Treatment of IGA nEphropathy according to Renal lesions (TIGER)

BIOMEDICAL RESEARCH PROTOCOL RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

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SIGNATURE page for a biomedical research PROTOCOL

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The research will be carried out in accordance with the protocol, with current good practices and with the legislative and regulatory provisions in force.

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The research received a favourable opinion from the CPP Ile de France III on 27/03/2018 and authorisation from the ANSM on 02/05/2018

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1 SUMMARY

Full title	Treatment of IGa nEphropathy according to Renal lesions
Acronym	TIGER
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Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Currently, IgAN treatment recommendations are only based on clinico-biological parameters. Steroids therapy appears to have a major role in IgAN treatment, but previous studies evaluating steroids lacked of optimal control group and reproducible evaluation criteria. No prospective study (including ongoing studies) with optimal RAS blockade had included renal pathology in patients selection criteria, although histological evaluation improves patients prognosis prediction. Until now, the lack of a reliable histological classification has precluded the use of histological lesions to evaluate IgAN prognosis and treatment. Given the recently identified major prognostic role of histological lesions in IgAN, we propose to introduce renal pathology to guide the treatment of IgAN in a multicenter study, using currently validated evaluation criteria of chronic kidney disease progression.
Primary objective and assessment criterion	**Primary objective** To evaluate the efficacy of early corticotherapy + RAS blockade (versus RAS blockade alone) after 2 years of evolution in IgAN patients with severe histological lesions **Assessment criterion** <u>Failure at 24 months, defined as:</u> - proteinuria/creatininuria ratio (PCR) > 0,5 g/g or mGFR < 80% of initial mGFR (or eGFR if unavailable) - or loss of more than 10 ml/min/1,73m^2 of initial mGFR (or eGFR if unavailable) - or end stage renal disease (ESRD) - or renal transplantation - or death
Secondary objectives and assessment criteria	**Secondary objectives** - to evaluate the efficacy of early corticotherapy + RAS blockade (versus RAS blockade alone) at 6 and 12 months of evolution - to compare the evolution of histological lesions between treatment groups at 12 months - to compare the evolution of measured GFR (mGFR) between treatment groups at 12 and 24 months (or estimated GFR (eGFR) if unavailable) - to compare the evolution of proteinuria in each group - to compare the quality of life in each therapeutic group - to assess the tolerance of treatments of each therapeutic group - to identify prognosis markers of failure at 24 months **Assessment criteria** <u>Failure at 6 months will be defined as:</u> - PCR > 0.75 g/g

	- or PCR > 0.5 g/g and >30% of initial PCR - or eGFR < 80% of initial eGFR - or ESRD - or renal transplantation - or death. <u>Failure at 12 months will be defined as:</u> - PCR > 0.75 g/g - or PCR > 0.5 g/g and > 30% of initial PCR - or mGFR < 80% of initial mGFR (or eGFR if unavailable) - or ESRD - or renal transplantation - or death. <u>Histological lesions evolution at 12 months :</u> The evolution of histological lesions will be assessed as the proportion of patients of both therapeutic group with persistent severe histological lesions in repeat kidney biopsy at 12 months. <u>Measured GFR (mGFR or eGFR if unavailable) evolution:</u> The evolution of GFR at 12 and 24 months will be assessed as: - the absolute value of GFR - the absolute difference of GFR from the baseline - the annual degradation (ml/min /1,73m^2/year) of GFR during the 24 months <u>Proteinuria evolution</u> The evolution of proteinuria will be assessed as : - the absolute value of proteinuria at 12 and 24 months - the absolute difference of proteinuria from baseline at 12 and 24 months <u>Identification of prognosis markers of failure at 24 months:</u> Clinical, histological, and biological data (including PCR ratio, eGFR and mGFR, renal histological lesions) will be compared between patients with or without failure. <u>Comparison of side effects in each therapeutic group.</u> <u>Comparison of life quality scale in each therapeutic groupwith SF36 scale at 12 and 24 months</u>
Experimental design	Multicenter, open-labelled randomized phase III trial
Population involved	≥18 years IgA Nephropathy patients
Inclusion criteria	a. Age ≥18 years b. IgAN diagnosed on renal biopsy < 45 days c. PCR ratio >0.75 g/g (within 30 days before or after the renal biopsy) d. Renal biopsy with at least 8 glomeruli, disclosing at least 2 criteria among: • mesangial proliferation (according to Oxford criteria) • endocapillary proliferation (according to Oxford criteria) • tubulointerstitial fibrosis (according to Oxford criteria) >25% of the biopsy • segmental glomerulosclerosis (according to Oxford criteria)

	• ≥10% cellular/fibrocellular crescents. e. Patient with Social Security System Insurance or CMU f. Patient having signed an informed consent
Non-inclusion criteria	a. >30% increase of serum creatinine within 15 days after starting RAS blockade therapy b. >50% cellular/fibrocellular crescents or >50% tubulointerstitial fibrosis or >50% globally sclerotic glomeruli c. >50% plasma creatinine increase within the last 3 months before the renal biopsy d. Nephrotic syndrome with minimal change disease and IgA deposits e. eGFR <20 ml/min/1,73m^2 (CKD-EPI formula) within 30 days before or after the renal biopsy f. Uncontrolled blood pressure (Systolic blood pressure >180 mmHg or diastolic blood pressure > 110 mmHg) g. Previous corticosteroids treatment (>20 mg/d during more than 15 days, within the last 3 months before the renal biopsy) h. Pregnancy or breast feeding or women without sufficient contraception i. Secondary known forms of IgAN j. Henoch-Schoenlein purpura k. Additional other chronic renal disease l. Contraindication for immunosuppressive therapy, including active intestinal bleeding, active gastric or duodenal ulcer; active infection; any malignancy in a last years before the inclusion; severe psychiatric disease; living vaccines; anti-inflammatory dosages of acetylsalicylic acid m. Contraindication for RAS blockade therapy n. Known allergy or intolerance to corticoids or lactose o. Organ transplant patient **The absence of measured GFR availability on the site is not an exclusion criterion.**
Treatment being tested	3 IV pulses steroids followed by oral steroids for 4 months
Benchmark treatment	Renin angiotensin system blockade
Risks added by the research	*B*
Number of subjects chosen	122
Number of centres	27
Research period	Inclusion period : 24 months Participation period : 24 months+ 21 days max Total research period : 48 months
Number of inclusions expected per centre and per month	0.3
Funding source	French Health Ministery
Data Safety Monitoring Board anticipated	Non

2 SCIENTIFIC JUSTIFICATION FOR THE RESEARCH

2.1 Hypothesis for the research

In Immunoglobulin A (IgA) nephropathy, the deleterious prognosis of severe histological lesions can be improved with early corticosteroid therapy.

2.2 Description of knowledge relating to the hypothesis for the research

Immunoglobulin A nephropathy (IgAN) is defined by predominant IgA deposits localized in the mesangium area of glomeruli, associated with IgG, IgM or C3 deposits. It is suggested that these deposits lead to mesangial proliferation, podocyte injury, glomerulosclerosis and then tubulo-interstitial fibrosis and chronic kidney disease.

Epidemiology

IgAN is the most common primary glomerulonephritis in the world. It is responsible of about 4% of new cases of end stage renal disease (ESRD) each year in France, although IgAN is probably underdiagnosed because of the frequent lack of renal histological examination. In autopsy series or allograft biopsies performed before transplantation, mesangial IgA deposits are detected in 5 to 20% of all cases[1,2]; full-blown IgAN (mesangial IgA deposits with cellular proliferation and C3 deposits) is observed in 1,6% of allograft biopsies before implantation in Japan[2].

IgAN evolution is highly variable, ranging from spontaneous remission to a rapidly progressive course. Spontaneous remission could occur in 14% of patients, notably in children [3,4], eventhough urinary abnormalities could re-occur in 20% of cases after initial remission[3]. Overall, it is estimated that 10 to 20% of patients reach ESRD within 10 years, and 20 to 30% within 20 years after the diagnosis[5]. In a recent retrospective study of 703 asiatic patients, renal survival was 91% after 45 months of mean follow-up, and annual glomerular filtration rate (GFR) loss was 3.1 ml/min/1,73m^2[6]. IgAN is then a major public health problem.

Prognosis factors

Given the high variability of IgAN evolution, prognosis factors have an essential role in IgAN characterization. However, until recently, only few prognosis factors have been reported and widely reproduced: high blood pressure (HBP), renal insufficiency, proteinuria (including residual proteinuria despite RAS blockade[7]), glomerulosclerosis and tubulointerstial fibrosis[8,9]. Several histological prognostic classifications have been reported[10,11]. However, these classifications had not been tested regarding inter-observer reproducibility. Moreover, the prognostic value of these criteria had not been compared to clinico-biological data. Recently, a large international retrospective study aimed to identify histological prognosis factors was reported[12,13]. An essential element of this work was the strong inter-observer reproducibility of the classification, allowing a wide use of these criteria. Moreover, these "Oxford criteria" (mesangial proliferation, endocapillary proliferation, segmental glomerulosclerosis, interstitial fibrosis/tubular atrophy) had a prognostic value independent of clinico-biological data[12,13]. These criteria have been secondarily validated in numerous studies, in cohorts with various characteristics (age, race, median GFR, immunosuppresion use)[14-21]. Cellular and fibrocellular crescents, which have a good inter-observer reproducibility, have also demonstrated a pejorative prognosis value in populations with more advanced IgAN[22]. These histological criteria thus allow a better identification of IgAN patients with a high risk of progressive kidney disease.

Treatment

Despite the frequency and the severity of the disease, only few prospective therapeutic studies have been developed in IgAN, the main "specific" therapy remaining corticotherapy[5].

Evaluation criteria of therapeutic response

It should be noted that in most therapeutic studies of IgAN, renal function was evaluated with creatinine-based formula. However, it has been demonstrated that this type of evaluation criteria (such as doubling-serum creatinine or estimated GFR evolution) can overlook significative variations of renal function in chronic nephropathies[23 , 24]. In fact, when annual GFR loss is calculated by using estimated GFR (eGFR) (MDRD formula) or measured GFR (mGFR), GFR decline is similar between both methods in only 60% of cases[23]. Other cases show difference between both methods of more than 2 ml/min/1,73m^2/year (whereas mean GFR decline of IgAN with oxford criteria is approximately 5 ml/min/1,73m^2/year) [12,13,23] . Then eGFR decline should be interpreted with caution in chronic nephropathies, including IgAN.

