# RaDiCo COHORT STUDY INFORMATION SHEET

## RaDiCo-EURBIO-Alport

**Full title:**

**Study of the natural history of Alport Syndrome by establishment of an international database**


**Study sponsor: Inserm**

**Principal Investigator: Dr Laurence Heidet**

**Co-Principal Investigator: Prof Bertrand Knebelmann**

Inserm U1151 / Service de Néphrologie Adulte

AP-HP - Hôpital Necker-Enfants Malades, Paris, FRANCE


### Current status of regulatory authorisations

**Inserm's sponsorship agreement:** 30/10/2015 / **Ethical clearance:** 31/03/2016 / **CCTIRS clearance:** 17/02/2016 / **CNIL authorisation:** 13/03/2017 / **Biocollection clearance:** 15/04/2016 / **Information System security conformity audit (HADS):** Q4 2017

| Study kick off date | Inclusion period | Follow-up period |
|---|---|---|
| **Q4 2017** | **2 years** | **3 years (min 1 visit/year)** |

### Background and rationale

- Alport Syndrome (AS) is a rare genetic disease, characterized by the association of a glomerular nephropathy progressing toward end-stage renal failure, with deafness, and ocular defect
- Significant progress made in understanding the molecular mechanisms responsible for the disease, but little in the comprehension of the progression of renal failure and in the field of therapeutics
- Realization of therapeutic trials in humans requires knowing perfectly the natural history of the disease and to enrol a sufficient number of patients
- Studies and treatment indications would be greatly facilitated by the discovery of biomarkers allowing to predict, earlier than the date of onset of proteinuria, the progression to renal failure
- The reference center MARHEA, only site in France performing molecular diagnosis of the disease in routine, has established a national database on AS, with the support of the National Databank on Rare Disease BNDMR (CEMARA petal) which currently includes 440 patients and a collection of clinical, biological, morphological and molecular information, and is regularly updated
- The project will allow to expand to Europe the database on AS

### Study type

European multicentre, observational

### Objectives

**Primary objective**

- To study the natural history of AS

**Secondary objectives**

- Evaluation of tolerance and compliance to treatments with RAAS blockers (for French sites only)
- Evaluation of the disease impact on quality of life as well as social impact

**Exploratory objectives**

- To study the feasibility of therapeutic trial in term of number of patients that may be enrolled, at the different stages of the disease
- To search for early biomarkers able to predict the progression of the disease and to evaluate the efficacy of treatments. This will be done through the establishment of a collection of urine samples from patients affected with early stage AS
- Evaluation of the ease for patients and families of access to molecular diagnosis and genetic counselling

### Inclusion and non-inclusion criteria

**Inclusion criteria**

- Diagnosis of AS based on:
  (i) electron microscopic examination of the renal biopsy, and/or
  (ii) molecular studies, and/or
  (iii) abnormal expression of type IV collagen chains on skin and/or glomerular basement membranes
- Signed informed consent

**Non-inclusion criteria**

- Patients not able to give their informed consent

### Evaluation criteria

**Evaluation criteria of the primary endpoint**

- Description of the symptoms and variations in the disease's course
  - Renal function: eGFR, age at ESRD, requirement of Renal Replacement Therapy (RRT) and type of RRT
  - Urine bio-analysis results: presence or not and quantification of haematuria, microalbuminuria and proteinuria
  - Presence or not of hypertension
  - Level of hearing loss
  - Ocular symptoms

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**Secondary evaluation criteria**

- Records of adverse events for the long-term safety of RAAS blockers treatment
- Impact of disease on QoL evaluation through scores of QoL questionnaires SF36 for adult et SF10 for paediatric patients
- Compliance evaluation using X. Girerd Compliance Questionnaire

## Power

- Prevalent patients: From 1500 among Germany, Spain, United Kingdom, Italy, Belgium, and France and up to 2500 with USA
- Estimated incident patients: 400 (200 per year (global incident rate for participating countries: Germany, Spain, United Kingdom, Italy, Belgium, Hungary, France and possibly USA) during 2 years (inclusion period))
- Therefore, it is possible to enrol a maximum of **about 2000 patients** or with the possible addition of the ASTOR database (USA), up to **about 3000 patients**. However, only patients willing to participate will be included
- Even with a high attrition rate, the number of **1000 included patients seems reachable** and will allow to answer study objectives

## Statistical analysis

- Descriptive analysis of the disease progression, occurrence of complications given the treatments, according to gender and mode of heritability, to look for peculiar patient profiles to be included in randomized controlled trials
- Analysis of patients' compliance according to Girerd's questionnaire
- Predictive analysis looking for biomarkers of disease progression, using a propensity score approach, and according to clinical/biological covariates
- Search for genotype – phenotype relationships
- Qol analysis according to age, disease stage and treatments

## Biocollections

- Urine samples only for patients not at ESRD stage and followed by French sites. Two tubes of 15 ml will be collected: one with and one without protease inhibitors. The first tube will be used to measure the 5 biomarkers previously shown by F Terzi's group to be able to predict the evolution of the CKD better than albuminuria
- Tubes to be sent to: Laboratoire Inserm U1151, 6ème étage, Bâtiment Lavoisier, Hôpital Necker, 75015 Paris, FRANCE

| Number of recruiting sites | Prevalent cases retrieved / Inclusion targets vs. current status | |
|---|---|---|
| | Year 1 | Year 2 |
| **Potentially France 34, Germany 1, Spain 1, Italy 1, United-Kingdom 1, Hungary 1, Belgium 1 and potentially USA** | **440 (Fr)-1500 (EU) / 200 (EU)** | **2000 (EU)** |
| | 600 / 0 | - |

## Public-Private Partnerships valorising the cohort resources

Pending project

## European valorisation / extension of the cohort

- The study will be initiated in France. To be extended to Europe in a second step
- Will be a key database within ERKNet, the European Rare Kidney Disease Reference Network (ERN)