [CRF p11]
      - Dosage (mg) [CRF p11]
      - Route of administration [CRF p11]
      - Number of sockets [CRF p11]
      - Taking frequency [CRF p11]
    - History of taking Adalimumab (yes/no) [CRF p11]
      - Dosage (mg) [CRF p11]
      - Route of administration [CRF p11]
      - Number of sockets [CRF p11]
      - Taking frequency [CRF p11]
    - History of taking Infliximab (yes/no) [CRF p11]
      - Dosage (mg) [CRF p11]
      - Route of administration [CRF p11]
      - Number of sockets [CRF p11]
      - Taking frequency [CRF p11]
    - History of taking Certolizumab pegol (yes/no) [CRF p11]
      - Dosage (mg) [CRF p11]
      - Route of administration [CRF p11]

- Number of sockets [CRF p11]
- Taking frequency [CRF p11]

- History of taking Golimumab (yes/no) [CRF p11]
  - Dosage (mg) [CRF p11]
  - Route of administration [CRF p11]
  - Number of sockets [CRF p11]
  - Taking frequency [CRF p11]
- History of taking Abatacept (yes/no) [CRF p11]
  - Dosage (mg) [CRF p11]
  - Route of administration [CRF p11]
  - Number of sockets [CRF p11]
  - Taking frequency [CRF p11]
- History of taking Tocilizumab (yes/no) [CRF p11]
  - Dosage (mg) [CRF p11]
  - Route of administration [CRF p11]
  - Number of sockets [CRF p11]
  - Taking frequency [CRF p11]
- History of taking Anakinra (yes/no) [CRF p11]
  - Dosage (mg) [CRF p11]
  - Route of administration [CRF p11]
  - Number of sockets [CRF p11]
  - Taking frequency [CRF p11]
- History of taking Bariticinib (yes/no) [CRF p11]
  - Dosage (mg) [CRF p11]
  - Route of administration [CRF p11]
  - Number of sockets [CRF p11]
  - Taking frequency [CRF p11]
- History of taking Tofacitinib (yes/no) [CRF p11]
  - Dosage (mg) [CRF p11]
  - Route of administration [CRF p11]
  - Number of sockets [CRF p11]
  - Taking frequency [CRF p11]
- History of taking another biological DMARD (yes/no) [CRF p11]
  - Dosage (mg) [CRF p11]
  - Route of administration [CRF p11]
  - Number of sockets [CRF p11]
  - Taking frequency [CRF p11]

Other disease-modifying treatments taken for RA :

- Taking another disease-modifying treatment for RA (yes/no) [CRF p12]
- If yes, specify:
  - Name of treatment [CRF p12]
    - Dosage (mg) [CRF p12]
    - Route of administration [CRF p12]
    - Number of sockets [CRF p12]
    - Taking frequency [CRF p12]
  - History of taking Rituximab (yes/no) [CRF p12]
    - Dosage (mg) [CRF p12]
    - Route of administration [CRF p12]
    - Number of sockets [CRF p12]

- Taking frequency [CRF p12]

Current background treatment and corticosteroids at inclusion (ITT population)

Current disease-modifying treatments taken for RA :

- Duration of treatment per background treatment [Derived variable]
- Current treatment for RA (yes/no) [CRF p13]
- Current intake of a synthetic DMARD at T0 (yes/no) [Derived variable]
- Number of synthetic DMARDs currently consumed at T0 (yes/no) [Derived variable]
- If yes which :
  - Current methotrexate intake at T0 (yes/no) [Derived variable]
  - Current intake of Leflunomide at T0 (yes/no) [Derived variable]
  - Current Hydroxychloroquine intake at T0 (yes/no) [Derived variable]
  - Current intake of Sulfasalazine at T0 (yes/no) [Derived variable]
  - Currently taking another synthetic DMARD at T0 (yes/no) [Derived variable]
- Current intake of a biological DMARD at T0 (yes/no) [Derived variable]
- Number of biological DMARDs currently consumed at T0 (yes/no) [Derived variable]
  - Current intake of Etanercept at T0 (yes/no) [Derived variable]
  - Current intake of Adalimumab at T0 (yes/no) [Derived variable]
  - Current intake of Infliximab at T0 (yes/no) [Derived variable]
  - Current intake of Certolizumab pegol at T0 (yes/no) [Derived variable]
  - Current intake of Golimumab at T0 (yes/no) [Derived variable]
  - Current intake of Abatacept at T0 (yes/no) [Derived variable]
  - Current intake of Tocilizumab at T0 (yes/no) [Derived variable]
  - Current Anakinra intake at T0 (yes/no) [Derived variable]
  - Current Bariticinib intake at T0 (yes/no) [Derived variable]
  - Current intake of Tofaticinib at T0 (yes/no) [Derived variable]
  - Currently taking another biological DMARD at T0 (yes/no) [Derived variable]
- Current Rituximab intake at T0 (yes/no) [Derived variable]

NSAID treatments

- Current oral NSAID intake (even occasional) (yes/no) [CRF p10]

Corticosteroids

- Duration of treatment with corticosteroids (years) [Derived variable]
- Maximum oral dosage/day (mg/) [CRF p13]
- Cumulative dose of corticosteroid since the start of the disease (mg) [CRF p13]
- Number of boluses/attacks received since the start [CRF p13]
- Number of corticosteroid infiltrations received (all pathologies) [CRF p13]
- Duration of treatment with prednisone at 5 mg/day (months) [CRF p13]
- Name of corticosteroid currently received:
  - Corticosteroid currently received: Prednisone 5 mg/d (yes/no) [Derived variable]
    - Type (generic/princeps) [CRF p13]
  - Corticosteroid currently received: Prednisolone 5 mg/day [Derived variable]
    - Type (generic/princeps) [CRF p13]
  - Corticosteroid currently received: Methylprednisolone 5 mg/day [Derived variable]
    - Type (generic/princeps) [CRF p13]

Treatment with corticosteroids at M1

- Treatment with prednisone 5 mg/day stopped permanently (yes/no) [CRF p20]
- Treatment with prednisone 5 mg/d temporarily stopped (yes/no) [CRF p20]
  - Number of temporary stops [Derived variable]
  - temporary discontinuation (RA flare-up/Adverse effect/Physician/patient decision/Appearance of a contraindication/Pregnancy/Patient death/unknown/other) [CRF p20, list]
- Treatment with prednisone 5 mg/day dose modification (yes/no) [CRF p20]
  - Number of dose modifications [Derived variable]
  - Reason for dose modification (RA flare/Adverse effect/Physician/patient decision/Appearance of a contraindication/Pregnancy/Patient death/unknown/other) [CRF p20]

- Use of assault or bolus (short course) (yes/no) [CRF p21]
- If yes, complete:
  - Yes, is it for a push? (Yes No) [CRF p21]
  - If No, specify the reason [CRF p21]
- Has the patient been injected with corticosteroids since the last visit? (Yes No) [CRF p21]
- If yes, complete:
  - Yes, is it for a push? (yes /no) [CRF p21]
  - If No, specify the reason [CRF p21]

Basic treatment at M1

- Change in background treatment since the last visit (yes/no) [CRF p21]
- If yes, complete:
  - Background treatment was reduced (yes/no) [CRF p21]
    - If yes, reason (Remission or low level of activity/Tolerance problem/Other) [CRF p21]
  - Background treatment was stopped
    - If yes, reason (Remission or low level of activity/Tolerance problem/Ineffectiveness/Other) [CRF p21]
  - The basic treatment has been increased
    - If yes, reason (Ineffectiveness/Other) [CRF p21]
  - The background treatment has been replaced
    - If yes, reason (I neffectiveness/Intolerance/Other) [CRF p21]

NSAID treatments at M1

- Current oral NSAID intake (even occasional) (yes/no) [CRF p 22]

Compliance with treatment at M4

- Level 1 followed correctly (yes/no) [CRF p43]
- Level 2 followed correctly (yes/no) [CRF p43]
- Level 3 followed correctly (yes/no) [CRF p43]
- If there is at least one "No" answer, specify:
- 1/ Has treatment with oral corticosteroids (prednisone, prednisolone, methylprednisolone) been received in addition to the treatment prescribed as part of the protocol since the last visit? (yes /no) [CRF p43]
    - If Yes, specify the reason:
        - Treatment of a disease flare-up documented by a rheumatologist (yes/no) [CRF p43]
        - Treatment of a flare-up by the attending physician (yes/no) [CRF p43]
        - Self-medication by the patient due to pain related to their rheumatoid arthritis (yes/no) [CRF p43]
        - Other, specify [CRF p43]
    - If Yes, do the prescribed dosages correspond to the rescue treatment provided for in the protocol? (yes /no) [CRF p43]
        - If Yes, Specify:
            - The number of attacks since the last visit [CRF p43]
        - If No, is it a one-off take? (yes /no) [CRF p43]
            - If yes, specify:
                - The number of attacks since the last visit [CRF p43]
                - Dose received (prednisone equivalent) (mg) [CRF p43]
                - The number of days of treatment [CRF p43]
        - If No, is it an addition of a long-term oral corticosteroid currently being taken? (yes /no) [CRF p43]
            - If Yes, specify:
                - daily dosage of prednisone or prednisone equivalent (mg/day) [CRF p43]
- 2/ Treatment with corticosteroids (other than hydrocortisone) IV or IM received in addition to the treatment prescribed as part of the protocol since the last visit? (yes /no) [CRF p44]
    - If Yes, specify:
        - The dose received (prednisone equivalent) (mg/day) [CRF p44]
        - The reason :
            - Treatment of a disease flare-up documented by a rheumatologist (yes/no) [CRF p44]
            - Treatment of a flare-up by the attending physician (yes/no) [CRF p44]
            - Other, specify (yes/no) [CRF p44]
- 3/ Corticosteroid infiltration has it been carried out since the last consultation? (yes /no) [CRF p44]
    - If Yes, specify:
    - The reason :
        - Related to RA (yes/no) [CRF p44]
            - The number of infiltrations received [CRF p44]
        - Not related to RA (yes/no) [CRF p44]
            - The number of infiltrations received [CRF p44]
        - Precision
- 4/ Has hydrocortisone treatment been received in addition to the protocol since the last consultation? (yes /no) [CRF p44]
    - If Yes, specify:
        - The dose received (mg/day) [CRF p44]
        - The reason :

- Acute adrenal insufficiency (yes/no) [CRF p44]
- Clinical signs of chronic adrenal insufficiency (yes/no) [CRF p44]
- Biological signs of chronic adrenal insufficiency (yes/no) [CRF p44]
- Prescribed in the context of traumatic stress, infectious during surgery (yes/no) [CRF p44]
- Other, precision [CRF p44]

- Has the patient had a flare-up of his illness documented by a doctor (defined by a DAS28 ≥ 3.2) since the last visit? (yes /no) [CRF p34]

Basic treatment at M4

- Change in background treatment since the last visit (yes/no) [CRF p 45]
- If yes, complete:
  - Background treatment was reduced (yes/no) [CRF p 45]
    - If yes, reason (Remission or low level of activity/Tolerance problem/Other) [CRF p45]
  - Background treatment was stopped
    - If yes, reason (Remission or low level of activity/Tolerance problem/Ineffectiveness/Other) [CRF p45]
  - The basic treatment has been increased
    - If yes, reason (Ineffectiveness/Other) [CRF p45]
  - The background treatment has been replaced
    - If yes, reason (I neffectiveness/Intolerance/Other) [CRF p45]

NSAID treatments at M4

- Current oral NSAID intake (even occasional) (yes/no) [CRF p 46]

Bone densitometry at inclusion (ITT population)