Nephroprotection

Treatments inhibiting the renin angiotensin system (RAS), with strict blood pressure and proteinuria goals, have a major role in limiting the progression of IgAN[25 ,26]. In fact, in a Spanish study, RAS blockade allowed a reduction from 91% to 55% of proportion of patients with doubling serum creatinine after 7 years of follow-up[27]. Current recommendations include blood pressure target < 130/80mmHg and proteinuria < 0,5g/d (as recently validated by the VALIGA study[21]). It should be noted that these recommendations were not reached in previous therapeutic studies[25 ,26]. About 60% of patients do not respond to these therapies after 3 months of follow-up, according to a recent Asiatic serie[28]. Then, expert opinion supports the use of corticosteroids in patients with progressive disease despite RAS inhibition[25 ,26], in a 2-step strategy (initial RAS inhibition, then corticosteroids therapy).

Corticosteroids

A recent meta-analysis, evaluating the effect of steroids in 536 patients with significant proteinuria and preserved renal function, has shown a 68% reduction of a renal composite endpoint (ESRD, doubling serum creatinine and 50% decline of eGFR) in patients treated with steroids[5]. This treatment allowed also a significative reduction of proteinuria. Side effects (diabetes mellitus or impaired glucose intolerance, hypertension, gastrointestinal bleeding, cushingoid features, insomnia, headache, weight gain) were relatively well tolerated. However, most of the statistical power in this meta-analysis was obtained from only 2 Italian studies[5]. In the Pozzi *et al.* study, a 50% increase in serum creatinine had been observed in 9/43 patients treated with steroids vs 14/43 patients treated without steroids[29], a beneficial effect similar to the one obtained with RAS blockade only [27] (whereas RAS blockade was not systematic in the Pozzi study). In the other Italian study, about 30% of patients presented with persistent proteinuria >1g/d, suggesting optimal RAS blockade had not been reached[30]. Then, the beneficial effect of corticosteroids could be less pronounced, if strict RAS inhibition was obtained in controls patients treated without corticosteroids. Consequently, the role of steroids, a treatment with potentially severe side effects, in IgAN remains discussed.

2.3 Justification of the project

Eventhough steroids seem to have a place in IgAN treatment, an optimal strategy to identify the patients which could benefit from this treatment is still lacking.

Given the recently identified prognostic role of histological criteria, it appears to be essential to introduce these criteria in the pre-therapeutic evaluation of IgAN patients. In fact, in retrospective studies, the use of histological criteria improves the models predicting IgAN progression, compared to models based only on clinico-biological data[31].

Discrepancy between clinico-biologic and histological criteria

Introduction of histological evaluation to stratify the risk of progression of IgAN patients is justified by the potential discrepancy between histological and clinico-biological criteria of prognosis. In fact, in our retrospective serie of 96 patients diagnosed in Necker Hospital between 2002 and 2008, after exclusion of patients with >50% tubulointerstitial fibrosis, we

identified at least one of the oxford criteria in 70% of patients with proteinuria < 1 g/d (personnal data). Similar results were obtained from our cohort of Georges Pompidou European Hospital[32]. Moreover, among 39 patients with >50% tubulointerstitial fibrosis (a major prognosis factor of bad outcome) in the Necker cohort, 13% had proteinuria < 1 g/d. Finally, it has been demonstrated that proteinuria is subject to inherent biological variation, leading to potential misclassification of patients prognosis[33,34]. Altogether, these results argue for the addition of histological criteria to clinic-biological data, in order to stratify IgAN prognosis and then guide therapy.

Histological lesions may be responsive to steroids

Several retrospective studies have evaluated the response to therapy of specific histological lesions. Most of studies with appropriate statistical analyses demonstrated an interaction between therapy and histological lesions such as mesangial proliferation, endocapillary hypercellularity or cellular crescents. In a Japanese series of 35 patients treated with tonsillectomy and steroids for 12 months, crescents were present in 91% of the initial biopsies and 0% of the repeat biopsies at the end of treatment[35]. A significant reduction in mesangial proliferation score between the first and second biopsies was also observed[35]. Other studies showed a similar improvement of both mesangial proliferation and cellular crescents[36,37] in patients treated with steroids. Interestingly, segmental glomerulosclerosis could also be reduced after treatment with steroids[35,36], suggesting segmental glomerulosclerosis in IgAN includes lesions with podocytopathy similar to FSGS responsive to steroids[16]. Similarly, tubulointerstitial fibrosis could be significantly decreased after steroids therapy[35], showing fibrosis is a dynamic process in IgAN and not only a scarring lesion.

Importantly, these histological responses have been retrospectively associated with an improvement of disease outcome by steroids. A small study of 28 patients demonstrated that necrosis within glomeruli and cellular crescents were associated with response to therapy (proteinuria and serum creatinine decrease after 3 months of steroid therapy)[38]. In the Oxford classification cohort, patients with endocapillary hypercellularity had an improved outcome if they were treated with steroids[12,13]. In a 702 Asiatic patient's cohort, the risk of incident ESRD decreased significantly by steroids treatment in patients with segmental glomerulosclerosis[22]. Finally, the VALIGA study, evaluating oxford criteria in 1147 European patients, demonstrated that the predictive value of each lesion was reduced in patients treated with steroids; this result suggests oxford criteria could be responsive to steroid treatment in this serie.

Simultaneously, histological evaluation could also help identifying patients with no response to RAS blockade. Shi *et al* demonstrated in a serie of 294 patients that mesangial proliferation and tubulointerstitial fibrosis were predictive of persistent proteinuria after 3 months of RAS blockade: the presence of these lesions could then argue for the early use of corticosteroids[28].

Thus, these retrospective studies demonstrate that renal pathology could be used to guide the choice of steroids therapy.

The role of early steroids introduction

Renal pathology-based treatment has demonstrated a beneficial effect of early therapy in inflammatory glomerular diseases such as lupus nephritis, which can have similar histological patterns than IgAN (cellular crescents or endocapillary proliferation)[39].This histological similarity suggests similar pathophysiologic processes which could benefit from a therapeutic strategy with early steroids. Moreover, several studies suggest a role for early steroids treatment to produce a legacy effect in IgAN[40]. A legacy effect is an inheritance of a treatment, given in an early phase of a disease, which produces benefits long after the cessation of intervention[40]. This effect has been first described in the benefits of early and strict control of diabetes on cardiovascular complications[41]. In IgAN, Yoshikawa *et al* demonstrated that early intensive therapy in young patients with mesangial proliferation and minimal or no proteinuria improved renal prognosis after 10 years of follow-up[42]. Similarly, the 6-months therapy with steroids of Pozzi *et al* provides a long-term effectiveness with a

persistent renal benefit up to 10 years later[43]. These observations suggest that a legacy effect may be possible for IgAN, but it is more likely to be achieved in early stages with mesangial/endocapillary proliferations and relevant but not massive proteinuria[40]. It should be noted that proteinuria in IgAN can take years to develop after the first histological lesions[44]. Thus, looking for a legacy effect needs to propose steroids treatment in patients with early identified risk of progression. Given the strong prognosis role of histological lesions, renal pathology evaluation appears to be an excellent stratification strategy to identify patients with a long term benefit from early steroids treatment.

Conclusion
Currently, IgAN treatment recommendations are only based on clinico-biological parameters. Steroids therapy appears to have a major role in IgAN treatment, but (i) previous studies evaluating steroids lacked of optimal control group and reproducible evaluation criteria and (ii) this treatment could be complicated with severe side effects. No prospective study (including ongoing studies, *clinical trial identifier NCT00554502*) with optimal RAS blockade had included histological evaluation in patient's selection, although renal pathology improves prognosis prediction. Until now, the lack of a reliable histological classification has precluded the use of histological lesions to evaluate IgAN prognosis and treatment. Given the recently identified major prognostic role of oxford criteria in IgAN, we propose to introduce histological evaluation to guide the treatment of IgAN.
Our project will thus include:

- Optimal nephroprotection adapted to current recommendation in all patients and early
- Early steroids therapy in experimental group
- Renal pathology evaluation according to validated prognosis criteria
- Evaluation of CKD progression with both estimated and measured GFR
- Evaluation of histological evolution with repeat renal biopsy to characterize the lesions responsive to therapy

This study will then propose a new therapeutic strategy in IgAN, based on all the prognosis markers available at diagnosis.This strategy will allow to accurately identify patients who can benefit from early steroids therapy with a potential legacy effect of this treatment.

3 OBJECTIVES

3.1 Primary objective

The primary objective of this trial is to evaluate the efficacy of early corticotherapy + RAS blockade (versus RAS blockade alone) after 2 years of evolution in IgAN patients with severe histological lesions.

3.2 Secondary objectives

The secondary objectives are:
- to evaluate the efficacy of early corticotherapy + RAS blockade (versus RAS blockade alone) at 6 and 12 months of evolution
- to compare the evolution of histological lesions between treatment groups at 12 months
- to compare the evolution of measured GFR (mGFR) between treatment groups at 12 and 24 months (or estimated GFR (eGFR) if unavailable)
- to compare the evolution of proteinuria in each group
- to compare the quality of life in each therapeutic group
- to assess the tolerance of treatment of each therapeutic group
- to identify prognosis markers of failure at 24 months
- to assess the pharmacokinetics of corticosteroids in IgA nephropathy patients
- to assess the association between corticosteroid exposure and treatment failure
- to assess the association between corticosteroid exposure and genetic polymorphisms

- to assesse the association between genetic polymorphisms and treatment failure

3.3 Pharmacocinetic study

The pharmacokinetics of corticosteroids will be performed in the experimental group and in the control group in case of rescue treatment.
To assess the pharmacokinetics of methylprednisolone three blood samples (5ml/sample) will be done (i.e., one sample during each successive one-day hospitalization). The time delay between the drug infusion and blood draw sampling will be assigned according to the usual biolological exams planned during the hospitalization.
Then, two blood samples (5ml) for prednisone pharmacokinetic assessment at Month 2 (or after at least 8 days of rescue treatment) will be performed. These two blood samples will be taken within an interval of 2 hours without the imposition of a specific time frame. There must not be intake of prednisone within this interval of 2 hours. For the experimental group, one blood sample will be collected additionally at Month 4. Each dosage will require 5 ml of blood in heparin tube without separating gel. The dose of each drug, as well as the delay between the blood sampling and the administration of the drugs will be carefully recorded at each visit. All samples will be stored at -20°C on site and sent at the end of research by agreed transporter.

4 PLAN FOR THE RESEARCH

4.1 Concise description of the primary and secondary assessment criteria

For all endpoints, mGFR should be analysed at D0, M12 and M24, if available in the centre. If not, eGFR calculated according to CKD-EPI formula will be used.

4.1.1 Primary assessment criterion

The primary endpoint is the failure of treatment at 24 months, defined as:

- proteinuria/creatininuria ratio (PCR) > 0,5 g/g
- or mGFR < 80% of initial mGFR (or eGFR if unavailable)
- or loss of more than 10 ml/min/1,73m^2 of initial mGFR (or eGFR if unavailable)
- or end stage renal disease (ESRD)
- or renal transplantation
- or death.

4.1.2 Secondary assessment criteria

Failure at 6 months will be defined as:

- PCR > 0.75 g/g
- or PCR > 0.5 g/g and > 30% of initial PCR
- or eGFR < 80% of initial eGFR
- or ESRD
- or renal transplantation
- or death.

Failure at 12 months will be defined as:

- PCR > 0.75 g/g
- or PCR > 0.5 g/g and > 30% of initial PCR
- or mGFR < 80% of initial mGFR (or eGFR if unavailable)
- or ESRD
- or renal transplantation
- or death.

Histological lesions evolution at 12 months :
The evolution of histological lesions will be assessed as the proportion of patients of both therapeutic groups with persistent severe histological lesions in repeat kidney biopsy at 12 months.

GFR evolution (mGFR or eGFR if unavailable):
The evolution of GFR at 12 and 24 months will be assessed as:
- the absolute value of GFR
- the absolute difference of GFR from the baseline
- the annual degradation (ml/min/1,73m^2/year) of GFR during the 24 months

Proteinuria evolution
The evolution of proteinuria will be assessed as:
- the absolute value of proteinuria at 12 and 24 months
- the absolute difference of proteinuria from baseline at 12 and 24 months

Identification of prognosis markers of failure at 24 months:
Clinical, histological, and biological data (including PCR ratio, eGFR and mGFR, renal histological lesions) will be compared between patients with or without failure.

Comparison of side effects in each therapeutic group.

Comparison of life quality scale in each therapeutic group with SF36 scale at 12 and 24 months

4.2 Description of research methodology

4.2.1 Experimental plan

Phase III, prospective, multicenter, randomized open-labelled study.

Included patients will be randomized according to a 1:1 ratio:
- early corticotherapy + RAS blockade (experimental group)

or

- RAS blockade alone (control group), with corticosteroids in case of failure at 6, 9, 12 or 18 months or in case of rapid deterioration of renal function at 2 months and proposed corticosteroids in case of failure at 4 months.

4.2.2 Number of centres participating

This protocol is a multicentric study with 27 tertiary nephrology centres anticipated to participate.

4.2.3 Identification of the subjects

For this research, the subjects will be identified as follows:
Centre No. (3 numerical positions) - Selection order No. of the person in the centre (4 numerical positions) - surname initial - first name initial

| __|__|__| - | _|__|__|__| - |_ _|_ _|
N°centre N° patient initiales

This reference is unique and will be retained for the entire research period.

4.2.4 Randomization

Randomization will be stratified according to centre and will use permutation blocks, the size of each being not available to clinicians.
Centralised randomization will be carried out by the investigator after inclusion using the cleanWeb system (Telemedecine).

5 PROCEDURE FOR THE RESEARCH

5.1 Inclusion visit

This inclusion visit takes place after at least 15 +/- 2 days of RAS blocker treatment (low dosage if eGFR < 45 ml/min/1,73m^2, and median dosage if eGFR ≥ 45 ml/min/1,73m^2, equivalence tables being provided, see 16.3).
Clinical examination will be performed with sitting blood pressure measurement, checking for postural hypotension, weight measurement, general and cardiovascular examination. Urin and blood parameter should be available (≤ 7 days before inclusion visit): blood counts, plasma sodium, potassium, total proteins, urea, serum creatinine (enzymatic IDMS-traceable assay).

Inclusion and exclusion criteria, including histologic and clinico-biologic criteria, will be checked. The study will be presented and proposed by the nephrologist to the patient and the inform consent will be signed. The investigator will then complete an electronic enrolment form, accessible 24/7 on the internet via the e-CRF (secured access will be obtained in advance by each pre-declared investigator centre). Randomization will be carried out by a system of random allocation linked to the electronic case report form, in such a way that a patient enrolled in the form will be easily and automatically randomized.

For the control group, a one-day hospitalization for first mGFR (if available) will be organised according to local practices, as soon as possible within 21 days after the randomisation.

For the experimental group, 3 successive one-day hospitalizations for initation of therapy with methylprednisolone pulses (one per day) and first mGFR (if available) will be scheduled according to local practices, as soon as possible within 21 days after the randomisation. These 3 pulses will be followed at D3 morning by oral corticosteroids during 4 months. First mGFR will be performed before the first methylprednisolone pulse.

The one-day hospitalization (for the control group if mGFR is available), or the date of randomisation (for the control group if mGFR is not available), or the first day of the 3 one-day hospitalizations (for the experimental group) will be considered as D0 in this study, to organize follow-up visits.

If the patient is not hospitalized at D0 (control group and mGFR not available), the biological collection will be performed during the inclusion visit: DNA, blood and urine.

If the patient is hospitalized at D0, will be performed during the first day of hospitalization:
- Medical interview evaluating compliance for treatments and lifestyle recommendations
- Clinical examination with sitting blood pressure measurement, checking for postural hypotension, weight measurement, general and cardiovascular examination, and ethnic origin (caucasian, asiatic, african, african-american). The ethnic origin is necessary to calculate eGFR by the CKD-EPI formula.

eGFR =141 x min(SCr/κ, 1)α x max(SCr /κ, 1)-1.209 x 0.993Age x 1.018 [if female] (or x 1.159 [if Black])

Abbreviations/units
eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2

S_{Cr} (standardized serum creatinine) = mg/dL
κ = 0.7 (females) or 0.9 (males)
α = -0.329 (females) or -0.411 (males)
min = indicates the minimum of S_{Cr}/κ or 1
max = indicates the maximum of S_{Cr}/κ or 1
age = years

- Biochemistry: plasma sodium, potassium, albumin, total proteins, bicarbonate, chlorure, fasting glycemia, total and LDL cholesterol, triglycerides, urea, uric acid, serum creatinine (enzymatic IDMS-traceable assay), C reactive protein. Urinary protein, creatinine, sodium and urea will be evaluated on a 24-hour urinary collection (or urinary sample).
- Haematology: blood count.
Biochemistry and haematology analyses are associated with care.
- Biological collection : DNA, blood and urine (for the experimental group, before the first methylprednisolone pulse.

5.2 Follow-up Visits (M2 to M18)

Follow-up consultations with a nephrologist or hospitalizations will be performed at months 2, 4, 6, 9, 12, 18 and 24 from D0.
A two days hospitalization with mGFR, serum creatinine and proteinuria evaluation and repeat renal biopsy will be performed at month 12. Only one day hospitalization is scheduled if biopsy is not perfomed, or only one consultation is scheduled if biopsy is not perfomed and mGFR is not measured.
A one-day hospitalization with mGFR, serum creatinine and proteinuria evaluation will be performed at month 24. Only one consultation is scheduled if mGFR is not measured.

At each consultation (M2, M4, M6, M9 and M18) or hospitalization (M12 and M24) will be performed:
- Medical interview evaluating compliance for treatments and lifestyle recommendations
- Clinical examination with sitting blood pressure measurement, checking for postural hypotension, weight measurement, general and cardiovascular examination, and ethnic origin.
- Biochemistry: plasma sodium, potassium, albumin, total proteins, bicarbonate, chlorure, fasting glycemia, total and LDL cholesterol, triglycerides, urea, uric acid, serum creatinine (enzymatic IDMS-traceable assay), C reactive protein. Urinary protein, creatinine, sodium and urea will be evaluated on a 24-hour urinary collection (or urinary sample except to M2 and M4), eGFR.
- Haematology: blood count.
Biochemistry and haematology analyses are associated with care so they can be obtained before the consultation from private practice laboratories.
- at the visit M12 and M24, SF36 scale and biological collection (blood and urine)

5.3 End of research visit (M24)

The last visit is scheduled at month 24 from first GFR measurement, during a one-day hospitalization with mGFR, serum creatinine and proteinuria evaluation at the same exams as in the previous visits.

Expected length of participation and description of the chronology and duration of the research.

Maximum period between selection and	15 days min

inclusion Inclusion period	24 months
The included subjects' length of participation: • Treatment period: • Follow-up period:	 4 months 24 months+ 21 days max
Total research period:	48 months

5.4 Table or diagram summarising the chronology of the research

Actions	***Inclusion***	*D0*	*M2 M4*	*M6 M9*	*M12*	*M18*	*End of research M24*
Visit	Consultation*	hospitalization*	consultation	consultation	hospitalization**	consultation	Hospitalization***
History	X						
Clinical exam, Medical Interview	X	X	X	X	X	X	X
Inclusion/ Exclusion criteria	X						
Informed consent, randomization	X						
Measured GFR (or estimated)		X	eGFR	eGFR	X	eGFR	X
Tests (biochemistry, haematology)		X	X	X	X	X	X
*Biological collection (blood, urine)*****	X(if control group and mDFG not available)	X			X		X
Sample for PK (5ml)		X (D0,D1,D2)	X				
Dispensation of treatments		X	X (M2)				
Renal biopsy					X		
SF36 scale					X		X
Compliance CT		X	X				
Compliance RAS	X	X	X	X	X	X	X

Adverse events		X	X	X	X	X	X

** D0: for the control group, 1 one-day hospitalization (= 1 HDJ) if mDFG is available or only consultation (= inclusion/randomisation visit) if mDFG is not available and for the experimental group 3 one-day hospitalizations (=3 HDJ)*
*** 2 days hospitalization (= 2HC) if biopsy is perfomed and 1 one-day hospitalization (1 HDJ) if mGFR is measured, or only 1 consultation if biopsy is not perfomed and mGFR is not measured*
****1 one-day hospitalization (= 1 HDJ) or only 1 consultation if mGFR is not measured*
***** DNA sample will be obtained from one of blood samples of biological collection at D0 for control group.*

During the first year, the delay accepted to organise every visit is ±1 week.
During the second year, the delay accepted to organise every visit is ±1 month.