- Osteodensitometry performed (yes/no) [CRF p15]
- If yes, complete:
  - Spine T score [CRF p15]
  - T score pass [CRF p15]
- Vitamin-calcium supplementation (yes/no) [CRF p15]
- If yes, complete:
  - Type of supplementation (Vitamin D/Calcium/Both) [CRF p15]

Biological assessment at inclusion (ITT population)

- Biological assessment carried out (yes/no) [CRF p17]
- VS in the first hour (mm) [CRF p17]
- CRP (mg/L) [CRF p 17]
- Rheumatoid factors (yes/no) [CRF p17]
- If yes, specify:
  - Method (ELISA/Immunonephelometry) [CRF p17]
  - Rheumatoid factors (UI/L) [CRF p17]
  - Rheumatoid factors: Positive sample (yes/no) [Derived variable]
- Anti-CCP2 (yes/no) [CRF p17]
  - Anti-CCP2 (UI/L) [CRF p17]
  - Anti-CCP2: Positive sample (yes/no) [Derived variable]
- B -HCG (woman of childbearing age, blood or urine) (NA/positive/negative) [CRF p17]

Biological assessment at M1 (ITT population)

- Biological assessment carried out (yes/no) [CRF p35]
- VS in the first hour (mm) [CRF p35]
- CRP (mg/L) [CRF p 35]

Verification of eligibility criteria (ITT population)

Inclusion criteria

- Criterion 1 (yes/no) [CRF p18]
- Criterion 2 (yes/no) [CRF p18]
- Criterion 3 (yes/no) [CRF p18]
- Criterion 4 (yes/no) [CRF p18]
- Criterion 5 (yes/no) [CRF p18]
- Criterion 6 (yes/no) [CRF p18]
- Criterion 7 (yes/no) [CRF p18]

Non-inclusion criterion

- Criterion 1 (yes/no) [CRF p18]
- Criterion 2 (yes/no) [CRF p18]
- Criterion 3 (yes/no) [CRF p18]
- Criterion 4 (yes/no) [CRF p18]
- Criterion 5 (yes/no) [CRF p18]
- Criterion 6 (yes/no) [CRF p18]
- Criterion 7 (yes/no) [CRF p18]
- Criterion 8 (yes/no) [CRF p18]
- Criterion 9 (yes/no) [CRF p18]
- Criterion 10 (yes/no) [CRF p18]
- Criterion 11 (yes/no) [CRF p18]
- Criterion 12 (yes/no) [CRF p18]
- Criterion 13 (yes/no) [CRF p18]
- Criterion 14 (yes/no) [CRF p18]
- Criterion 15 (yes/no) [CRF p18]
- Criterion 16 (yes/no) [CRF p18]
- Criterion 17 (yes/no) [CRF p18]

- Patient included in the study (yes/no) [CRF p19]
- Reason for non-inclusion :
  - Not eligible (yes/no) [CRF p19]
  - Patient refusal (yes/no) [CRF p19]
  - Other, give details : …. (yes /no) [CRF p19]

- Delivery of an adrenal insufficiency card to the patient (yes/no) [CRF p19]
- Collection of consent (yes/no) [Derived variable]

Validation of eligibility criteria

- Increasing prednisone (yes/no) [CRF p35]
- Reduction of prednisone (yes/no) [CRF p35]
- Stopping prednisone (yes/no) [CRF p35]
- DAS28 > 3.2 (yes/no) [CRF p35]
- Corticosteroid infiltration (yes/no) [CRF p35]
- Parenteral corticosteroids (yes/no) [CRF p35]
- Modification of an inclusion/non-inclusion criterion (yes/no) [CRF p35]
- Withdrawal of consent (yes/no) [CRF p35]
- Other (yes/no) [CRF p35]
  - precision … (yes/no) [CRF p35]

Questionnaires for M1 and M4

HAQ-DI

- DRESS AND PREPARE (Without any difficulty/With some difficulty/With a lot of difficulty/Unable to do it) [CRF p25 , p49]
  - get dressed, including tying your shoelaces and buttoning your clothes?
  - your hair?
- GET UP (Without any difficulty/With some difficulty/With a lot of difficulty/Unable to do it) [CRF p25 , p49]
  - get up from a chair?
  - you in and out of bed?
- EAT (Without any difficulty/With some difficulty/With a lot of difficulty/Unable to do it) [CRF p25 , p49]
  - cut your meat?
  - bring a full cup or glass to your mouth?
  - open a “carton” of milk or fruit juice?
- WALK (Without any difficulty/With some difficulty/With a lot of difficulty/Unable to do it) [CRF p25 , p49]
  - walk on flat ground outside?
- HYGIENE (Without any difficulty/With some difficulty/With a lot of difficulty/Unable to do it) [CRF p25 , p49]
  - wash and dry yourself completely?
  - take a bath ?
  - sit down and get up from the toilet?
- REACH AND CATCH AN OBJECT (Without any difficulty/With some difficulty/With a lot of difficulty/Unable to do it) [CRF p25 , p49]
  - reach and pick up an object weighing 2.5 kg located above your head?
  - bend down to pick up an item of clothing from the floor?
- GRIP (Without any difficulty/With some difficulty/With a lot of difficulty/Unable to do it) [CRF p25 , p49]
  - open a car door?
  - unscrew the lid of a jar that has already been opened once?
  - open and close a tap?
- OTHER ACTIVITIES (Without any difficulty/With some difficulty/With a lot of difficulty/Unable to do it) [CRF p25 , p49]
  - do your shopping?
  - getting in and out of the car?
  - do housework such as vacuuming or doing light gardening?

Please indicate with a cross if you usually use one of these devices or accessories to perform these activities:

- Cane(s) (yes/no) [CRF p26 , p50]
- Accessories for dressing (yes/no) [CRF p26 , p50]
- Specially adapted utensil (yes/no) [CRF p26 , p50]
- Specially adapted chair (yes/no) [CRF p26 , p50]
- Walker (yes/no) [CRF p26 , p50]
- Crutches (yes/no) [CRF p26 , p50]
- Wheelchair (yes/no) [CRF p26 , p50]
- Others (specify) (yes/no) [CRF p26 , p50]

Please indicate the activities for which you need someone's help:

- Dress and prepare (yes/no) [CRF p26 , p50]
- Get up (yes/no) [CRF p26 , p50]
- Eat (yes/no) [CRF p26 , p50]

- Walk (yes/no) [CRF p26 , p50]

Please indicate with a cross if you usually use one of these devices or accessories to perform these activities:

- Raised toilet seat (yes/no) [CRF p26 , p50]
- Bathtub seat (yes/no) [CRF p26 , p50]
- Jar openers (for jars already opened) (yes/no) [CRF p26 , p50]
- Bathtub handle or bar (yes/no) [CRF p26 , p50]
- Long-handled instrument for catching objects (yes/no) [CRF p26 , p50]
- Long-handled instrument in the bathroom (yes/no) [CRF p26 , p50]
- Others (specify) (yes/no) [CRF p26 , p50]

Please mark the activities for which you need someone's help:

- Hygiene (yes/no) [CRF p26 , p50]
- Grasp and open objects (yes/no) [CRF p26 , p50]
- Reach and grab an object (yes/no) [CRF p26 , p50]
- Shopping and household chores (yes/no) [CRF p26 , p50]

- Total (0 to 3) [Derived variable]

Calculation method
There are 8 sections: dressing, getting up, eating, walking, hygiene, reaching, grasping, and activities. There are 2 or 3 questions for each section. The score for each section ranges from 0 to 3. Each question is allocated the following mark:
0 = without any difficulty
1 = with some difficulty
2 = with great difficulty
3 = unable to do so
The rating for each of the 8 domains is that corresponding to the highest score of the questions in this domain. That is, if one domain question is scored 1 and another 2, the section score is 2. If there is missing data in one or more questions in a particular area, the rating is that corresponding to the highest score of the questions with an answer (missing data is not taken into account). Additionally, if an aid or device is used or assistance from another person is required, the minimum score for this section is 2. If the section score is already 2 or higher, no change is made. brought. Aids and devices are assigned to specific sections of the QHA as follows:
• Getting dressed and getting ready: Accessories for dressing (button hook, zipper hook, long-handled shoe horn, etc.)
• Getting up: Specially adapted chair
• Eating: Specially adapted utensils
• Walking: Cane, walker, crutches, wheelchair
• Hygiene: Bathtub handle or bar, long-handled instrument in the bathroom, raised toilet seat, bathtub seat
• Reaching and grabbing an object: Long-handled devices for reaching
• Gripping: Jar openers (for jars already opened) The functional index is the sum of the ratings of the various domains divided by the number of domains evaluated (normally 8 but less in case of completely missing data for a particular domain). The score thus obtained is between 0 and 3. The result is the DI or FDI, the disability index or the functional disability index.

RAID

- Function : difficulty performing daily activities (from 0 to 10) [CRF p27 , p51, p76, p118]
- Sleep: difficulty sleeping (resting at night) (0 to 10) [CRF p27 , p51]
- Psychological well-being (0 to 10) [CRF p27 , p51]
- Physical well-being (0 to 10) [CRF p27 , p51]
- Adaptation, Coping, coping (from 0 to 10) [CRF p27 , p51]
- Pain (from 0 to 10) [CRF p24 , p48, p73]
- Fatigue (0 to 10) [CRF p24 , p48]

Calculation method

RAID is calculated based on 7 Numerical Rating Scale (NRS). Each NRS is rated by a number between 0 and 10. The 7 NRS correspond to pain, function, fatigue, sleep, emotional well-being, physical well-being and coping capacity /self-efficacy.

1. Calculation Final RAID value = (NRS value of pain (range 0-10) x 0.21) + (NRS value of function (range 0-10) x 0.16) + (NRS value of fatigue (range 0-10) x 0.15) + (NRS value of physical well-being (range 0-10) x 0.12) + (NRS value of sleep (range 0-10) x 0.12) + (NRS value of emotional well-being (range 0-10) x 0.12) + (NRS value of adaptation (range 0-10) x 0.12). So, the range of the final RAID value is 0 to 10, with higher numbers indicating a more serious condition.
2. Imputation of missing data If one of the 7 NRS values making up the RAID is missing, the imputation is as follows a) calculate the average value of the other 6 (non-missing) NRS values (range, 0-10) b) impute this value for missing NRS c) Next, calculate the RAID as explained above.