5.5 Distinction between care and research

TABLE: Distinction between procedures associated with "care" and procedures added because of the "research"

	Procedures and treatments associated with care	**Procedures and treatments added because of the research**
Treatments	RAS blockade	Corticosteroid treatment
Measured GFR		Day 0, Month12, Month 24
Blood and urinary samples	Month 2, 4, 6, 9, 12,18, 24	Biological collection: D0, Month 12, Month 24 Pharmacocinetic: D0, D1, D2, M2, M4
SF36 scale		Month12, Month24
Renal biopsy	Diagnosis renal biopsy	Month 12

5.6 Biological Collection

The samples (blood bank, urine bank, DNA bank) taken as part of the research will be included in a biological collection, stored at -80°C on site for urine and -20°C for DNA - blood bank. All samples sent at the end of the research by agreed transporter.

The collections will be stored:

Type of sample	**Quantity**	**Storage location**	**Collection supervisor**	**Purpose of the collection**	**Storage period (years)**	**Outcome (destruction, etc.)**
urine	D0, M12, M24: 2*15ml	Plateforme Ressources Biologiques H. Mondor	Pr Ghaleh Dr El Karoui	To identify urinary prognosis markers of failure at 24 months.	20	destruction
blood	D0: 2*7 ml M12, M24: 3*7ml	Plateforme Ressources Biologiques H. Mondor	Pr Ghaleh Dr El Karoui	To identify seric prognosis markers of failure at 24 months.	20	destruction
cells for DNA extraction	D0: 1*5ml	Laboratoire pharmacocinétique de Cochin	Pr Treluyer	To identify genetic markers of failure of treatment	20	destruction

The samples may be used with the explicit agreement of the subject on the consent form for further analyses not included in the protocol and which could be beneficial for the IgA nephropathy based on evolution in scientific knowledge.

At the end of the research, the samples will be preserved. The collection will be declared to the minister responsible for research [and to the director of the regional health authority with local jurisdiction if the entity is a health establishment] (Article L. 1243-3 of the CSP (French Public Health Code). All these samples (urine, blood, DNA) associated with research are under the responsibility of the sponsor of this research (APHP).

5.7 Termination rules

5.7.1 Criteria and methods for prematurely terminating the experimental treatment

Different situations:

- Temporary termination of treatment, the investigator must document the reason for stopping and restarting the treatment in the subject's source file and the case report form (CRF)
- Premature termination of treatment but the subject is still included in the research, until the end of the subject's participation, the investigator must document the reason.

The investigator must:

- Document the reason(s)
- Collect the assessment criteria when participation in the research ends, if the subject agrees

5.7.2 Follow-up of the subjects after the premature termination of experimental treatment

If a subject stops prematurely the treatment, the subject is still included in the research, until the end of the subject's participation. The subject will have to in minima realize the visits M6, M12 and M24.

Ending a subject's participation does not affect the normal management of the subject's illness in any way.
If there are serious adverse events, the investigator must notify the sponsor and monitor the subject until the end of the research. If treatment is stopped prematurely due to a serious adverse event, a serious adverse event notification form will be sent by fax (01 44 84 17 99) to the sponsor. The serious adverse event will be monitored until it is resolved.

5.7.3 Terminating part or all of the research

5.7.3.1 Criteria and methods for prematurely terminating all or part of the research by the patient

Any subject can withdraw from participating in the research at any time and for any reason.
In case of end stage renal disease (ESRD) or renal transplantation, the subject stay in the research but the patient will not have anymore visits in the protocol. Only infectious AE and SAE will be report.
The investigator can permanently end a subject's participation in the research for any reason that affects the subject's safety or which would be in the subject's best interests.
If the subject is lost to follow-up, the investigator has to make contact with the subject and draw it in the file source to know at least if the subject is alive or died.

If a subject leaves the research prematurely, data relating to the subject can be used.

The case report form must list the various reasons for ending participation in the research:

- ☐ Explicit withdrawal of consent
- ☐ Follow- up
- ☐ Death
- ☐ Other

5.7.3.2 Criteria and methods for prematurely terminating all or part of the research by sponsor

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely terminate all or part of the research, temporarily or permanently, in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are seen in an arm being treated or if there is a discrepancy in the serious adverse reactions between the 2 arms, and which require a reassessment of the benefit-risk ratio for the research.
- likewise, if unexpected facts, new information about the product, in light of which the objectives of the research are unlikely to be achieved.
- if it appears that the inclusion objectives are not met.

If the research is terminated prematurely, the decision and justification will be given by the sponsor, AP-HP, to the Competent Authority (ANSM) and to the CPP within 15 days.

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

a. Age ≥18 years
b. IgAN diagnosed on renal biopsy < 45 days
c. PCR ratio >0.75 g/g (within 30 days before or after the renal biopsy)
d. Renal biopsy with at least 8 glomeruli, disclosing at least 2 criteria among:
   - mesangial proliferation (according to Oxford criteria)
   - endocapillary proliferation (according to Oxford criteria)
   - tubulointerstitial fibrosis (according to Oxford criteria) >25% of the biopsy
   - segmental glomerulosclerosis (according to Oxford criteria)
   - ≥10% cellular/fibrocellular crescents.
e. Patient with Social Security System Insurance or CMU
f. Patient having signed an informed consent

6.2 Exclusion criteria

a. >30% increase of serum creatinine within 15 days after starting RAS blockade therapy
b. >50% cellular/fibrocellular crescents, or >50% tubulointerstitial fibrosis or >50% globally sclerotic glomeruli
c. >50% plasma creatinine increase within the last 3 months before the renal biopsy
d. Nephrotic syndrome with minimal change disease and IgA deposits
e. eGFR <20 ml/min/1,73m^2 (CKD-EPI formula) within 30 days before or after the renal biopsy
f. Uncontrolled blood pressure (Systolic blood pressure >180 mmHg or diastolic blood pressure > 110 mmHg)
g. Previous corticosteroids treatment (>20 mg/d during more than 15 days, within the last 3 months before the renal biopsy)
h. Pregnancy or breast feeding or women without sufficient contraception
i. Secondary known forms of IgAN
j. Henoch-Schoenlein purpura
k. Additional other chronic renal disease
l. Contraindication for immunosuppressive therapy, including active intestinal bleeding, active gastric or duodenal ulcer; active infection; any malignancy in a last years before the inclusion; severe psychiatric disease; living vaccines; anti-inflammatory dosages of acetylsalicylic acid
m. Contraindication for RAS blockade therapy
n. Known allergy or intolerance to corticoids or lactose

o. Organ transplant patient

The absence of measured GFR availability on the site is not an exclusion criterion.

6.3 Recruitment methods

About 20 diagnoses of primary IgAN are made each year in French tertiary nephrology centres. Among them, about 25% could be included in this protocol according to the inclusion and exclusion criteria, given the results of a retrospective study of 230 patients with IgAN diagnosed in Necker and HEGP hospitals in 2002-2008. 27 centres have already accepted to propose this protocol to their patients. Then, the expected number of inclusions could be reached in about 2 years.

7 TREATMENT ADMINISTERED TO RESEARCH PARTICIPANTS

7.1 Description of the experimental medications

For this study, two experimental medications will be administrated to the experimental group:

- 3 intravenous Methylprednisolone pulses (500 mg/pulse) will be administred during 3 successive one-day hospitalizations.
- oral corticosteroid treatment will be administred, during 4 months after the IV pulses, according to the following schedule and abacuses (see Annexe"1"):

1 mg/kg/d of prednisone during month 1 (begin at the D3 morning)
0.5 mg/kg/d of prednisone during month 2
0.25 mg/kg/d of prednisone during month 3
0.1 mg/kg/d of prednisone during month 4.
The maximum dose per day of prednisone is 80 mg.
Corticosteroids therapy is stopped at the end of the 4th month.
Corticosteroids dosage is rounded down to the closest multiple of 5 mg.

7.1.1 Methylprednisolone (IV)

Presentation :
- METHYLPREDNISOLONE 500 mg, powder for solution for injection (IV).

Storage :
Do not store above 25°C.

7.1.2 Prednisone (Per Os)

Presentation :
- PREDNISONE 20 mg, tablets
- PREDNISONE 5 mg, tablets

Storage ;
Prednisone does not require any special storage conditions.

7.1.3 Pharmaceutical circuit

Methylprednisolone and prednisone will be provided by clinical trial department of AGEPS (Agence Générale des Equipements et Produits de Santé) that will ensure the secondary

labelling according to the good manufacturing practices, and the supply to the pharmacy of each clinical site according to the good distributing practices.

Experimental drugs will be stored by the pharmacies. Dispensing will be made on presentation of a specific nominative prescription of the study.

7.2 Description of the non-experimental treatments

7.2.1 Non-experimental medication used in corticosteroids-treated patients

Prophylaxis against glucocorticoid-induced osteoporosis with bisphosphonate therapy is recommended during the treatment with corticosteroids. Alendronate or risedronate could be used according to local practices.
Calcium supplementation is recommended to achieve a minimum total calcium intake of 1200 mg/day.
Prophylaxis against glucocorticoid-induced Pneumocystis jiroveci (formerly P. carinii) pneumonia infections should include sulfamethoxazole-trimethoprim as a single strength tablet daily (i.e. 480 mg daily) or a double strength tablet every other day thrice weekly (i.e. 960 mg Monday, Wednesday, and Friday). In case of intolerance or allergy to sulfamethoxazole-trimethoprim, atovaquone treatment or pentamidine aerosols are recommended. The use of this Pneumocystis jiroveci prophylaxis is left to the discretion of local investigators.
Prophylaxis against strongyloides hyperinfection with ivermectine is recommended before starting corticosteroids in case of potential previous strongyloides exposure.
Peptic ulcer prophylaxis with proton pump inhibitors is recommended and is left to the discretion of the patient physician.
The use of other prophylactic therapies will be left to local practice and the discretion of local investigators.

Dietary regimen (RENIF file) and lifestyle counseling is provided during consultations or hospitalization, for avoiding high simple carbohydrates-diet while treated with corticosteroids.

7.2.2 Non-experimental medication used in all patients

The following treatments are part of current recommendations for IgAN treatment.

Vitamin D supplementation is recommended for all patients according to the patient physician discretion, with a minimum vitamin D administration equivalent to colecalciferol: 100000 UI each 3 months.

Dietary regimen and lifestyle counseling is provided during consultations or hospitalization, with the following objectives:

- Avoiding high protein intake (>1,3 g/kg/d)
- Lowering salt intake to <90 mmol/d of sodium (corresponding to 5 g of sodium chloride)
- Undertaking physical activity compatible with cardiovascular health and tolerance
- Achieving a healthy weight (BMI 20 to 25)
- Stop smoking.