If 2 or more of the NRS are missing, the RAID is considered a missing value (no imputation).

https://oml.eular.org/sysModules/obxOml/docs/ID_6/raid_fr_CA.pdf

Facit-F

Physical well-being (0 = Not at all/1 = A little/2 = Moderately/3 = A lot/4 = Very much)

- I lack energy (0/1/2/3/4) [CRF p28, 52]
- I feel nauseous (0/1/2/3/4) [CRF p28, 52]
- Because of my physical condition, I have difficulty meeting the needs of my family (0/1/2/3/4) [CRF p28 , 52]
- I have pain (0/1/2/3/4) [CRF p28, 52]
- I am bothered by the side effects of the treatment (0/1/2/3/4) [CRF p28, 52]
- I feel sick (0/1/2/3/4) [CRF p28, 52]
- I am forced to spend time lying down (0/1/2/3/4) [CRF p28, 52]

Family/social well-being (0 = Not at all/1 = A little/2 = Moderately/3 = A lot/4 = Very much)

- I feel close to my friends (0/1/2/3/4) [CRF p28, 52]
- My family supports me morally (0/1/2/3/4) [CRF p28, 52]
- My friends support me (0/1/2/3/4) [CRF p28, 52]
- My family accepted my illness (0/1/2/3/4) [CRF p28, 52]
- I am satisfied with the communication with my family about my illness (0/1/2/3/4) [CRF p28, 52]
- I feel close to my partner (or the person who is my main support) (0/1/2/3/4) [CRF p28, 52]
- I am satisfied with my sex life (0/1/2/3/4) [CRF p28, 52]

Emotional well-being (0 = Not at all/1 = A little/2 = Moderately/3 = A lot/4 = Very much)

- I feel sad (0/1/2/3/4) [CRF p29, 53]
- I am satisfied with the way I cope with my illness (0/1/2/3/4) [CRF p29, 53]
- I am losing hope in the fight against my illness (0/1/2/3/4) [CRF p29, 53]
- I feel nervous (0/1/2/3/4) [CRF p29, 53]
- I am concerned about dying (0/1/2/3/4) [CRF p29, 53]
- I am concerned that my health condition may worsen (0/1/2/3/4) [CRF p29, 53]

Functional well-being (0 = Not at all/1 = A little/2 = Moderately/3 = A lot/4 = Very much)

- I am able to work (including working at home) (0/1/2/3/4) [CRF p29, 53]
- My work (including work at home) gives me satisfaction (0/1/2/3/4) [CRF p29, 53]
- I am able to enjoy life I have accepted my illness (0/1/2/3/4) [CRF p29, 53]
- I sleep well (0/1/2/3/4) [CRF p29, 53]
- I enjoy my usual hobbies (0/1/2/3/4) [CRF p29, 53]
- I am satisfied with my current quality of life (0/1/2/3/4) [CRF p29, 53]

Other areas of concern (0 = Not at all/1 = A little/2 = Moderately/3 = A lot/4 = Very much)

- I feel exhausted (0/1/2/3/4) [CRF p30 , 5 4]
- I feel general weakness (0/1/2/3/4) [CRF p30, 54]
- I am without energy [washed out] (0/1/2/3/4) [CRF p30, 54]
- I feel tired (0/1/2/3/4) [CRF p30, 54]
- I have trouble starting things because I'm tired (0/1/2/3/4) [CRF p30, 54]
- I have trouble finishing things because I'm tired (0/1/2/3/4) [CRF p30, 54]
- I have energy (0/1/2/3/4) [CRF p30, 54]
- I am able to do what I usually do (0/1/2/3/4) [CRF p30, 54]
- I need to sleep during the day (0/1/2/3/4) [CRF p30, 54]
- I'm too tired to eat (0/1/2/3/4) [CRF p30, 54]
- I need help to do my usual activities (0/1/2/3/4) [CRF p30, 54]

- I'm frustrated that I'm too tired to do what I want (0/1/2/3/4) [CRF p30, 54]
- I have to limit my social activities because I am tired (0/1/2/3/4) [CRF p30, 54]

Méthode de calcul

1. Write the answers in the "answer to question" column. If missing, mark with an X
2. Perform the reversals as indicated, and add the individual items to obtain a score.
3. Multiply the sum of item scores by the number of items in the subscale, then divide by the number of items answered. This gives the subscale score.
4. Add the subscale scores to obtain the total scores (TOI, FACT-G and FACIT-F).
5. The higher the score, the better the QOL.

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL WELL-BEING (PWB)	GP1	4	-	_____	=_____
	GP2	4	-	_____	=_____
	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____
				Sum individual item scores: _____	
				Multiply by 7: _____	
				Divide by number of items answered: _____	**=PWB subscale score**
SOCIAL/FAMILY WELL-BEING (SWB)	GS1	0	+	_____	=_____
	GS2	0	+	_____	=_____
	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____
				Sum individual item scores: _____	
				Multiply by 7: _____	
				Divide by number of items answered: _____	**=SWB subscale score**
EMOTIONAL WELL-BEING (EWB)	GE1	4	-	_____	=_____
	GE2	0	+	_____	=_____
	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____
				Sum individual item scores: _____	
				Multiply by 6: _____	
				Divide by number of items answered: _____	**=EWB subscale score**
FUNCTIONAL WELL-BEING (FWB)	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____
				Sum individual item scores: _____	
				Multiply by 7: _____	
				Divide by number of items answered: _____	**=FWB subscale score**

Subscale	Item Code	Reverse item?		Item response	Item Score
FATIGUE SUBSCALE (FS)	HI7	4	-	_____	=_____
	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 13: _____
Divide by number of items answered: _____**=F Subscale score**

To derive a FACIT-F Trial Outcome Index (TOI):
Score range: 0-108

_____ + _____ + _____ =_____**=FACIT-F TOI**
(PWB score) **(FWB** score) **(FS** score)

To Derive a FACT-G total score:
Score range: 0-108

_____ + _____ + _____ + _____ =_____**=FACT-G Total score**
(PWB score) **(SWB** score) **(EWB** score) **(FWB** score)

To Derive a FACIT-F total score:
Score range: 0-160

_____ + _____ + _____ + _____ + _____ =_____**=FACIT-F Total score**
(PWB score) **(SWB** score) **(EWB** score) **(FWB** score) **(FS** score)

https://www.facit.org/measures-scoring-downloads/facit-f-scoring-downloads

EQ-5D

- Mobility (I have no problem getting around on foot/I have problems getting around on foot/I am forced to stay in bed) [CRF p31, 55]
- Personal autonomy (I have no problem taking care of myself/I have problems washing or dressing myself/ I am unable to wash or dress myself on my own [CRF p31, 55]
- Current activities (examples: work, studies, housework, family activities or leisure activities) (I have no problem carrying out my current activities/I have problems carrying out my current activities/I am unable to carry out my current activities) [CRF p31, 55]
- Pain/discomfort (I have no pain or discomfort/I have moderate pain or discomfort/I have extreme pain or discomfort) [CRF p31, 55]
- Anxiety / Depression (I am neither anxious nor depressed/I am moderately anxious or depressed/I am extremely anxious or depressed) [CRF p31, 55]

Visual analog scale

- Your health today (from 0 to 100) [CRF p32, 56]

Calculation method

■ **Matrice de pondération**

Dimension	Niveau de réponse	Score de préférence	
Mobilité	1		0
	2	u1	0,15
	3		0,37
Autonomie de la personne	1		0
	2	u2	0,21
	3		0,32
Activités courantes	1		0
	2	u3	0,16
	3		0,19
Douleurs / gênes	1		0
	2	u4	0,11
	3		0,26
Anxiété / dépression	1		0
	2	u5	0,09
	3		0,20
Constante	Si au moins une dimension est au niveau 3	N3	0,17

Source : Chevalier 2010

■ **Fonction de scorage**

U(E) = 1 – u1 - u2 - u3 - u4 - u5 – N3

1. Chevalier J, de Pouvourville G. Valuing EQ-5D using Time Trade-Off in France. Eur J Health Econ. févr 2013;14(1):57-66.
1. Choix méthodologiques pour l'évaluation économique à la HAS. 2020;118.
https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiwiYHcrpv4AhWu7rsIHZy8BHQQFnoECAoQAQ&url=https%3A%2F%2Feuroqol.org%2Fwp-content%2Fuploads%2F2021%2F01%2FEQ-5D-5LUserguide-08-0421.pdf&usg=AOvVaw0vD2pUiFOQxDSkLM7ySgTx

FLARE (doctor assessment)

(5 = Completely true / 4 = True / 3 = Mostly true / 2 = Mostly false / 1 = False / 0 = Completely false)

- You have noticed the appearance or worsening of morning joint rust for several days in a row [CRF p33 , 57]
- You have noticed the appearance or worsening of pain in one or more joints for several days in a row [CRF p33 , 57]
- You have noticed the appearance or worsening of swelling in one or more joints for several days in a row [CRF p33 , 57]
- You have noticed the appearance or worsening of waking up several nights in a row due to the pain of your polyarthritis [CRF p33 , 57]
- You think that your polyarthritis has worsened significantly for several days in a row [CRF p33 , 57]
- You have increased your pain medication (analgesics or anti-inflammatories) for several days in a row (If you are not taking any pain medication, check “Completely false”) [CRF p33 , 57]
- You have increased your cortisone intake for several days in a row due to your polyarthritis (If you do not take cortisone, check “completely false”) [CRF p33 , 57]
- You felt very tired for several days in a row due to your polyarthritis [CRF p33 , 57]
- You were so limited that you could “no longer do anything” for several days in a row due to your polyarthritis [CRF p34 , 58]
- You felt more irritable for several days in a row due to your polyarthritis [CRF p34 , 58]
- You have felt a drop in morale for several days in a row due to your polyarthritis [CRF p34 , 58]
- You felt like withdrawing into yourself or isolating yourself for several days in a row because of your polyarthritis [CRF p34 , 58]
- You felt a greater need for help for several days in a row due to your polyarthritis [CRF p34 , 58]

Méthode de calcul

Briefly, the questionnaire includes 13 questions examining 13 domains identified as being associated with RAflare by both patients and physicians (joint swelling, joint pain,night awakening, pain killer intake), only patients (fatigue,impossibility to do a thing, need for help, withdrawal fromsocial activities, bad mood, and irritability), or only physicians(morning stiffness, daily dose of steroids, patient’s globalassessment). Every domain was formulated as follows: “In thelast 3 months, or at some time since the last medical310FAUTREL ET AL
consultation, please indicate how true the statement fits foryou.” For each statement, the respondent had to indicateagreement, using a numerical rating scale from 0 (completelyuntrue) to 10 (absolutely true). The total FLARE-RA scorewas the mean of the scores for the 13 items.

FLARE (Patient assessment) at M1, M2, M3 and M4

(6 = Completely true / 4 = True / 3 = Mostly true / 2 = Mostly false / 1 = False / 0 = Completely false)

- You have noticed the appearance or worsening of morning joint rust for several days in a row [CRF p3 7]
- You have noticed the appearance or worsening of pain in one or more joints for several days in a row [CRF p3 7]
- You have noticed the appearance or worsening of swelling in one or more joints for several days in a row [CRF p3 7]
- You have noticed the appearance or worsening of awakenings several nights in a row because of the pain of your polyarthritis [CRF p3 7]
- You think that your polyarthritis has worsened significantly for several days in a row [CRF p3 7]
- You have increased your pain medication (analgesics or anti-inflammatories) for several days in a row (If you are not taking any pain medication, check "Completely false") [CRF p3 7]
- You have increased your cortisone intake for several days in a row due to your polyarthritis (If you do not take cortisone, check "completely false") [CRF p3 7]
- You felt very tired for several days in a row due to your polyarthritis [CRF p3 7]
- You were so limited that you could "no longer do anything" for several days in a row due to your polyarthritis [CRF p3 8]
- You felt more irritable for several days in a row due to your polyarthritis [CRF p3 8]
- You have felt a drop in morale for several days in a row due to your polyarthritis [CRF p3 8]
- You felt like withdrawing into yourself or isolating yourself for several days in a row because of your polyarthritis [CRF p3 8]

You felt a greater need for help for several days in a row due to your polyarthritis

Synacthen test at M4, M7, M9, M12, VAdd 1, VAdd 2

- Test carried out (yes/no) [CRF p60, p85, p102, p127, p144, p155]
  If Yes, specify:
  - Cortisol without stimulation (yes/no) [CRF p60, p85, p102, p127, p144, p155]
    - Test value (µg/100mL) [CRF p60, p85, p102, p127, p144, p155]
  - Cortisol 60 minutes after stimulation with 0.25 mg of Synacthène® (yes/no) [CRF p60, p85, p102, p127, p144, p155]
    - Test value (µg/100mL) [CRF p60, p85, p102, p127, p144, p155]
- Is the Synacthen test considered pathological? (yes /no) [Derived variable]
  If No, if cortisol at 60 minutes is normal and the patient is on open-label hydrocortisone, specify:
  - Maintenance of hydrocortisone, specify dosage (mg/day) (yes/no) [CRF p61, p86, p103, p128, p145, p156]

    If Yes, specify why
    - Hydrocortisone withdrawal (yes/no) [CRF p61, p86, p103, p128, p145, p156]
    - Other, specify (yes/no) [CRF p61, p86, p103, p128, p145, p156]
      - Accuracy (listing) [CRF p61, p86, p103, p128, p145, p156]
  - If Yes, is the patient summoned again for the introduction of hydrocortisone in accordance with the protocol? (yes /no) [CRF p61, p86, p103, p128, p145, p156
  -]If No, another attitude is adopted towards the results of a pathological Synacthen test, please specify:
    - The patient was already on Hydrocortisone before this visit (yes/no) [CRF p61, p86, p103, p128, p145, p156]
    - Other, specify (yes/no) [CRF p61, p86, p103, p128, p145, p156]
      - Accuracy (listing) [CRF p61, p86, p103, p128, p145, p156]

We will identify discordant patients, that is to say, those having a pathological test after recalculation [derived variable] although they were declared as normal in the eCRF, as well as patients who did not receive a open-label hydrocortisone until the next visit as planned in the protocol (patients to be classified in the protocol deviation group).