Treatment with RAS blockade therapy (one molecule or in association) is systematically administred in all patients.
RAS blockade with ACE-inhibitors or angiotensin receptor blockers is initiated using the drug chosen by the patient physician. Low dosage is initiated if eGFR is <45 ml/min/1,73m^2.

Medium dosage is initially used if eGFR is >45 ml/min/1,73m^2. Every modification of RAS blockade is followed by a control of plasma creatinine and potassium within 3 weeks. These results can lead to diminution or interruption of RAS blockade according to local decision.
RAS blockade should be increased at each visit to achieve the following objectives, according to the patient physician decision:

- Blood pressure <130/80 mmHg while sitting
- PCR <0,5 g/g or PCR <0.75 g/g and <30% of initial PCR

Patients can be converted to an ARB when an ACE-inhibitor is not tolerated. Dose equivalence tables for ACE-inhibitors and ARB's will be provided. Bitherapy with ACE inhibitors and ARB is allowed. All other antihypertensive medications, including diuretics, calcium-channel blockers and ß-blocker can be used at any time-point during the study depending on the clinical decision of the patient physician.
Hyperkalemia is treated according to current guidelines.

7.3 Description of the traceability elements that accompagny the experimental medication

The modality of traceability elements that accompagny the experimental medication are in the “pharmaceutical circuit”.

7.4 Authorised and prohibited treatments (medicinal, non medicinal, surgical), including rescue medications

7.4.1. Authorised rescue medication in the control group

In the control group, atM2, corticosteroid treatment (4 months of treatment, same protocol of experimental group) should be administred in case of rapid deterioration of renal function (i.e. eGFR (CKD-EPI formula) is < 70% of initial eGFR). Before corticosteroid administration, eGFR will be re-evaluated on a second sample, within an interval of at least 14 days.

At 4 months, rescue corticosteroid treatment (4 months of treatment, same protocol of experimental group) could be administred in case of failure defined by:

- PCR > 0.75 g/g
- or PCR > 0.5 g/g and >30% of initial PCR
- or eGFR (CKD-EPI formula) < 80% of initial eGFR,

In case of failure, before corticosteroid administration, proteinuria and eGFR will be re-evaluated on a second sample, within an interval of at least 14 days.

At 6, 9, 12, or 18 months, rescue corticosteroid treatment (4 months of treatment, same protocol of experimental group) should be administred in case of failure defined by:

- PCR > 0.75 g/g
- or PCR > 0.5 g/g and >30% of initial PCR
- or eGFR (CKD-EPI formula) < 80% of initial eGFR,

In case of failure, before corticosteroid administration, proteinuria and eGFR will be re-evaluated on a second sample, within an interval of at least 14 days.

7.4.2. Prohibited treatments

No treatments are prohibited, except from those contra-indicated with the use of corticosteroids (cf SmPC). A patient have already received a corticosteroid treatment, he should not receive a new corticotherapy.

7.5 Methods for monitoring compliance with the treatment

Compliance is evaluated orally by the patient physician at each visit with the “patient pad” and by the RCA during the monitoring of the pharmacy of each centre.

8 ASSESSMENT OF EFFICACY

Proteinuria/creatininuria ratio (PCR) and eGFR (CKD-EPI formula) evaluation

Serum creatinine will be evaluated with an enzymatic IDMS-traceable assay. Urinary protein, creatinine, sodium and urea will be evaluated on a 24-hour urinary collection (or urinary sample) at each visit.

Biochemistry analyses can be performed in private practice laboratories.

In case of failure, Proteinuria and eGFR will be re-evaluated on a second sample, within an interval of at least 14 days. For each visit, the final GFR and PCR value will be calculated from the second dosage.

Histological lesions evaluation

Renal biopsy will be performed and processed according to local practices. Histologic assessment will be performed according to the Oxford criteria studies. For patient inclusion, each inclusion criterium (mesangial proliferation, endocapillary proliferation, focal segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, cellular/fibrocellular crescents) will be scored by local pathologists. Secondarily, all renal biopsies will be re-evaluated *a posteriori* in the Necker pathology department.

Measured GFR evolution will be evaluated as follows:

mGFR will be performed according to local practice (iohexol clearance, inuline clearance,CrEDTA clearance, …).

Given that the randomization is stratified by centre, the difference between the mGFR techniques should not have a major effect in data interpretation.

Identification of prognosis markers of failure at 24 months:

These factors will include (but are not restrited to):

- clinical factors (blood pressure, history of macroscopic haematuria, familial history of IgAN),
- biological factors (initial and time-average proteinuria, initial eGFR, time-average sodium chloride consumption),
- renal histological lesions evaluated *a posteriori* (oxford criteria, thrombotic microangiopathy, focal segmental glomerulosclerosis with features of podocytopathy)

9 STATISTICAL ASPECTS

9.1 Calculation of sample size

Given the results of previous studies, we assume that 60% of the patients in the control group will achieve the failure criteria at 24 months. We aim to obtain a decrease to 35% of failure with early corticotherapy (i.e in the experimental group). With 80% power and an 2-sided alpha risk equal to 5%, 61 subjects per group are required. Consequently, 122 patients will be included in this study.

9.2 Description of statistical methods to be used

All statistical analyses will be performed by Dr C. Elie (Paris Centre Clinical Research Department) using R software (http://cran.r-project.org).

Primary analyses will include all patients who underwent randomization and will be conducted on the intention-to-treat principle for efficacy outcomes and according to treatment received for toxicity end points. A per protocol analysis will be also performed, after exclusion of the subjects with at least one significant protocol deviation.

Descriptive analyses will be done for the two arms of treatment. Continuous variables will be summarized as mean (standard deviation) or median [range] and categorical variables as frequencies and percentages.

Primary end-point

Percentages of patient with failure at 24 months (as defined earlier) will be compared between groups using Chi2 test. Treatment effect will be presented as Relative Risk (RR) and its 95% CI.

Secondary end-points

Secondary efficacy and safety end points were analysed using Chi2 test (or Fisher's test if appropriate) and Student t test (or Wilcoxon test if appropriate).

To explore the emergence of any time-related patterns of response to treatment, means and 95% confidence intervals (CIs) for changes relative to baseline in proteinuria and GFR were plotted vs time from randomization until end of follow-up at 24 months. Means and 95% CIs for changes from baseline were compared at 6, 12 and 24 months using Student t test. In addition linear marginal regression models will be performed, if appropriate.

Three subgroups analyses are planned to explore whether the primary outcome results differed in particular groups of patients. Histological subgroups will be defined as the presence of mesangial proliferation or not, the presence of endocapilary proliferation or not and the presence of cellular or fibrocellular crescents or not. Log binomial regression models will be used for the subgroup analyses and will include terms for treatment group, subgroup, and the interaction between treatment group and subgroup. The interaction terms represent potential subgroup differences in treatment effects.

For efficacy and safety comparisons, P values of less than 0.05 were considered to indicate statistical significance.

The pharmacokinetics of corticosteroids will be evaluated by population approach. The population approach allows, from a small number of samples per subject, collected at variable times between drug intake and sampling, to estimate the pharmacokinetic parameters of the drug as well as the variability in the population. Individual pharmacokinetic parameters will be derived using Bayesian estimation from the population model. Association between individual exposures (i.e. through concentration, area under the curve) and treatment failure will then be investigated.

10 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE RESEARCH

10.1 Definitions

According to Article R1123-39 of the French Public Health Code and the guideline on good pharmacovigilance practices (EMA, 2012) :

Adverse event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction

Any response to a medicinal product which is noxious and unintended.

Serious adverse event

Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Unexpected adverse reaction

An adverse reaction, the nature, severity or outcome of which is not consistent with the applicable product information: the summary of product characteristics (SmPC) for an authorised product or the investigator's brochure for an unauthorised investigational product.

According to the notice to sponsors of clinical trials for medications (ANSM):

New safety issue

Any new information regarding safety:

- that could significantly alter the assessment of the benefit-risk ratio for the experimental medication, or for the trial
- or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the trial

10.2 The investigator's roles

Regulatory obligations of the investigator (Art R1123-54 of the French Public Health Code)

The investigator must notify the sponsor, immediately on the day when the sponsor becomes aware, of all the serious adverse events, except those that are listed in the protocol or in the investigator's brochure as not requiring immediate notification.

These serious adverse events are recorded in the "serious adverse event" section of the case report form and the investigator must immediately notify the sponsor's Vigilance division.

The investigator's other roles

The investigator must document the serious adverse event as thoroughly as possible and provide the medical diagnosis, if possible.

The investigator assesses the severity of the adverse events:

- *Mild: tolerated by the patient, does not interfere with daily activities*
- *Moderate: sufficiently uncomfortable to affect daily activities*
- *Serious: preventing daily activities*

The investigator assesses the causal relationship between the serious adverse events and the experimental medication(s).

10.3 Specific features of the protocol

All serious and non-serious adverse events must be reported in the CRF.

Serious adverse events that do not require the investigator to notify the sponsor

These serious adverse events are only recorded in the "adverse event" section of the case report form. They include the events associated with:

- Normal and natural evolution of the pathology, for example:

High blood pressure, headaches except for the first 2 months of corticotherapy
Lower limbs edema except for the first 2 months of corticotherapy
Gross haematuria

Acute renal failure
Nephrotic syndrome

- Special circumstances

Hospitalization for pre-existing pathology
Hospitalization for a medical treatment or scheduled surgery before the research
Admission for social or administrative reason
Hospitalization in an emergency department (<12 hours)

- Adverse events likely to be associated with the treatments prescribed as part of the patient's care during the monitoring of the research, for example adverse events related to the prescription of RAS blockers :

Hypotension
Acute renal failure
Glucose metabolism disequilibrium

Serious adverse events that require the investigator to immediately notify the sponsor

The investigator must report all adverse events that meet one of the seriousness criteria below:
1- Death
2- Life threatening situation
3- Requiring hospitalization or prolonging hospitalization
4- Persistent or significant disability or incapacity
5- Congenital abnormality or birth defect
6- Or any other adverse event considered "medically significant"

The serious adverse events the most related are:

- High blood pressure (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥120mmHg), headaches and lower limbs edema in the first 2 months of corticotherapy, diabetes, infections, osteoporosis with fracture and cardiac insufficiency.

Other events that require the investigator to immediately notify the sponsor

- *In utero* exposure

The sponsor must be notified immediately about any pregnancy during which the foetus (from the pre-embryonic stage up to birth) could have been exposed at a given time to an experimental medication, even if the pregnancy is not associated with an adverse event.
Notification is required if the exposure involves the mother.