End of study sheet

- Follow-up duration [Derived variable]
- Did the patient complete the trial according to protocol? (yes /no) [CRF p157]
    - Specify the reason for premature termination:
    - Adverse event or serious adverse event (yes/no) [CRF p157]
    - Resumption of RA activity/prescription of long-term prednisone or prednisolone (yes/no) [CRF p157]
    - Patient's refusal to prosecute (yes/no) [CRF p157]
    - Withdrawal of consent (yes/no) [CRF p157]
    - Death (yes/no) [CRF p157]
    - Patient lost to follow-up (yes/no) [CRF p157]
    - Protocol violation (yes/no) [CRF p157]
        - Specify (listing) [CRF p157]
    - Other (yes/no) [CRF p157]
        - Specify (listing) [CRF p157]
- Has the blind been lifted? (yes /no) [CRF p157]
    - The reason for unblinding (listing) [CRF p157]

ANALYSIS OF THE MAIN JUDGMENT ENDPOINT

1) Redefinition of the primary endpoint (ITT)

The primary endpoint is the proportion of patients who were able to wean off prednisone or hydrocortisone (success rate) in each group at the end of the study (12 months).

The withdrawal strategy will be considered a failure for:

- Patients who are still receiving oral prednisone and/or hydrocortisone at the end of the study. *Modality 1*
- Patients who received more than two intra-articular or periarticular injections during the entire study to treat RA-related synovitis, bursitis, or tenosynovitis. *Modality 2*
- Patients who received more than two short GC therapies during the entire study period. *Modality 3*
- Patients who presented clinical or biological signs of adrenal insufficiency leading to the use of hydrocortisone until the end of the protocol. *Modality 4*
- Patients who received more than two weeks of GC for a reason other than their illness. *Modality 5*

Variable name	Derivations
Total number of infiltrations received in relation to RA over the duration of post-randomization follow-up	From the variable " *number of infiltrations received* " [*CRFp44, p69, p94, p111*], we will create a discrete quantitative variable from the number of infiltrations carried out between each visit. The value of this variable will correspond to the sum of all infiltrations carried out if: • " *was a corticosteroid infiltration carried out*" = yes • AND " *related to RA* " = yes ○ AND " *the number of infiltrations received* " = not missing It will take the value 0 in all other cases.
Total number of attacks corresponding to rescue treatment received over the duration of post-randomization follow-up	From the variables " *The number of attacks since the last visit* " [*CRFp43, p68, p93, p110*], we will create a discrete quantitative variable from the number of attacks used between each visit. The value of this variable will correspond to the sum of all the attacks corresponding to the emergency processing carried out if: • " was *treatment with oral corticosteroids received in addition*" = yes • AND " *do the prescribed dosages correspond to rescue treatment*" = yes ○ AND " *number of attacks*" = not missing It will take the value 0 in all other cases.

Variable name	Derivations
Total number of attacks not corresponding to rescue treatment received over the duration of post-randomization follow-up	From the variables " *The number of attacks since the last visit* " [*CRFp43, p68, p93, p110*], we will create a discrete quantitative variable from the number of attacks used between each visit. The value of this variable will correspond to the sum of all the attacks carried out not corresponding to emergency treatment if: • " was *treatment with oral corticosteroids received in addition"* = yes • AND " *do the prescribed dosages correspond to rescue treatment"* = no o AND " *number of attacks"* = not missing It will take the value 0 in all other cases.
Number of days taking oral GC for reasons other than their illness (in days)	From the variables " *Date of addition of oral corticosteroid therapy* " [*CRFp43, p68, p93, p110*] and " *date of visit* ", we will create a quantitative variable corresponding to the number of days between the initiation of treatment and the date of the visit. The value of this variable will correspond to the sum of all periods where the patient consumed corticosteroids if: • " was *treatment with oral corticosteroids received in addition"* = yes • AND " *other reason "* = yes • AND " *do the prescribed dosages correspond to rescue treatment"* = no • AND " *addition of a long-term corticosteroid"* = yes o AND " *date of addition of oral corticosteroid therapy"* = not missing It will take the value 0 in all other cases.

Variable name	Derivations
Number of days of taking GC by IV or IM route for reasons other than their illness (in days)	From the variables "Date *of resumption of parenteral corticosteroid therapy* ", " *Date of stopping parenteral corticosteroid therapy",* " *Date of visit* " [*CRFp43-44, p68-69, p93-94, p110-111*] we will create a quantitative variable corresponding to the number of days between the initiation of the treatment and the cessation or between the date of initiation of the treatment and the date of the visit if " *in progress* " is checked. The value of this variable will correspond to the sum in days of all periods where the patient received corticosteroids IV or IM if: • " was *treatment with IV or IM corticosteroids received in addition"* = yes • AND " *other reason* " = yes ○ AND " *date of resumption of parenteral corticosteroid therapy"* = not missing ○ AND " *date of stopping parenteral corticosteroid therapy"* = not missing OR " *in progress"* = yes It will take the value 0 in all other cases.
Number of days of taking GC for reasons other than their illness (in days)	From the variables "Number of days of taking GC by oral route for other reason *"* [*Derived variable*] and "Number of days of taking GC by IV or IM route for other reason" [*Derived variable*] we will create a quantitative variable corresponding to the sum of the two variables. That is, the total number of days the patient received GC orally, IM or IV.
Prednisone/hydrocortisone at the end of the study (yes/no) *Modality 1*	From the variables of [*CRFp110 and p111*] to M12, we define 2 modalities: • " If yes : ○ " *Has the patient received corticosteroid treatment with prednisone, prednisolone or methylprednisolone since the last visit?* » = yes AND ▪ " *Has treatment with oral corticosteroids been received in addition to the treatment prescribed as part of the protocol since the last visit?* » = yes ▪ OR if " *Has hydrocortisone treatment been received in addition to the protocol since the last consultation?* » = yes • "No" in all other cases

Variable name	Derivations
More than 2 joint injections during the study period (yes/no) *Modality 2*	From the variable " *Total number of infiltrations received in relation to RA* " [*Derived variable*], we define 2 modalities: • " If yes : ○ " ***Total number of infiltrations received in relation to RA*** " [*Derived variable*] > 2 • " Not if : ○ " ***Total number of infiltrations received in relation to RA*** " [*Derived variable*] ≤ 2
More than 2 short GC therapies corresponding to rescue treatment for the entire duration of the study (yes/no) *Modality 3.1*	From the variable " *Total number of assaults* " [*Derived variable*], we define 2 modalities: • " If yes : ○ " **Total number of attacks corresponding to emergency treatment "** [Derived *variable*] > 2 • " Not if : ○ " **Total number of attacks corresponding to rescue treatment "** [Derived *variable*] ≤ 2
Taking at least one short GC therapy not corresponding to rescue treatment for the entire duration of the study (yes/no) *Condition 3.2*	From the variable " *Total number of assaults* " [*Derived variable*], we define 2 modalities: • " If yes : ○ " **Total number of attacks not corresponding to rescue treatment "** [Derived *variable*] ≥ 1 • " Not if : ○ " **Total number of attacks not corresponding to emergency treatment "** [Derived *variable*] = 0
Clinical or biological **signs of adrenal insufficiency treated** with hydrocortisone at the end of the protocol (yes/no) *Modality 4*	From the variables of [*CRFp111*] to M12, we define 2 modalities: • " If yes : ○ " *Has hydrocortisone treatment been received in addition to the protocol since the last consultation?* » = yes ▪ AND " *Hydrocortisone end date* " = in progress ▪ AND Reason: " *Acute adrenal insufficiency* " = yes • OR " *Clinical signs of chronic adrenal insufficiency" = yes* • OR " *Biological signs of chronic adrenal insufficiency" = yes* • "No" otherwise

Variable name	Derivations
More than 2 weeks of GC for reasons other than their illness (yes/no) *Modality 5*	From the variable " *Number of days of taking GC for reasons other than their illness (in days)"* [*Derived variable*], we define 2 modalities: • " If yes : ○ " ***Number of days of taking GC for other reasons*** " [*Derived variable*] > 15 • " Not if : ○ " ***Number of days of taking GC for other reasons*** " [*Derived variable*] ≤ 15
Main judgment criterion : Effectiveness of the strategy (FAILURE/SUCCESS)	From the following derived variables: " *Prednisone/hydrocortisone at the end of the study (yes/no)*", " *More than 2 joint injections during the duration of the study (yes/no)"*, " *More than 2 therapies short periods of GC for the entire duration of the study (yes/no)* ", " *Clinical or biological signs of adrenal insufficiency treated with hydrocortisone at the end of the protocol (yes/no)* ", " *More than 2 weeks of GC for reason other than their illness (yes/no)"* we define 2 modalities: • "FAIL" if: ○ " ***Prednisone/hydrocortisone at end of study*** " [*Derived variable*] = Yes ○ OR " ***More than 2 joint injections*** *during the study period* " [*Derived variable*] = Yes ○ OR " ***More than 2 short GC therapies corresponding to rescue treatment*** *for the entire duration of the study* » [*Derived variable*] = Yes ○ OR " ***Taking at least one short GC therapy not corresponding to rescue treatment*** *for the entire duration of the study"* [*Derived variable*] = Yes ○ OR " *Clinical or biological* ***signs of adrenal insufficiency treated*** *with hydrocortisone at the end of the protocol* » [*Derived variable*] = Yes ○ OR " ***More than 2 weeks of GC for reasons other*** *than their illness"* [*Derived variable*] = Yes • "SUCCESS" if: ○ " ***Prednisone/hydrocortisone at end of study*** " [*Derived variable*] = No ○ AND " ***More than 2 joint injections*** *during the study period"* [*Derived variable*] = No ○ AND " ***More than 2 short GC therapies corresponding to rescue treatment*** *for the entire duration of the study* » [*Derived variable*] = No ○ AND " ***Taking at least one short GC therapy not corresponding to rescue treatment*** *for the entire duration of the study* » [*Derived variable*] = No ○ AND " *Clinical or biological* ***signs of adrenal insufficiency treated*** *with hydrocortisone at the end of the protocol* » [*Derived variable*] = No ○ AND " ***More than 2 weeks of GC for reasons other*** *than their illness"* [*Derived variable*] = No

2) Handling missing data

In the randomized population, those lost to follow-up, that is to say patients for whom the endpoint is missing, will be analyzed as a failure of the strategy (conservative approach). This result will be easy to collect, blindly.

For explanatory variables, descriptive analyzes will be conducted on available data. The number of non-missing subjects (n) will be specified for each explanatory variable.

3) Primary analysis of the primary endpoint (ITT)

The main endpoint will be compared in the two groups using a Chi2 test after verification of the application conditions: theoretical numbers greater than 5. In the event that the application conditions are not respected, a Fisher's exact test will be used.

The significance threshold for the tests is set at 0.05.

4) analysis of the primary endpoint (ITT)

Sensitivity analyzes of the primary outcome will include:

- An analysis on complete data (excluding subjects lost to follow-up and with missing data on the primary endpoint) (analysis 1)
- A stratified descriptive analysis (without testing) according to the duration of corticosteroid therapy before inclusion (≤ 2 years or > 2 years) (analysis 2)
- An analysis adjusted for potentially confounding criteria, based on a multiple logistic regression model adjusted for the randomization group as well as the initial characteristics if there is a significant imbalance between the comparison groups regarding the following characteristics (analysis 3):

- Duration of corticosteroid therapy ≤ 2 years / > 2 years [CRF p19]
- Duration of remission (in years) [Derived variable]
- Duration of corticosteroid therapy at 5 mg/day
- Duration of treatment with prednisone at 5 mg/day (in months) [Derived variable]
- Age at inclusion date [Derived variable]
- Sex [CRF p9]
- Duration of illness on inclusion (in years) [Derived variable]
- Rheumatoid factors (positive/negative) [Derived variable]
- Anti-CPP2 (positive/negative) [Derived variable]
- Presence of erosions [CRF p9]
- Charlson Index [Derived variable]
- HAQ score [Derived variable]
- Synthetic background treatment during the study [Derived variable]
- Biological background treatment during the study [Derived variable]
- DAS28 at inclusion [Derived variable]
- VAS fatigue at inclusion [CRF p16]

will describe the result by estimating an adjusted OR which will be presented with a 95% confidence interval.

This analysis will be carried out provided that the number of events (Success) is sufficient. Indeed, this analysis will only be implemented if a minimum of 10 events per variable included in the model are observed in the analysis population (Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis II. Accuracy and precision of regression estimates. Journal of Clinical Epidemiology. Dec 1995;48(12):1503 -10.).
A bivariate analysis exploring the association between the primary outcome and the factors listed above will be performed. This bivariate analysis will be based on percentage comparison tests (chi-square test or Fisher's exact test depending on the theoretical numbers) for the qualitative variables and on means comparison tests (Student's test, if normality and equality of variances) or distributions (non-parametric Mann-Whitney test) for quantitative variables.
The variables significantly associated with the primary endpoint in bivariate analysis (at the threshold of 0.20) will be introduced into a logistic regression model together with the weaning strategy (group A and group B). Log-linearity will be checked for each of the quantitative variables. If this assumption is not verified, we will transform the variables into categorical qualitative variables.

The significance threshold for the tests is set at 0.05.

5) Per-protocol analysis of the primary endpoint

This analysis will make it possible to verify the stability of the results.

The endpoint will be compared in the two groups according to the methods defined for the analysis of the endpoint in the ITT population (conservative approach). As a reminder, in the randomized population, those lost to follow-up, that is to say patients for whom the endpoint is missing, will be analyzed as a failure of the strategy (conservative approach).

ANALYZES OF SECONDARY JUDGMENT CRITERIA

1) Proportion of patients who could forego prednisone

Proportion of patients who were only able to wean off prednisone, even though they were prescribed a large amount of supplemental hydrocortisone. If the patient was able to wean himself off prednisone while still receiving hydrocortisone for biological adrenal insufficiency, for example, this will be considered a success.

Variable name	**Derivations**
Weaning off prednisone only (yes/no)	From the variable " *Has the patient received corticosteroid treatment with prednisone, prednisolone or methylprednisolone since the last visit* " [*CRFp110*] we define 2 modalities: • " If yes : ○ " **Has the patient received corticosteroid treatment with prednisone, prednisolone or methylprednisolone since the last visit** " = No • " Not if : ○ " **Has the patient received corticosteroid treatment with prednisone, prednisolone or methylprednisolone since the last visit** " = Yes

The proportion of patients weaned from glucocorticoid only will be compared in the two groups using a Chi2 test after verification of the application conditions: theoretical numbers greater than 5. In the event that the application conditions are not respected, a test Fisher's exact will be used.

The significance threshold for the tests is set at 0.05.

2) Proportion of patients with acute adrenal insufficiency at one year

The second secondary endpoint is the proportion of patients with acute adrenal insufficiency at one year. Acute adrenal insufficiency will be suspected in the following cases:

- fatigue .
- Digestive disorders, including nausea, diarrhea and abdominal pain.
- Myalgia.
- Psychiatric disorders and confusion.
- Dehydration.
- Unexplained fever.
- Weightloss.
- Hypotension.
- Biological abnormality such as hyponatremia, hyperkalemia, renal salt loss and hypoglycemia.

If acute adrenal insufficiency is suspected, an additional visit will be performed as an emergency and if acute adrenal insufficiency is confirmed, the patient will be hospitalized for treatment at the discretion of the investigator. If the serum cortisol dosage confirms clinical adrenal insufficiency, open therapy with hydrocortisone 20 mg/day will be started and an appointment with the endocrinologist will be made. If the serum level does not confirm adrenal insufficiency, hydrocortisone will be stopped and other causes of the symptoms will be sought. If no serious concomitant illness is found, the patient can resume treatment.
All reports of clinical adrenal insufficiency will be reviewed by an independent committee to decide whether, according to the report, the diagnosis of clinical adrenal insufficiency can be validated and recorded for the study. This deficiency will be reported as a serious adverse event.
It is anticipated that less than 1% of patients in this study will have clinical adrenal insufficiency.

The proportion of patients with acute adrenal insufficiency will be described in both groups. This result will be expressed as a percentage. We anticipate that less than 1% of patients included in this study will experience acute adrenal insufficiency and therefore no tests are planned for comparison.

For this analysis, the variable **"Acute adrenal insufficiency"** [CRF p111] will be described in the two groups.

3) Proportion of patients with biological adrenal insufficiency at one year

Proportion of patients with biological adrenal insufficiency.
Two blood tests will be scheduled with a Synacthène® test at 4 and 7 months. A pathological Synacthène® test will be diagnosed if, one hour after Synacthène®, serum cortisol is below 200 ng/mL or 600 nmol/L, or 20 µg/100 ml. In the event of an abnormal test, at the latest, another Synacthène® test will be carried out at M12.

Variable name	**Derivations**
Presence of biological adrenal insufficiency at one year (yes/no)	From the variables " *Test performed (Synacthen test) (yes/no)* " at M12 [*CRFp127*], " *Is the Synacthen test considered pathological? (yes /no)* " to M12 [*Derived variable*], " *Has hydrocortisone treatment been received in addition to the protocol since the last consultation?* » and " *Biological signs of chronic adrenal insufficiency* " [*CRFp111*], we define 2 modalities: " If yes : • " **Test carried out (Synacthen test)** " = Yes • AND " **Is the Synacthen test considered pathological?** » = Yes OR • " *Has hydrocortisone treatment been received in addition to the protocol since the last consultation? »* = Yes • AND " *Biological signs of chronic adrenal insufficiency* " = Yes " Not if : • " **Test carried out (Synacthen test)** " = No • AND " *Has hydrocortisone treatment been received in addition to the protocol since the last consultation? »* = No OR • OR if " **Test carried out (Synacthen test)** " = Yes • AND " **Is the Synacthen test considered pathological?** » = No • AND " *Has hydrocortisone treatment been received in addition to the protocol since the last consultation? »* = No

4) Proportion of Patients Needing Supplemental Prednisone to Control Flares

Proportion of patients who required salvage GC treatment during the protocol.

To meet this secondary endpoint, we will use the Treatment Compliance Variables at M4, M7, M9, M12, Vadd 1 and Vadd2 which will be combined to create a new binary derived variable as presented below :

Variable name	Derivation
Taking at least one long-term oral corticosteroid during the protocol (yes/no)	From the variable *Addition of a long-term corticosteroid orally to M4, M7, M9, M12, VAdd1 and Vadd2* [*CRFp43, p68, p93, p110*], Reason: *Treatment of a flare-up of the disease objectified by a rheumatologist* [*CRFp43, p68, p93, p110*], Reason: *Treatment of a flare-up by the attending physician* [*CRFp43, p68, p93, p110*] and Reason: *Self-medication by the patient due to pain related to their polyarthritis rheumatoid* [*CRFp43, p68, p93, p110*], we define two modalities " If yes : • *Addition of a long-term corticosteroid not orally to M4* = Yes AND ○ Reason: *Treatment of a disease flare-up documented by a rheumatologist at M4* = Yes ○ OR *Treatment of a flare-up by the attending physician at M4* = Yes ○ OR *Self-medication by the patient due to pain related to their rheumatoid arthritis at M4* = Yes OR • *Addition of a long-term corticosteroid not orally at M7* = Yes AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist at M7* = Yes ○ OR *Treatment of a flare-up by the attending physician at M7* = Yes ○ OR *Self-medication by the patient due to pain related to their rheumatoid arthritis at M7* = Yes OR • *Addition of a long-term corticosteroid not orally at M9* = Yes AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist at M9* = Yes ○ OR *Treatment of a flare-up by the attending physician at M9* = Yes ○ OR *Self-medication by the patient due to pain related to his rheumatoid arthritis at M9* = Yes OR • *Addition of a long-term corticosteroid not orally at M12* = Yes AND

	○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist at M12* = Yes ○ OR *Treatment of a flare-up by the attending physician at M12* = Yes ○ OR *Self-medication by the patient due to pain related to their rheumatoid arthritis at M12* = Yes OR • *Addition of a long-term oral corticosteroid to VAdd1* = Yes AND ○ Reason: Treatment of a flare-up of the disease documented by a rheumatologist *at VAdd1* = Yes ○ OR Treatment of a flare-up by the attending physician *at VAdd1* = Yes ○ OR Self-medication by the patient due to pain related to their rheumatoid arthritis *at VAdd1* = Yes OR • *Addition of a long-term oral corticosteroid to Vadd2* = Yes AND ○ Reason: Treatment of a flare-up of the disease documented by a rheumatologist *at VAdd2* = Yes ○ OR Treatment of a flare-up by the attending physician *at VAdd2* = Yes ○ OR Self-medication by the patient due to pain related to their rheumatoid arthritis *at VAdd2* = Yes It will take the value “No” in all other cases.
Taking at least one attack corresponding to rescue treatment during the protocol (yes/no)	From the *prescribed dosage variables, do they correspond to the rescue treatment provided for by the protocol* [*CRFp43, p68, p93, p110*], *the number of attacks since the last visit* [*CRFp43, p68, p93, p110*], Reason: *Treatment a flare-up of the disease documented by a rheumatologist* [*CRFp43, p68, p93, p110*], Reason: *Treatment of a flare-up by the attending physician* [*CRFp43, p68, p93, p110*] and Reason: *Self-medication by the patient for cause of pain related to rheumatoid arthritis* [*CRFp43, p68, p93, p110*], we define two modalities: " If yes : • *dosages correspond to the rescue treatment provided for in the protocol to be M4* = Yes • AND *The number of attacks since the last visit to M4* > 0 AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist M4* = Yes