Other events occurring following an interaction between corticosteroids and antihypertensive treatments (Beta blockers and diuretics):

Hyperkalemia (> 6mmol/l)

Torsade de pointes

10.4 Procedures and deadlines for notifying the sponsor

Notification of an SAE must initially be provided in a written report using the special form for reporting SAE. The report must be signed by the investigator.

Each item in the form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.
This initial notification must be followed by one or more detailed follow-up report(s), in writing and signed, within a maximum of 8 days in the case of a fatal or life-threatening event and within 15 days for all other cases.
Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results of additional exams, etc.). These documents must be made anonymous. In addition, the documents must include the following: research acronym, number and initials of the subject, nature and date of the serious adverse event.
Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the subject has left the trial.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor via fax only to the Vigilance Division of the DRCI, fax No. **01 44 84 17 99**.

For this study using e-CRF:
- the investigator completes the SAE notification form in the e-CRF, validates, prints and signs the form before sending it *via* fax.
- if it is not possible to connect to the e-CRF, the investigator will complete, sign and send the SAE notification form**.** As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.
The investigator must comply with all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Vigilance Division of the DRCI can be contacted via email: vigilance.drc@aphp.fr

In utero exposure
The investigator completes the "form for monitoring a pregnancy that developed during a biomedical research" and sends it by fax to the Vigilance Division at **01 44 84 17 99**.
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy, using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAE.
If the exposure involves the father, the investigator must obtain the mother's permission before collecting information about the pregnancy.

The initial pregnancy notification, the SAE follow-up reports and all other documents must be sent to the sponsor via fax only to the Vigilance Division - of the DRCI, fax No. **01 44 84 17 99**.

10.5 Period for notifying the sponsor
The investigator must report all SAE that occur in research subjects:
- After the date of the first procedure specific to the research
- Throughout the period during which the participant is monitored, as determined by the research

10.6 The sponsor's roles
The sponsor, represented by its Vigilance Division, continuously assesses the safety of each experimental medication throughout the research.

Analysis and declaration of serious adverse events

The sponsor assesses:

- the seriousness of all adverse events reported
- the causal relationship of these events with each experimental medication and/or specific medical procedures/exams added by the research and with other possible treatments
- the expected or unexpected nature of these adverse reactions

For serious adverse events related to the experimental medications and which are expected, the SmPC for METHYLPREDNISOLONE 500 mg and Prednisone should be consulted.

All serious adverse events which the investigator and/or the sponsor believe could reasonably have a causal relationship with the experimental medication are considered as suspected adverse reactions.

All suspected unexpected serious adverse reactions (SUSAR) are declared by the sponsor, within the legal time frame, to the Agence Française de Sécurité Sanitaire des Produits de Santé (ANSM, French Health Products Safety Agency) and to the relevant Comité de Protection des Personnes (CPP, ethical committee).

- The initial declaration must be made no later than 7 calendar days after the date on which the serious adverse event occurs in the case of death or of a life-threatening diagnosis.
- The initial declaration must be made no later than 15 calendar days after the date on which the serious adverse event occurs in the case of other serious situations.
- The follow-up declaration must be made no later than 8 days after the 7- or 15-day deadline (depending on the seriousness).

Any suspected unexpected serious adverse reaction must also be declared electronically in the Eudravigilance European database for adverse events due to medications, established by the European Medicines Agency (EMA).

The sponsor must notify all relevant investigators about any data that could adversely affect the safety of the research subjects.

Specific cases of serious adverse events of special interest:

At the request of ANSM, the sponsor may be asked to declare serious adverse events of special interest, in accordance with the same procedures and deadlines as SUSARs.

Analysis and declaration of other safety data

This relates to any safety data or new fact that could significantly alter the assessment of the benefit-risk ratio for the experimental medication, or for the research, or which could lead to the possibility of altering the administration of the experimental medication or altering the conduct of the research.

New facts must be declared to the competent authorities within 15 calendar days of the sponsor becoming aware. Additional relevant information must be sent within an additional 8 days after the 15 day deadline.

Annual safety report

Once a year for the duration of the clinical trial, the sponsor must draw up an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:

- an analysis of the safety of the research subjects
- a description of the patients included in the trial (demographic characteristics, etc.)
- a line listing of suspected serious adverse reactions that occurred during the period covered by the report
- a cumulative summary tabulation of serious adverse events that have occurred since the start of the research

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorised the trial.

10.7 Data Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) can be established by the sponsor. Its primary mission is to serve as a committee for monitoring safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The DSMB is mentioned in Article L. 1123-7 of the French Public Health Code.

The sponsor is responsible for justifying the creation or absence of a supervisory committee to the Competent Authority (ANSM) and to the CPP.

For this biomedical research, it has not been considered beneficial to convene a DSMB because this study is a research with low risk (B risk) according the sponsor procedure and the coordinating investigator.

11 DATA MANAGEMENT

11.1 Data collection methods

Information required in the research protocol must be collected in the case report form (CRF) and an explanation must be given by the investigator for each missing data.
Data must be reported in the electronic CRF when they are available, for clinical or para-clinical data.
Correction of discordant data on CRF will be asked through queries. In the CRF, the changes in the data will be tracked.
Anonymization of the patients will ensured using a code number and initials, reported on each needed documents for the research, or by erasing nominative data on copies of source documents.

11.2 Right to access source data and documents

Access to data

In accordance with GCPs:
- the sponsor is responsible for obtaining the permission of all parties involved in the research to guarantee direct access to all locations where the research will be carried out, to the source data, to the source documents and the reports, with the goal of quality control and audit by the sponsor
- the investigators will make available to those in charge of monitoring, quality control and audit relating to the biomedical research the documents and personal data strictly necessary for these controls, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

Source documents

Source documents are defined as any original document or object that can prove the existence or accuracy of a piece of information or a fact recorded during the research. These documents will be kept for 15 years by the investigator or by the hospital in the case of a hospital medical file.
In this research, the source documents will be: paper and electronic medical file, nurse file, and anapathology results.

Data confidentiality

Those responsible for biomedical research quality control (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information about the experimental medications, the research, the research subjects and in particular the identity of the subjects and the results obtained.

These individuals, as well as the investigators themselves, are subject to professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code).
During or after the biomedical research, the data collected about the research subjects and sent to the sponsor by the investigators (or any other specialised parties) will be made non-identifying.
Under no circumstances should the names and addresses of the subjects involved be shown.
The sponsor will ensure that each research subject has given permission in writing for access to personal information about him or her which is strictly necessary for the quality control of the research.

11.3 Data processing and storage of documents and data

Data entry

Data entry will be carried out on an electronic case report form system (e-CRF), filled in on the internet after each visit by the investigator-physicians in each centre. Access to the on-line data entry form by the investigator-physicians will be restricted by an access code and a personal and unique password system for each user. Each investigator will, in addition, have access to a specific profile that attributes or withholds access to certain functions of the system (entering data, or simply viewing the data of the enrolled patient or all the study data, possibility of change and validation by the CRAs, etc…). Data will be stored on a secure server, with data encrypted during transmission and automatic internal saving of a copy on the server that will host the electronic case report form.

Data processing (CNIL, the French Data Protection Authority) in France

This research falls under the "Méthodologie de référence" (MR-001) according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of 6 January 1978 relating to information technology, data files and privacy. This change was approved in a decision made on 5 January 2006. AP-HP, the research sponsor, has signed a commitment to comply with this " Méthodologie de référence "

Archival

Specific documents for biomedical research relating to a medication for human use will be archived by the investigator and the sponsor for a period of 15 years after the end of the research.

11.4 Ownership of the data

AP-HP is the owner of the data, which cannot be used or disclosed to a third party without its prior approval.

12 QUALITY CONTROL AND ASSURANCE

Each biomedical research project managed by AP-HP is ranked from A to D according to the projected risk incurred by research subjects using the classification of biomedical research sponsored by AP-HP.

12.1 General organisation

The sponsor must be responsible for the safety and respect of those subjects who have agreed to participate in the research. The sponsor must implement a quality assurance system to best monitor the conduct of the research in the investigation centres.

For this purpose, the sponsor shall delegate Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the research locations, after having carried out initial visits.
The objectives of monitoring the research, as defined in the French Good Clinical Practices (BPC section 5.18.1), are to verify that:

- the rights, safety and protection of the research subjects are met
- the data reported is exact, complete and consistent with the source documents
- the research is carried out in accordance with the protocol in force, with the French GCPs and with the legislative and regulatory provisions in force

12.2 Strategy for opening the centres

The strategy for opening the centres established for this research is determined using the appropriate monitoring plan. The mails of sponsor and the contracts with centres will be sent to all the centres at first and the opening will take place gradually on site or by phone.

12.3 Level of centre monitoring

In the case of this research, which is considered B risk, the appropriate monitoring level will be determined based on the complexity, the impact and the budget for the research. Thus, the sponsor and the coordinating investigator have agreed on the logistic score and impact, resulting in a research monitoring level to be implemented.

12.4 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper conduct of the research, for collecting and documenting, recording and reporting the data generated in writing, in accordance with the Standard Operating Procedures applied within the DRCI and in accordance with the French Good Clinical Practices as well as with the legislative and regulatory provisions in force.
The investigator and the members of the investigator's team agree to make themselves available during Quality Control visits carried out at regular intervals by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent
- compliance with the research protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

12.5 Case Report Form

All information required according to the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Each missing data item must be coded.
This digital case report form will be implemented in each of the centres thanks to a web-based data collection medium. Investigators will be given a document offering guidance in using this tool.
When the investigators complete the case report via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. Thus, the investigator must validate any changes to the values in the case report form. These modifications will be subject to an audit trail. A justification can be added when applicable, as a comment.

12.6 Management of non-compliances

Any events that occur as a result of non-compliance, by the investigator or any other individual involved in conducting the research, with the protocol, with the standard operating procedures, with the good clinical practices or with the legislative and regulatory provisions in force must be noted.

12.7 Audits/inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. Medical secrecy cannot be invoked in opposition to these audits and inspections.

An audit can be carried out at any time by individuals appointed by the sponsor and who are not associated with the research directors. The objective of the audit is to ensure the quality of the research, the validity of the results and compliance with the legislation and regulations in force.

The individuals who lead and monitor the research agree to comply with the sponsor's requirements and with the competent authority regarding research audits or inspections.

The audit may be applicable to all stages of the research, from the development of the protocol to the publication of the results and the organisation of the data used or produced as part of the research.