	○ OR *Treatment of a flare-up by the attending physician at M4* = Yes ○ OR *Self-medication by the patient due to pain related to their rheumatoid arthritis at M4* = Yes OR • *dosages correspond to the rescue treatment provided for in the protocol to be M7* = Yes • AND *The number of attacks since the last visit to M7* > 0 AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist M7* = Yes ○ OR *Treatment of a flare-up by the attending physician at M7* = Yes ○ OR *Self-medication by the patient due to pain related to his rheumatoid arthritis at M7* = Yes OR • *dosages correspond to the rescue treatment provided for in the protocol to be M9* = Yes • AND *The number of attacks since the last visit to M9* > 0 AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist M9* = Yes ○ OR *Treatment of a flare-up by the attending physician at M9* = Yes ○ OR *Self-medication by the patient due to pain related to his rheumatoid arthritis at M9* = Yes OR • *dosages correspond to the rescue treatment provided for in the protocol to be M12* = Yes • AND *The number of attacks since the last visit to M12* > 0 AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist M12* = Yes ○ OR *Treatment of a flare-up by the attending physician at M12* = Yes ○ OR *Self-medication by the patient due to pain related to their rheumatoid arthritis at M12* = Yes OR • *dosages correspond to the rescue treatment provided for in the protocol to be Vadd1* = Yes • AND *The number of attacks since the last visit to Vadd1* > 0 AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist in Vadd1* = Yes

	○ OR *Treatment of a flare-up by the attending physician at Vadd1* = Yes ○ OR *Self-medication by the patient due to pain related to their rheumatoid arthritis in Vadd1* = Yes OR • *dosages correspond to the rescue treatment provided for in the protocol to be Vadd2* = Yes • AND *The number of attacks since the last visit to Vadd2* > 0 AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist in Vadd2* = Yes ○ OR *Treatment of a flare-up by the attending physician at Vadd2* = Yes ○ OR *Self-medication by the patient due to pain related to their rheumatoid arthritis in Vadd2* = Yes It will take the value "No" in all other cases.
Taking at least one short GC therapy not corresponding to rescue treatment throughout the duration of the study (yes/no)	From the variables *is it a one-off* [*CRFp43, p68, p93, p110*], *the number of attacks since the last visit* [*CRFp43, p68, p93, p110*], Reason: Treatment of a flare-up of the disease documented by a rheumatologist [*CRFp43, p68, p93, p110*], Reason: Treatment of a flare-up by the attending physician [*CRFp43, p68, p93, p110*] and Reason: Self-medication by the patient due to pain in relation to his rheumatoid arthritis [*CRFp43, p68, p93, p110*], we define two modalities: " If yes : • *Is this a point socket at M4* = Yes • AND *The number of attacks since the last visit to M4* > 0 AND ○ Reason: *Treatment of a disease flare-up documented by a rheumatologist at M4* = Yes ○ OR *Treatment of a flare-up by the attending physician at M4* = Yes ○ OR *Self-medication by the patient due to pain related to their rheumatoid arthritis at M4* = Yes OR • *Is this a point socket at M7* = Yes • AND *The number of attacks since the last visit to M7* > 0 AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist at M7* = Yes ○ OR *Treatment of a flare-up by the attending physician at M7* = Yes

	○ OR *Self-medication by the patient due to pain related to his rheumatoid arthritis at M7* = Yes OR • *Is this a point socket at M9* = Yes • AND *The number of attacks since the last visit to M9* > 0 AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist at M9* = Yes ○ OR *Treatment of a flare-up by the attending physician at M9* = Yes ○ OR *Self-medication by the patient due to pain related to his rheumatoid arthritis at M9* = Yes OR • *Is this a point socket at M12* = Yes • AND *The number of attacks since the last visit to M12* > 0 AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist at M12* = Yes ○ OR *Treatment of a flare-up by the attending physician at M12* = Yes ○ OR *Self-medication by the patient due to pain related to their rheumatoid arthritis at M12* = Yes OR • *Is this a one-off take at Vadd1* = Yes • AND *The number of attacks since the last visit to Vadd1* > 0 AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist in Vadd1* = Yes ○ OR *Treatment of a flare-up by the attending physician to Vadd1* = Yes ○ OR *Self-medication by the patient due to pain related to their rheumatoid arthritis in Vadd1* = Yes OR • *Is this a one-off take at Vadd2* = Yes • AND *The number of attacks since the last visit to Vadd2* > 0 AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist in Vadd2* = Yes ○ OR *Treatment of a flare-up by the attending physician to Vadd2* = Yes ○ OR *Self-medication by the patient due to pain related to their rheumatoid arthritis in Vadd2* = Yes It will take the value “No” in all other cases.

Taking at least one IV or IM corticosteroid treatment during the protocol (yes/no)	From the variables: *Was treatment with corticosteroids (other than hydrocortisone) by IV or IM received in addition to the treatment prescribed as part of the protocol* [*CRFp44, p69, p94, p111*], Reason: *Treatment 'a flare-up of the disease documented by a rheumatologist* [*CRFp44, p69, p94, p111*] and Reason: *Treatment of a flare-up by the attending physician* [*CRFp44, p69, p94, p111*], Two modalities are defined: " If yes : • *Was treatment with corticosteroids (other than hydrocortisone) IV or IM received in addition to the treatment prescribed as part of the protocol at M4* = Yes AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist at M4* = Yes ○ OR *Treatment of a flare-up by the attending physician at M4* = Yes OR • *Was treatment with corticosteroids (other than hydrocortisone) IV or IM received in addition to the treatment prescribed as part of the protocol at M7* = Yes AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist at M7* = Yes ○ OR *Treatment of a flare-up by the attending physician at M7* = Yes OR • *Was treatment with corticosteroids (other than hydrocortisone) IV or IM received in addition to the treatment prescribed as part of the protocol at M9* = Yes AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist at M9* = Yes ○ OR *Treatment of a flare-up by the attending physician at M9* = Yes OR • *Was treatment with corticosteroids (other than hydrocortisone) IV or IM received in addition to the treatment prescribed as part of the protocol at M12* = Yes AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist at M12* = Yes ○ OR *Treatment of a flare-up by the attending physician at M12* = Yes OR • *Was treatment with corticosteroids (other than hydrocortisone) IV or IM received in addition to the*

	treatment prescribed as part of the protocol at Vadd1 = Yes AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist in Vadd1* = Yes ○ OR *Treatment of a flare-up by the attending physician at Vadd1* = Yes OR • *Was treatment with corticosteroids (other than hydrocortisone) IV or IM received in addition to the treatment prescribed as part of the protocol at Vadd2* = Yes AND ○ Reason: *Treatment of a flare-up of the disease documented by a rheumatologist in Vadd2* = Yes ○ OR *Treatment of a flare-up by the attending physician at Vadd2* = Yes It will take the value "No" in all other cases.
P atient having received at least one corticosteroid infiltration during the protocol (yes/no)	From the variables: *Total number of infiltrations received in relation to RA over the duration of post-randomization follow-up* [Derived Variable], we define two modalities: " If yes : • *Total number of infiltrations received in relation to RA over the duration of post-randomization follow-up* > 1 " Not if : • *Total number of infiltrations received in relation to RA over the duration of post-randomization follow-up* =0
Need for GC salvage treatment during protocol (yes/no)	*From the following derived variables: Taking at least one long-term oral corticosteroid during the protocol (yes/no)* [Derived Variable], *Taking at least one attack corresponding to rescue treatment during the protocol (yes /no)* [Derived Variable], *Taking at least one short GC therapy not corresponding to rescue treatment for the entire duration of the study (yes/no)* [Derived Variable], *Taking at least one treatment by IV or IM corticosteroid during the protocol (yes/no)* [Derived Variable], *Patient having received at least one corticosteroid infiltration during the protocol (yes/no)* [Derived Variable], we define two modalities: " If yes : • *Taking at least one long-term oral corticosteroid during the protocol* = Yes • OR *Taking at least one attack corresponding to rescue treatment during the protocol* = Yes

	• OR *Taking at least one short GC therapy not corresponding to rescue treatment for the entire duration of* the study = Yes • OR Taking *at least one IV or IM corticosteroid treatment during the protocol* = Yes • OR *Patient having received at least one corticosteroid infiltration during the protocol* = Yes " Not if : • *Taking at least one long-term oral corticosteroid during the protocol* = No or missing • AND *Taking at least one attack corresponding to rescue treatment during the protocol* = No or missing • AND *Taking at least one short GC therapy not corresponding to rescue treatment for the entire duration of* the study = No or missing • AND Taking *at least one IV or IM corticosteroid treatment during the protocol* = No or missing • AND *Patient having received at least one corticosteroid infiltration during the protocol* = No or missing

The proportion of patients supplemented with prednisone will be compared in the two groups using a Chi2 test after verification of the application conditions: theoretical numbers greater than 5. In the event that the application conditions are not respected, an exact test of Fisher will be used.

The significance threshold for the tests is set at 0.05.

5) Proportion of patients who received intra-articular injections

Proportion of patients who required intra-articular or periarticular GC injection during RA-related protocol.

Variable name	**Derivations**
Intra-articular injections (yes/no)	From the variables " *Total number of infiltrations received in relation to RA over the duration of post-randomization follow-up* " [Derived variable], we define two modalities: " If yes : • " *Total number of infiltrations received in relation to RA over the duration of post-randomization follow-up* " ≥ 1 " Not if : • " *Total number of infiltrations received in relation to RA over the duration of post-randomization follow-up* " = 0

The proportion of patients having received intra-articular injections will be compared in the two groups using a Chi2 test after verification of the application conditions: theoretical numbers greater than 5. In the event that the application conditions are not respected , a Fisher exact test will be used.

The significance threshold for the tests is set at 0.05.

Off-protocol analysis:

For exploratory purposes, without implementing a statistical test, we will carry out a descriptive analysis of secondary judgment criteria no. 4 and no. 5 in a combined manner.

Variable name	**Derivations**
Intra-articular injections and Need for short GC salvage treatment (yes/no)	From the variables " *Need for a short rescue treatment with GC during the protocol* " [Derived variable] and " *Intra-articular injections* " [Derived variable], we define two modalities: " If yes : • " *Need for short GC salvage treatment during protocol* " = Yes OR • " *Intra-articular injections* " = Yes " Not if : • " *Need for short GC salvage treatment during protocol* " = No AND • " *Intra-articular injections* " = No

The results will be presented using numbers and percentages.

6) Proportion of patients who had at least one relapse during the protocol

Proportion of patients with a flare-up confirmed by the clinician. In the event of flare-up symptoms, the patient will have an additional visit to their center. For DAS28 >3.2, a surge will be confirmed. A flare will also be diagnosed if the DAS28 is >3.2 at any scheduled visit.

Variable name	Derivations
Disease outbreak (yes/no)	Based on the variables " *Has the patient had a flare-up of his illness documented by a doctor (defined by a DAS28 ≥ 3.2) since the last visit? (yes /no) "* [*CRFp45, p70, p95, p112, p137, p148*], we define two modalities: " If yes : • " **Has the patient had a flare-up of his illness documented by a doctor since the last visit?** » = Yes to M4 • OR " **Has the patient had a flare-up of his illness documented by a doctor since the last visit?** » = Yes to M7 • OR " **Has the patient had a flare-up of his illness documented by a doctor since the last visit?** » = Yes to M9 • OR " **Has the patient had a flare-up of his illness documented by a doctor since the last visit?** » = Yes to M12 • OR " **Has the patient had a flare-up of his illness documented by a doctor since the last visit?** » = Yes to ADDITIONAL VISIT 1 • OR " **Has the patient had a flare-up of his illness documented by a doctor since the last visit?** » = Yes to ADDITIONAL VISIT 2 " Not if : • " **Has the patient had a flare-up of his illness documented by a doctor since the last visit?** » = No or missing at M4 • AND " **Has the patient had a flare-up of his illness documented by a doctor since the last visit?** » = No or missing at M7 • AND " **Has the patient had a flare-up of his illness documented by a doctor since the last visit?** » = No or missing at M9 • AND " **Has the patient had a flare-up of his illness documented by a doctor since the last visit?** » = No or missing at M12 • AND " **Has the patient had a flare-up of his illness documented by a doctor since the last visit?** » = No or missing at ADDITIONAL VISIT 1 • AND " **Has the patient had a flare-up of his illness documented by a doctor since the last visit?** » = No or missing at ADDITIONAL VISIT 2

The proportion of patients having had at least one flare-up of the disease (defined by a DAS28 ≥ 3.2) will be compared in the two groups using a Chi2 test after verification of the application conditions: theoretical numbers greater than 5. In the event that the application conditions are not respected, a Fisher's exact test will be used.

7) Area under the curve of the means of the FLARE self-questionnaire at one year

FLARE is an approved self-assessment questionnaire that will be completed at each visit and in case of home FLARE by the patient. Results are expressed as continuous data.

For the analysis of the FLARE doctor questionnaire:

In the ITT population, we will carry out a mixed linear model for repeated data modeling the results of the FLARE questionnaires as a function of the time of administration of the questionnaire (M1 to M12) and the randomization group. We will describe the evolution of the results according to the time of administration of the questionnaire by a graphical representation of these models, in which the time of administration (visit) will be considered as a categorical variable and in which we will take into account a potential interaction between the time of administration and the randomization group.

If the evolution of scores over time is linear and there is no interaction between the time of administration and the randomization group, we will carry out models with the time of administration as a continuous variable (in month). In this case, we will describe the result by estimating a coefficient β with a 95% confidence interval, corresponding to the average difference in scores between the groups between M1 and M12.

If these two conditions are not met (absence of interaction and non-linearity of the relationship), the results of the FLARE questionnaires will be described for each arm at M4 and M7. The difference in distribution between the two arms will be tested using a two-sided Student's test (or a Wilcoxon test if the conditions for applying the Student's test are not verified) for each of these 2 visits. The significance threshold for the tests is set at 0.05.
In the event of missing data on one of the items, the value of the missing item will be replaced by the median value of the item at the visit concerned according to the patient's randomization group.

One approach will be to add up the scores at each time. We will therefore obtain a cumulative sum of the scores. The difference in distribution of the cumulative sums between the two arms will be tested using a two-sided Student's test (or a Wilcoxon test if the conditions for applying the Student's test are not verified) for each of these 2 visits. The significance threshold for the tests is set at 0.05.
In the event of missing data we will use the following imputation methods:

- In the event of missing data on one of the items, the value of the missing item will be replaced by the median value of the item at the visit concerned according to the patient's randomization group.
- In the event of missing data at one or more visits, we will impute the non-missing values of the randomization group from which the patient came at the visit in question by the median value.

Patient FLARE scores should have a large number of missing data (questionnaires poorly completed during follow-up). These scores present will be described in each group using the mean, standard deviation, median and interquartile range. In the event of missing data on one of the items, the value of the missing item will be replaced by the median value of the item at the visit concerned according to the patient's randomization group.

No bivariate analysis will be performed on these scores.

8) Proportion of patients in remission or at low activity level according to the DAS28 at 7 and 12 months

Proportion of patients in remission and with low disease activity at 7 months and one year.
Patients with a DAS28 < 2.6 will be considered in remission, patients with a DAS28 between 2.6 and 3.2 will be considered in LDA.

The DAS28 formula is as follows:

$$DAS28 = (0.56 * sqr(TJC)) + (0.28 * sqr(SJC)) + (0.7 * ln(VS)) + (0.014 * GH)$$

Where TJC = Number of painful joints [*CRFp72, p114*]
SJC = Number of swollen joints [*CRFp72, p114*]
VS = the sedimentation rate [*CRFp84, p126*]
GH = overall health represents the patient's assessment of disease activity on a scale of 0 to 100 where 100 corresponds to maximum activity [*CRFp81, p123*].
The DAS28 is calculated automatically in the e-CRF.

Variable name	**Derivations**

Remission according to DAS28 (Yes No)	From the DAS28 scores at M7 and M12 (variable present in the database or programmed), we define two modalities:
	• " If yes :
	  ○ DAS28 < 2.6
	• " Not if :
	  ○ DAS28 ≥ 2.6
	For each of times M7 and M12, a variable will be created using the same methods.

Low level of activity according to DAS28 (yes/no)	From the DAS28 scores at M7 and M12 (variable present in the database or programmed), we define two modalities:
	• " If yes :
	  ○ DAS28 ≥ 2.6 and < 3.2
	• " Not if :
	  ○ DAS28 ≥ 3.2
	  ○ OR if DAS28 > 2.6
	For each of times M7 and M12, a variable will be created using the same methods.

Remission or low level of activity according to DAS28 (Yes No)	From the variables " *Remission according to DAS28* " and " *Low activity level according to DAS28* " [Derived variable], we define two modalities: " If yes : • " *Remission according to DAS28* " = Yes OR • " *Low activity level according to DAS28* " = Yes " Not if : • " *Remission according to DAS28* " = No **AND** • " *Low level of activity according to DAS28* " = No For each of times M7 and M12, a variable will be created using the same methods.

The proportion of patients in remission or at a low level of activity will be compared in the two groups using a Chi2 test after verification of the application conditions: theoretical numbers greater than 5. In the event that the application conditions are not not respected, a Fisher exact test will be used.

The significance threshold for the tests is set at 0.05.

9) HAQ-DI score at 4, 7 and 12 months

Functional impairment assessed by the Health Assessment Questionnaire (HAQ) at baseline, 4, 7 months and one year.
The HAQ will be calculated at baseline [*CRFp25-26*], at 4 [*CRFp49-50*], 7 months [*CRFp74-76*] and one year [*CRFp116-117*], and is expressed as continuous data.

The HAQ-DI SCORE at inclusion 4, 7 and 12 months will be compared in the two groups using a Student t test if the application conditions are met and a non-parametric Mann-Whitney Wilcoxon test otherwise.

The significance threshold for the tests is set at 0.05.

10) RAID score at 4, 7 and 2 months

Patient-reported outcomes assessed by the Rheumatoid Arthritis Impact of Disease (RAID) questionnaire at baseline, 4, 7 months, and 1 year.
The RAID questionnaire will be calculated at baseline [*CRFp27*], 4 [*CRFp51*], 7 [*CRFp76*] and 12 [*CRFp118*] months and is expressed as continuous data.

The RAID SCORE at inclusion, 4, 7 and 12 months will be compared in the two groups using a Student t test if the application conditions are met and a non-parametric Mann-Whitney Wilcoxon test otherwise.

The significance threshold for the tests is set at 0.05.

11) EQ-5D score at 4, 7 and 12 months

The EuroQol 5-Dimension Descriptive System (EQ-5D) will be completed at baseline [*CRFp31*], at 4 [*CRFp55*], 7 [*CRFp80*] and 12 [*CRFp27*] months. The EQ-5D questionnaire will be calculated at baseline, after 4, 7 and 12 months and is expressed as continuous data.

The EQ-5D scores at inclusion 4, 7 and 12 months will be compared in the two groups using a Student t test if the application conditions are met and a non-parametric Mann-Whitney Wilcoxon test otherwise.

The significance threshold for the tests is set at 0.05.

12) FACIT-F score at 4, 7 and 12 months

Functional Assessment of Chronic Disease Therapy - Fatigue Scale (FACIT-F): The FACIT-F questionnaire explores patient-reported fatigue. It will be completed at baseline [*CRFp28-30*], at 4 [*CRFp52-54*], 7 [*CRFp77-79*] and 12 [*CRFp119-121*] months. It will be expressed as continuous data.

The responses to the FACIT-F questionnaire at inclusion 4, 7 and 12 months will be compared in the two groups using a Student t test if the application conditions are met and a non-parametric Mann-Whitney Wilcoxon test in the case. opposite.

The significance threshold for the tests is set at 0.05.

13) Proportion of serious adverse events at 1 year

The next secondary outcome is the proportion of patients who experienced at least one serious adverse event over a 1-year period.

Variable name	**Derivations**
Serious adverse events (yes/no)	From the tables " *Adverse events 1/3, 2/3, 3/ 3 "* [*CRFp169-171*] and the variable " *Severity (serious/non-serious) "* present in these same tables, we define 2 modalities: " If yes : • Event title is not missing • AND if "G *ravité "* = serious " Not if : • Event title is not missing • AND if "G *delighted "* = not serious • OR if the event title is missing

Depending on the numbers, the proportion of patients having had one or more serious adverse events can be compared between the two groups using a Chi2 test after checking the conditions of application: theoretical numbers greater than 5. In the case where the conditions applications would not be respected, a Fisher exact test will be used.

The significance threshold for the tests is set at 0.05.

SECURITY ANALYSIS

The population for the safety analysis is composed of all included and randomized patients who received at least one dose of treatment (prednisone and hydrocortisone placebo / Hydrocortisone and prednisone placebo).
Patients will be analyzed in the weaning strategy group actually received (particularly in the event of an error in allocation of treatment and placebo).
All expected or unexpected serious adverse events, and all unexpected non-serious adverse events, occurring from the date of signing the consent, during the duration of the study and until the end of the participant's follow-up provided for by the research (1 year); or up to 24 hours after stopping the experimental treatment (prednisone or hydroxycortisone) in the event of premature exit from the study, will be collected and will be included in an adverse event form after coding according to the dictionary. standardized medical MedDRA.
Adverse events will be described according to the different hierarchical levels of the MedDRA classification. The listing of these adverse events will be presented after grouping into “Preferred Term” and organization by “System-Organ Class”. The listing will contain the following information:

- identifier of the subject and center,
- date and time of start of the adverse event,
- date and time of end of the adverse event (or mention of the persistence of the adverse event),
- description of the event (“Reported Term” and “Preferred Term”),
- gravity ,
- attributability to the test or the treatment of the test,
- action on the processing of the test,
- other action and evolution.

Will be presented by arm (prednisone and hydrocortisone placebo / Hydrocortisone and prednisone placebo):

- The incidence of adverse events according to their causality and severity.
- The incidence of adverse events leading to treatment discontinuation.
- Adverse events occurring between signing the consent and the first use of the experimental technique.

TECHNICAL DETAILS

Data analysis will be carried out using Stata software (Statistical Software: Release 18.0 Stata Corporation, College Station, Texas, USA). The statistical analysis will be carried out by a biostatistics engineer, under the responsibility of an epidemiologist from the Methodological Research Support Unit (USMR).

Data verification:
Before any analysis, a phase of checking for missing, aberrant or inconsistent data will be carried out. At the end of this the corrected database will be frozen. The analyzes will be carried out on this frozen base.