12.8 Primary investigator's commitment to assume responsibility

Before starting the research, each investigator will give the sponsor’s representative a copy of his/her personal curriculum vitæ, signed and dated, with his/her number in the RPPS (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals).

Each investigator will undertake to comply with the legislation and to carry out the research according to French GCP, adhering to the Declaration of Helsinki terms in force.

The primary investigator at each participating centre will sign a responsibility commitment (standard DRCI document) which will be sent to the sponsor's representative.

The investigators and their employees will sign a delegation of duties form specifying each person's role.

13 ETHICAL AND LEGAL CONSIDERATIONS

13.1 Methods for obtaining information and consent from research participants

In accordance with Article L1122-1-1 of the French Public Health Code, no biomedical research can be carried out on a person without free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code.

The subject will be granted a reflection period of 15 days between the time when the subject receives the first information (during the screening phase) and the time when he or she signs the consent form.

The free and informed consent, in writing, of the subject is obtained by the investigator, or by a doctor representing the investigator, before the inclusion of the subject in the research.

The information sheet and a copy of the consent form, signed and dated by the research subject and by the investigator or the doctor representing the investigator, are given to the individual prior to his or her participation in the research.

In addition, the investigator will specify in the research participant's medical file the methods used for obtaining his or her consent as well as the methods used for providing information

with the goal of obtaining their consent. The investigator will retain the original signed and dated copy of the subject's consent form.
The patient is considered as include in the research at the moment of his(her) randomization.

13.2 Legal obligations

The sponsor's role

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this research and by delegation, the Clinical Research and Innovation Delegation (DRCI) carries out the research's missions in accordance with Article L.1121-1 of the French Public Health Code. Assistance Publique - Hôpitaux de Paris reserves the right to halt the research at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

Request for an opinion from the Comité de Protection des Personnes (CPP, ethical review board)

AP-HP, as sponsor, obtains for this biomedical research relating to a medication for human use and prior to starting the research, the favourable opinion of the appropriate CPP, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

Request for authorisation to ANSM

AP-HP, as sponsor, obtains for this biomedical research relating to a medication for human use and prior to starting the research, authorisation from the ANSM, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

Commitment to compliance with the MR 001 "Méthodologie de Reference"

AP-HP, the research sponsor, has signed a commitment to comply with this "Méthodologie de reference".

13.3 Modifications to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to starting the research, a favourable opinion from the CPP and authorisation from the ANSM within the scope of their respective authorities.
The information sheet and the consent form can be revised if necessary, in particular if there is a substantial modification to the research or if adverse reactions occur.

13.4 Final research report

The final biomedical research report referred to in Article R1123-60 of the French Public Health Code is drawn up and signed by the sponsor and the investigator. A summary of the report written according to the competent authority’s reference plan will need to be sent to the competent authority and ethical review board within one year after the end of the research, meaning the end of the participation of the last research subject.

14 FUNDING AND INSURANCE

14.1 Funding source

The PHRC

14.2 Insurance

For the duration of the research, the Sponsor will take out an insurance policy covering the sponsor's own civil liability as well as the civil liability of all the doctors involved in carrying out the research. The sponsor will also provide full compensation for all harmful consequences of the research for the research subjects and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. The act of a third party or the voluntary withdrawal of the person who initially consented to participate in the research cannot be invoked against said compensation.
Assistance Publique- Hôpitaux de Paris (AP-HP) has taken out insurance from HDI-GERLING through BIOMEDIC-INSURE for the full research period, covering its own civil liability and that of any agent (doctor or research staff), in accordance with Article L.1121-10 of the French Public Health Code.

15 PUBLICATION RULES

15.1 Mention of the AP-HP manager (DRCI) and URC in the acknowledgements of the text

"The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l'Innovation, Clinical Research and Innovation Delegation)".

"The authors thank URC-CIC Paris Centre for the implementation, monitoring and data management of the study."

15.2 Mention of the financier in the acknowledgements of the text

"The research was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2014 (Ministère de la Santé)" and sponsored by the Délégation à la Recherche Clinique et à l'Innovation de l'Assistance Publique–Hôpitaux de Paris.

This research will be registered on the website http://clinicaltrials.gov/

16 LIST OF ADDENDA

16.1 List of Investigators

16.2 Equivalence Table RAS blockade

Tableau d'équivalence des doses pour les antagonistes du récepteur de l'angiotensine de type 2

nom	Faible dose (quotidienne)	Demi-dose (quotidienne)	Pleine dose (quotidienne)	Forte dose (quotidienne)
Candésartan	4 mg	8 mg	16 mg	> 16 mg
Eprosartan	-	300 mg	600 mg	> 600 mg
Irbésartan	75 mg	150 mg	300 mg	> 300 mg
Losartan	25 mg	50 mg	100 mg	> 100 mg
Olmésartan	10 mg	20 mg	40 mg	>40 mg
Telmisartan	20 mg	40 mg	80 mg	> 80 mg
Valsartan	40 mg	80 mg	160 mg	> 160 mg

Tableau « d'équivalence » de doses pour les inhibiteurs de l'enzyme de conversion

	Faible dose (quotidienne)	Demi-dose (quotidienne)	Pleine dose (quotidienne)	Forte dose (quotidienne)
Captopril	25 mg	50 mg	100 mg	>150 mg
Cilazapril	0,5 mg	1 mg	2,5 mg	>5 mg
Bénazépril	2,5 mg	5 mg	10 mg	>20 mg
Enalapril	5 mg	10 mg	20 mg	>40 mg
Fosinopril	5 mg	10 mg	20 mg	>40 mg
Imidapril	2,5 mg	5 mg	10 mg	>20 mg
Lisinopril	5 mg	10 mg	20 mg	>40 mg
Moexipril	-	7,5 mg	15 mg	>30 mg
Périndopril	2 mg	4/5 mg	8/10mg	>16/20 mg
Quinapril	5 mg	10 mg	20 mg	>40 mg
Ramipril	1,25 mg	2,5 mg	5 mg	>10 mg
Trandolapril	0,5 mg	1 mg	2 mg	>4 mg
Zofénopril	-	15 mg	30 mg	>60 mg

16.3 Summary of Product Characteristics

METHYLPREDNISOLONE 500 mg, poudre pour solution injectable
http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=62628873&typedoc=R

PREDNISONE 5 mg, comprimé sécable
http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=66640556&typedoc=R

PREDNISONE 20 mg, comprimé sécable
http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=64233693&typedoc=R

16.4 Abaques

Etude TIGER : Abaques prednisone

POSOLOGIE 1 mg/kg/jour

Poids (kg)	Dose en mg (poso 1mg/kg/j)	Arrondi dose (mg/jour)	Nb de cpr de 20 mg par jour	Nb de cpr de 5 mg par jour	Nb total de cpr par jour
30	30	**30**	1	**2**	3
31	31	**30**	1	2	3
32	32	**30**	1	2	3
33	33	**35**	1	3	4
34	34	**35**	1	3	4
35	35	**35**	1	3	4
36	36	**35**	1	3	4
37	37	**35**	1	3	4
38	38	**40**	2	0	2
39	39	**40**	2	0	2
40	40	**40**	2	0	2
41	41	**40**	2	0	2
42	42	**40**	2	0	2
43	43	**45**	2	1	3
44	44	**45**	2	1	3
45	45	**45**	2	1	3
46	46	**45**	2	1	3
47	47	**45**	2	1	3
48	48	**50**	2	2	4
49	49	**50**	2	2	4
50	50	**50**	2	2	4
51	51	**50**	2	2	4
52	52	**50**	2	2	4
53	53	**55**	2	3	5
54	54	**55**	2	3	5
55	55	**55**	2	3	5
56	56	**55**	2	3	5
57	57	**55**	2	3	5
58	58	**60**	3	0	3
59	59	**60**	3	0	3
60	60	**60**	3	0	3
61	61	**60**	3	0	3
62	62	**60**	3	0	3
63	63	**65**	3	1	4
64	64	**65**	3	1	4
65	65	**65**	3	1	4

Poids (kg)	Dose en mg (poso 1mg/kg/j)	Arrondi dose (mg/jour)	Nb de cpr de 20 mg par jour	Nb de cpr de 5 mg par jour	Nb total de cpr par jour
66	66	**65**	3	1	4
67	67	**65**	3	1	4
68	68	**70**	3	2	5
69	69	**70**	3	2	5
70	70	**70**	3	2	5
71	71	**70**	3	2	5
72	72	**70**	3	2	5
73	73	**75**	3	3	6
74	74	**75**	3	3	6
75	75	**75**	3	3	6
76	76	**75**	3	3	6
77	77	**75**	3	3	6
78	78	**80**	4	0	4
79	79	**80**	4	0	4
80	80	**80**	4	0	4
81	80	**80**	4	0	4
82	80	**80**	4	0	4
83	80	**80**	4	0	4
84	80	**80**	4	0	4
85	80	**80**	4	0	4
86	80	**80**	4	0	4
87	80	**80**	4	0	4
88	80	**80**	4	0	4
89	80	**80**	4	0	4
90	80	**80**	4	0	4
91	80	**80**	4	0	4
92	80	**80**	4	0	4
93	80	**80**	4	0	4
94	80	**80**	4	0	4
95	80	**80**	4	0	4
96	80	**80**	4	0	4
97	80	**80**	4	0	4
98	80	**80**	4	0	4
99	80	**80**	4	0	4
100	80	**80**	4	0	4
101	80	**80**	4	0	4
102	80	**80**	4	0	4
103	80	**80**	4	0	4
104	80	**80**	4	0	4
105	80	**80**	4	0	4
106	80	**80**	4	0	4

Poids (kg)	Dose en mg (poso 1mg/kg/j)	Arrondi dose (mg/jour)	Nb de cpr de 20 mg par jour	Nb de cpr de 5 mg par jour	Nb total de cpr par jour
107	80	**80**	4	0	4
108	80	**80**	4	0	4
109	80	**80**	4	0	4
110	80	**80**	4	0	4