APPENDICES

Table 1: List of patients with a socket error in the indicated levels [CRF p45] at M4

Patient ID	center	Number of prednisone capsules consumed at level 1 V2	Number of prednisone capsules consumed at level 2 V2	Number of prednisone capsules consumed at level 3 V2	Number of hydrocortisone capsules consumed at level 1 V2	Number of hydrocortisone capsules consumed at level 2 V2	Number of hydrocortisone capsules consumed at level 3 V2	Commentary V2	Principal investigator's decision
01-002	1	28	31	8	47	55	12	FORGOTTEN SEVERAL TIMES TO TAKE HYDROCORTISONE OR PLACEBO AT NOON	no respect
01-003	1	31	31	30	53	46	25	CAME BEFORE THE THEORETICAL DATE BECAUSE NOT AVAILABLE AFTER LEFT WITH THE BOX OF MONTH 3. WRONGLY TAKEN THE MIDI HYDROCORTISONE CPS	no respect
01-004	1	31	27	31	63	54	62	WRONG TAKE OF HYDORCORTISONE FORGOTTEN TO TAKE AT 12:00	no deviation
01-005	1	35	35	25	70	70	50	TOOK ALL THE CPS FROM THE M1 BOTTLES THEN ALL THE CPS FROM THE M2 BOTTLE AND THEN DISREGED THE CPS FROM THE M3 BOTTLES	no deviation
01-007	1	35			0			DID NOT BRING BACK THE TREATMENT BOXES AND FINISHED ALL THE CPS IN EACH VIAL EACH TIME CONTRARY TO OUR RECOMMENDATIONS	no deviation
01-010	1	31	31	20	61	62	63	DURING THE M3 FORGOTTEN TO TAKE THE HDROCORTISONE FOR 3 DAYS AT 12:00	no deviation
02-002	2	35	35	35	70	70	70	LEVEL 3 DO NOT RETURN BECAUSE TOO EARLY. GO FINISH THE BOX	no deviation

Patient ID	center	Number of prednisone capsules consumed at level 1 V2	Number of prednisone capsules consumed at level 2 V2	Number of prednisone capsules consumed at level 3 V2	Number of hydrocortisone capsules consumed at level 1 V2	Number of hydrocortisone capsules consumed at level 2 V2	Number of hydrocortisone capsules consumed at level 3 V2	Commentary V2	Principal investigator's decision
02-004	2	24	31	15	41	63	27	RESUMPTION OF DISEASE ACTIVITY	no respect
03-001	3	29	34	28	49	51	39	YES AT THE 3 LEVEL LEVEL - THERE REMAINS 26 HYDROCORTISONE CAPSULES NOT TAKEN BY THE PATIENT - SEVERAL FORGOTTEN	no respect
03-004	3	31	31	33	59	60	62	OVER 3 MONTHS: 7 MIDI CAPSULES FORGOTTEN TO TAKE	no deviation
05-002	5	35	34	23	69	66	45	THE PATIENT FINISHED THE VIALS BEFORE CHANGING LEVELS	no deviation
06-006	6	17	0	0	36	0	0	DISCONTINUATION OF STUDY TREATMENT ; RESUMPTION 5 MG CORTISONE LONG SHORT	no respect
07-001	7	30	35	24	54	69	49	THE PATIENT NO LONGER REMEMBERS VERY WELL OF THEIR TAKES IN AUGUST BUT FOLDED THE NOTEBOOK AS IF EVERYTHING HAD BEEN TAKEN	no deviation
07-002	7	31	31	29	70	47	64	THE PATIENT GROUPED THE CAPSULES FROM THE HYDROCORTISONE BOTTLE, COMPLIANCE DIFFICULT TO VERIFY	no respect
07-004	7	31	31	35	62	56	66	THE PATIENT OFTEN FORGOTTEN TO TAKE THEIR CAPSULES, SO THEY WERE TAKEN AT ANY TIME	no respect
08-002	8	35	35	35	70	70	58	ERROR AT LEVEL 3 (PREDNISONE)	no deviation
11-002	11	31	30	26	61	63	53	THERE ARE MISSING CAPSULES IN THE HYDROCORTISONE VIALS OF LEVELS 1 - 2 AND 3 BUT THE	no deviation

Patient ID	center	Number of prednisone capsules consumed at level 1 V2	Number of prednisone capsules consumed at level 2 V2	Number of prednisone capsules consumed at level 3 V2	Number of hydrocortisone capsules consumed at level 1 V2	Number of hydrocortisone capsules consumed at level 2 V2	Number of hydrocortisone capsules consumed at level 3 V2	Commentary V2	Principal investigator's decision
								PATIENT SAYS THAT HE TOOK THE RIGHT NUMBER. LOST?	
11-003	11	31	32	23	61	62	44	LEVEL 1: 1 GEL FROM THE HYDROCORTISONE BOTTLE FORGOTTEN ON 07/18/18 - LEVEL 2: ONE DAY OF PROCESSING THE 2 VIALS TAKEN IN MORE THAN WHAT WAS PLANNED ON 08/28/18 AND 1 GEL FROM THE FORGOTTEN HYDROCORTISONE BOTTLE	no deviation, but check the duration of stage 3 or delays between M1 and M4
11-004	11	32	31	31	60	62	59	STAGE 1: FORGOTTEN TO TAKE 1 GEL IN THE PREDNISONE BOTTLE AND FORGOTTEN TO TAKE 2 GEL IN THE HYDROCORTISONE BOTTLE. LEVEL 3: LOST 1 GEL FROM THE PREDNISONE BOTTLE AND FORGOTTEN TO TAKE 1 GEL FROM THE HYDRO BOTTLE	no deviation
11-005	11	30	27	34	52	43	51	M1 HYDROCORTISONE 10 FORGOTTEN MIDI TAKES/PREDNISONE 1 GEL FORGOTTEN TAKE-M2 HYDROCORTISONE 19 FORGOTTEN MIDI TAKES/PREDNISONE 4 FORGOTTEN TAKES-M3 HYDRO 11 FORGOTTEN MIDI TAKES/PRED 3 GEL SUP TAKES	no respect
11-006	11	31	32	25	55	62	52	M1 HYDROCORTISONE 7 FORGET THE MIDI-M2 PREDNISONE 1GEL	no deviation

Patient ID	center	Number of prednisone capsules consumed at level 1 V2	Number of prednisone capsules consumed at level 2 V2	Number of prednisone capsules consumed at level 3 V2	Number of hydrocortisone capsules consumed at level 1 V2	Number of hydrocortisone capsules consumed at level 2 V2	Number of hydrocortisone capsules consumed at level 3 V2	Commentary V2	Principal investigator's decision
11-008	11	31	30	26	60	59	51	EGAREE-M3 HYDROCORTISONE 2 FORGET THE MIDI/PREDNISONE 2 FORGET M 1 2 GEL FROM THE HYDROCORTISONE-PLACEBO BOTTLE FORGOTTEN TO TAKE / M2 1 GEL FROM THE HYDROCORTISONE-PLACEBO BOTTLE FORGOTTEN TO TAKE / M3 SAME M2	no deviation
14-002	14	31	31	31	62	61	62	1 CAPSULE OF HYDROCORTISONE TYPE IS IN THE CARTON BUT OUTSIDE THE BOTTLE.	no deviation
16-007	16		0	25		0	65	ERROR IN TAKEN IN THE LEVELS DID NOT UNDERSTAND HOW TO TAKE THE TREATMENTS	no respect
18-002	18	35	35	19	70	53	55	LEVEL 2: ONLY 26 1/2 DAYS OF TREATMENT TAKEN FOR HYDROCORTISONE	no respect

Table 2: List of patients with a socket error in the indicated levels [CRF p70] at M7

Patient ID	center	Number of prednisone capsules consumed at level 4 V3	Number of prednisone capsules consumed at level 5 V3	Number of prednisone capsules consumed at level 6 V3	Number of hydrocortisone capsules consumed at level 4 V3	Number of hydrocortisone capsules consumed at level 5 V3	Number of hydrocortisone capsules consumed at level 6 V3	Commentary V3	Principal investigator's decision
01-003	1	32	0	0	67	64	61	HYDRO BOTTLE. LEVEL 6 BACK ON 01/19 LAST DOSE TAKEN ON 01/18	no deviation
01-004	1	32	0	0	32	28	12	NO ERROR BUT FINISHED LEVEL 6 BEFORE THE THEORETICAL DATE	no respect
01-007	1	35	0	0	35	35	0	FINISHED EACH BOTTLE BEFORE THE NEXT DESPITE EXPLANATIONS	no deviation
01-008	1	28	0	0	28	31	35	SYNACTHENE TEST REFUSED BY THE PATIENT ONLY HAD 0 TIME	no deviation
02-003	2	31			30	29	20	RAS	no deviation
03-001	3	32	0	0	0	0	0	31 DAYS OF TAKING AT LEVEL 4 (RETURN OF 3 CAPSULES OUT OF 35 DATA)	no deviation
03-004	3	31	0	0	0	0	0	SOME HYDROCORTISONE TABLETS FORGOTTEN AT SOME NOONS	no deviation
03-007	3	30	0	0	29	27	0	THE PATIENT AT MONTH 4 TOOK HYDROCORTISONE/PLACEBO FROM BOTTLE 5, AND AT MONTH 5 TOOK BOTTLE 6 (HYDROCORTISONE/PLACEBO)	no respect
06-003	6	31			31	11	0	NO ERROR: STOP PROCESSING OF THE ACTIVE PR STUDY	no respect
07-002	7	31			23	32	35	THE PATIENT MIXED THEIR CAPSULES INTO THE BOTTLES	no deviation
11-002	11	32	0	0	30	31	31	LEVEL 4: 1 HYDROCORTISONE GEL FORGOTTEN TO TAKE AND 1 PREDNISONE GEL LOST	no deviation

Patient ID	center	Number of prednisone capsules consumed at level 4 V3	Number of prednisone capsules consumed at level 5 V3	Number of prednisone capsules consumed at level 6 V3	Number of hydrocortisone capsules consumed at level 4 V3	Number of hydrocortisone capsules consumed at level 5 V3	Number of hydrocortisone capsules consumed at level 6 V3	Commentary V3	Principal investigator's decision
11-003	11	30	0	0	31	34	26	M4 1GEL PRED OULI/M5 1 LOST GEL AND 2 SOCKETS IN +/M6 1 SOCKET IN +	no deviation
11-004	11	31	0	0	31	30	27	LEVEL 5: 1 FORGOTTEN FREEZE - LEVEL 6: 1 FORGOTTEN FREEZE	no deviation
11-005	11	35	0	0	7	0	0	M4 PREDNISONE-PLACEBO BOTTLE CONTINUATION OF TT BEYOND 31 DAYS: +4 DAYS	no deviation but check if the patient took hydrocortisone during the 3 months (question specifically asked)
11-006	11	32	0	0	32	32	6	1 GEL FROM EACH BOTTLE TAKEN IN ADDITION TO M4 - 1 GEL TAKEN IN ADDITION TO M5	no deviation
11-007	11	35			5			LEVEL 4 PREDNISONE 4 GEL BOTTLE TAKEN IN ADDITION AT D32-33-34 ET35	no deviation but check if the patient took hydrocortisone during the 3 months (question specifically asked)

Patient ID	center	Number of prednisone capsules consumed at level 4 V3	Number of prednisone capsules consumed at level 5 V3	Number of prednisone capsules consumed at level 6 V3	Number of hydrocortisone capsules consumed at level 4 V3	Number of hydrocortisone capsules consumed at level 5 V3	Number of hydrocortisone capsules consumed at level 6 V3	Commentary V3	Principal investigator's decision
18-001	18	35	0	0	30	28	29	TAKING PREDNISONE 1MG/PB FOR 6 DAYS INSTEAD OF HYDROCORTISONE/PB	no deviation

SIGNATURE PAGE

Function	Name, CONTACT INFORMATION	DATE	Signature
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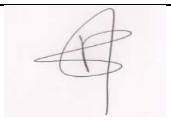
Methodologist	Professor BONGARD Vanina Methodological Research Support Unit (USMR), Epidemiology Department, Toulouse University Hospital. Email: vanina.bongard@univ-tlse3.fr	06/29/2023	
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