POSOLOGIE 0,50 mg/kg/jour

Poids (kg)	Dose en mg (Poso 0,50 mg/kg/j)	Arrondi dose (mg/jour)	Nb de cpr de 20 mg par jour	Nb de cpr de 5 mg par jour	Nb total de cpr par jour
30	15	**15**	0	3	3
31	15,5	**15**	0	3	3
32	16	**15**	0	3	3
33	16,5	**15**	0	3	3
34	17	**15**	0	3	3
35	17,5	**20**	1	0	1
36	18	**20**	1	0	1
37	18,5	**20**	1	0	1
38	19	**20**	1	0	1
39	19,5	**20**	1	0	1
40	20	**20**	1	0	1
41	20,5	**20**	1	0	1
42	21	**20**	1	0	1
43	21,5	**20**	1	0	1
44	22	**20**	1	0	1
45	22,5	**25**	1	1	2
46	23	**25**	1	1	2
47	23,5	**25**	1	1	2
48	24	**25**	1	1	2
49	24,5	**25**	1	1	2
50	25	**25**	1	1	2
51	25,5	**25**	1	1	2
52	26	**25**	1	1	2
53	26,5	**25**	1	1	2
54	27	**25**	1	1	2
55	27,5	**30**	1	2	3
56	28	**30**	1	2	3
57	28,5	**30**	1	2	3
58	29	**30**	1	2	3

Poids (kg)	Dose en mg (Poso 0,50 mg/kg/j)	Arrondi dose (mg/jour)	Nb de cpr de 20 mg par jour	Nb de cpr de 5 mg par jour	Nb total de cpr par jour
59	29,5	**30**	1	2	3
60	30	**30**	1	2	3
61	30,5	**30**	1	2	3
62	31	**30**	1	2	3
63	31,5	**30**	1	2	3
64	32	**30**	1	2	3
65	32,5	**35**	1	3	4
66	33	**35**	1	3	4
67	33,5	**35**	1	3	4
68	34	**35**	1	3	4
69	34,5	**35**	1	3	4
70	35	**35**	1	3	4
71	35,5	**35**	1	3	4
72	36	**35**	1	3	4
73	36,5	**35**	1	3	4
74	37	**35**	1	3	4
75	37,5	**40**	2	0	2
76	38	**40**	2	0	2
77	38,5	**40**	2	0	2
78	39	**40**	2	0	2
79	39,5	**40**	2	0	2
80	40	**40**	2	0	2
81	40	**40**	2	0	2
82	40	**40**	2	0	2
83	40	**40**	2	0	2
84	40	**40**	2	0	2
85	40	**40**	2	0	2
86	40	**40**	2	0	2
87	40	**40**	2	0	2
88	40	**40**	2	0	2
89	40	**40**	2	0	2
90	40	**40**	2	0	2
91	40	**40**	2	0	2
92	40	**40**	2	0	2
93	40	**40**	2	0	2
94	40	**40**	2	0	2
95	40	**40**	2	0	2
96	40	**40**	2	0	2
97	40	**40**	2	0	2
98	40	**40**	2	0	2
99	40	**40**	2	0	2

Poids (kg)	Dose en mg (Poso 0,50 mg/kg/j)	Arrondi dose (mg/jour)	Nb de cpr de 20 mg par jour	Nb de cpr de 5 mg par jour	Nb total de cpr par jour
100	40	**40**	2	0	2
101	40	**40**	2	0	2
102	40	**40**	2	0	2
103	40	**40**	2	0	2
104	40	**40**	2	0	2
105	40	**40**	2	0	2
106	40	**40**	2	0	2
107	40	**40**	2	0	2
108	40	**40**	2	0	2
109	40	**40**	2	0	2
110	40	**40**	2	0	2

POSOLOGIE 0,25 mg/kg/jour

Poids (kg)	Dose en mg (Poso 0,25 mg/kg/j)	Arrondi dose (mg/jour)	Nb de cpr de 20 mg par jour	Nb de cpr de 5 mg par jour	Nb total de cpr par jour
30	7,5	**10**	0	2	2
31	7,75	**10**	0	2	2
32	8	**10**	0	2	2
33	8,25	**10**	0	2	2
34	8,5	**10**	0	2	2
35	8,75	**10**	0	2	2
36	9	**10**	0	2	2
37	9,25	**10**	0	2	2
38	9,5	**10**	0	2	2
39	9,75	**10**	0	2	2
40	10	**10**	0	2	2
41	10,25	**10**	0	2	2
42	10,5	**10**	0	2	2
43	10,75	**10**	0	2	2
44	11	**10**	0	2	2
45	11,25	**10**	0	2	2
46	11,5	**10**	0	2	2
47	11,75	**10**	0	2	2
48	12	**10**	0	2	2
49	12,25	**10**	0	2	2
50	12,5	**15**	0	3	3
51	12,75	**15**	0	3	3

Poids (kg)	Dose en mg (Poso 0,25 mg/kg/j)	Arrondi dose (mg/jour)	Nb de cpr de 20 mg par jour	Nb de cpr de 5 mg par jour	Nb total de cpr par jour
52	13	**15**	0	3	3
53	13,25	**15**	0	3	3
54	13,5	**15**	0	3	3
55	13,75	**15**	0	3	3
56	14	**15**	0	3	3
57	14,25	**15**	0	3	3
58	14,5	**15**	0	3	3
59	14,75	**15**	0	3	3
60	15	**15**	0	3	3
61	15,25	**15**	0	3	3
62	15,5	**15**	0	3	3
63	15,75	**15**	0	3	3
64	16	**15**	0	3	3
65	16,25	**15**	0	3	3
66	16,5	**15**	0	3	3
67	16,75	**15**	0	3	3
68	17	**15**	0	3	3
69	17,25	**15**	0	3	3
70	17,5	**20**	1	0	1
71	17,75	**20**	1	0	1
72	18	**20**	1	0	1
73	18,25	**20**	1	0	1
74	18,5	**20**	1	0	1
75	18,75	**20**	1	0	1
76	19	**20**	1	0	1
77	19,25	**20**	1	0	1
78	19,5	**20**	1	0	1
79	19,75	**20**	1	0	1
80	20	**20**	1	0	1
81	20	**20**	1	0	1
82	20	**20**	1	0	1
83	20	**20**	1	0	1
84	20	**20**	1	0	1
85	20	**20**	1	0	1
86	20	**20**	1	0	1
87	20	**20**	1	0	1
88	20	**20**	1	0	1
89	20	**20**	1	0	1
90	20	**20**	1	0	1
91	20	**20**	1	0	1
92	20	**20**	1	0	1

Poids (kg)	Dose en mg (Poso 0,25 mg/kg/j)	Arrondi dose (mg/jour)	Nb de cpr de 20 mg par jour	Nb de cpr de 5 mg par jour	Nb total de cpr par jour
93	20	**20**	1	0	1
94	20	**20**	1	0	1
95	20	**20**	1	0	1
96	20	**20**	1	0	1
97	20	**20**	1	0	1
98	20	**20**	1	0	1
99	20	**20**	1	0	1
100	20	**20**	1	0	1
101	20	**20**	1	0	1
102	20	**20**	1	0	1
103	20	**20**	1	0	1
104	20	**20**	1	0	1
105	20	**20**	1	0	1
106	20	**20**	1	0	1
107	20	**20**	1	0	1
108	20	**20**	1	0	1
109	20	**20**	1	0	1
110	20	**20**	1	0	1

POSOLOGIE 0,10 mg/kg/jour

Poids (kg)	Dose en mg (Poso 0,10 mg/kg/j)	Arrondi dose (mg/jour)	Nb de cpr de 20 mg par jour	Nb de cpr de 5 mg par jour	Nb total de cpr par jour
30	3	**5**	0	1	1
31	3,1	**5**	0	1	1
32	3,2	**5**	0	1	1
33	3,3	**5**	0	1	1
34	3,4	**5**	0	1	1
35	3,5	**5**	0	1	1
36	3,6	**5**	0	1	1
37	3,7	**5**	0	1	1
38	3,8	**5**	0	1	1
39	3,9	**5**	0	1	1
40	4	**5**	0	1	1
41	4,1	**5**	0	1	1
42	4,2	**5**	0	1	1
43	4,3	**5**	0	1	1
44	4,4	**5**	0	1	1

Poids (kg)	Dose en mg (Poso 0,10 mg/kg/j)	Arrondi dose (mg/jour)	Nb de cpr de 20 mg par jour	Nb de cpr de 5 mg par jour	Nb total de cpr par jour
45	4,5	**5**	0	1	1
46	4,6	**5**	0	1	1
47	4,7	**5**	0	1	1
48	4,8	**5**	0	1	1
49	4,9	**5**	0	1	1
50	5	**5**	0	1	1
51	5,1	**5**	0	1	1
52	5,2	**5**	0	1	1
53	5,3	**5**	0	1	1
54	5,4	**5**	0	1	1
55	5,5	**5**	0	1	1
56	5,6	**5**	0	1	1
57	5,7	**5**	0	1	1
58	5,8	**5**	0	1	1
59	5,9	**5**	0	1	1
60	6	**5**	0	1	1
61	6,1	**5**	0	1	1
62	6,2	**5**	0	1	1
63	6,3	**5**	0	1	1
64	6,4	**5**	0	1	1
65	6,5	**5**	0	1	1
66	6,6	**5**	0	1	1
67	6,7	**5**	0	1	1
68	6,8	**5**	0	1	1
69	6,9	**5**	0	1	1
70	7	**5**	0	1	1
71	7,1	**5**	0	1	1
72	7,2	**5**	0	1	1
73	7,3	**5**	0	1	1
74	7,4	**5**	0	1	1
75	7,5	**10**	0	2	2
76	7,6	**10**	0	2	2
77	7,7	**10**	0	2	2
78	7,8	**10**	0	2	2
79	7,9	**10**	0	2	2
80	8	**10**	0	2	2
81	8	**10**	0	2	2
82	8	**10**	0	2	2
83	8	**10**	0	2	2
84	8	**10**	0	2	2
85	8	**10**	0	2	2

Poids (kg)	Dose en mg (Poso 0,10 mg/kg/j)	Arrondi dose (mg/jour)	Nb de cpr de 20 mg par jour	Nb de cpr de 5 mg par jour	Nb total de cpr par jour
86	8	**10**	0	2	2
87	8	**10**	0	2	2
88	8	**10**	0	2	2
89	8	**10**	0	2	2
90	8	**10**	0	2	2
91	8	**10**	0	2	2
92	8	**10**	0	2	2
93	8	**10**	0	2	2
94	8	**10**	0	2	2
95	8	**10**	0	2	2
96	8	**10**	0	2	2
97	8	**10**	0	2	2
98	8	**10**	0	2	2
99	8	**10**	0	2	2
100	8	**10**	0	2	2
101	8	**10**	0	2	2
102	8	**10**	0	2	2
103	8	**10**	0	2	2
104	8	**10**	0	2	2
105	8	**10**	0	2	2
106	8	**10**	0	2	2
107	8	**10**	0	2	2
108	8	**10**	0	2	2
109	8	**10**	0	2	2
110	8	**10**	0	2	2

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