

RaDiCo COHORT STUDY INFORMATION SHEET

RaDiCo-MPS

Full title:

Mucopolysaccharidosis patients in France in the era of specific therapeutics

Study sponsor: Inserm

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Inserm UMR_ 1141

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Current status of regulatory authorisations

Inserm's sponsorship agreement: 25/05/2016 / **Ethical clearance:** 06/09/2016 / **CCTIRS clearance:** 16/09/2016 / **Biocollection clearance:** 24/09/2016 / **Information System security conformity audit (HADS):** Nov 2017

Study kick off date

November 2017

Inclusion period

2 years

Follow-up period

5 years (inclusion + min 1 visit/year)

Background and rationale

- Rare diseases with an estimated global incidence of 1/25-30,000 births
- Lysosomal storage disorders caused by accumulation of sulphated carbohydrate polymers deriving from sulphated monosaccharides or glycosaminoglycans (GAG) in the lysosomes leading to multisystemic disease manifestations
- Autosomal recessive inheritance for all but MPS-II, Hunter disease, an X-linked disorder
- Genes responsible for the 11 enzyme deficiencies corresponding to 7 clinical subtypes (MPS I-IV, VI et IX)
- Chronic, progressive multivisceral diseases. Age at first symptoms may vary according to the severity of the disease, in early infancy or childhood in severe cases (even antenatal)
- Neurological complications, spinal cord compression and carpal tunnel syndrome common in most MPS; cognitive impairment and behavioural disturbance in some MPS
- Diagnostic methods: urinary GAG assay and enzyme activities measurement, molecular analysis
- Disease-specific treatments available for some of the disorders: enzyme replacement therapy (ERT) and haematopoietic stem cell transplantation (HSCT) offer substantial benefit but no cure
- Several therapeutic options under development; gene therapy and substrate inhibitors

Study type

French multicenter, non-interventional, associated with a biocollection (urine and plasma)

Objectives

objective

- To characterize the epidemiology and natural history of MPS diseases

Secondary objectives

- To evaluate the global benefit (including Quality of Life) of current treatments
- To establish correlations between phenotypes and genotypes for each type of MPS
- To evaluate the global direct and indirect costs of MPS care

Exploratory objectives

- To Identify new and meaningful biomarkers for future clinical trials, in terms of therapeutic strategies to improve patient care

Inclusion and non-inclusion criteria

Inclusion criteria

- Confirmed diagnosis of MPS (based on significant enzyme deficiency, with abnormally elevated GAG urinary excretion (completed or not by mutational analysis))
- Signed informed consent

Non-inclusion criteria

- None

Evaluation criteria

Primary objective

- Description of MPS natural progression based on clinical, radiological, electrophysiological, biochemical, and molecular data
- Definition of diseases subgroups based on (i) the type of MPS, (ii) the variables considered (e.g. some variables are overlapping between all or one subgroup of MPS), (iii) the treatment status: ERT, HSCT, symptomatic (iv) other relevant events

Secondary objectives

- Description of the relevant MPS outcomes given the treatment received
- Analysis of the QoL score per MPS group and subgroups
- Evaluation of the general trends of the medico-social burden

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- Medico-economic evaluation of MPS care
- Genotype / phenotype association study between based on explicative multivariate analysis

Exploratory objectives

- Association study between candidate biomarkers and the positive response to treatment

Power

- Considering the context of rare disease and the low number of patients per sub-groups, all available patients willing to participate will be included. To date, there are no data that would allow relevant hypotheses leading to a sample size calculation
- According to the number of known MPS patients (about 1000 to date including deceased patients and covering all MPS' types) and the estimated incidence rate in France (about 30 new MPS patients/year), it is expected to include more than **1000 patients** within a 2-year inclusion period
- This will be the largest international cohort on this topic

Statistical analysis

Primary objective

- Descriptive analysis including MPS progression based on clinical, radiological, electrophysiological, biochemical, and molecular data (i) type of MPS, (iii) ongoing treatment: ERT, HSCT, symptomatic (iv) intercurrent events, including treatment adverse events
- Exploratory analysis to further aid characterizing MPS subgroups
- Survival analysis and predictive modelling according to the occurrence of relevant MPS outcomes, to search for prognostic markers of disease evolution

Secondary objectives

Evaluation of the global benefit (including Quality of Life) of current treatments using multivariate models and propensity scores

- Analysis of the QoL score in each group and subgroup
- Assessment of the medico-social burden
- medico-economic evaluation of MPS care on the basis of a micro-costing analysis

Search for associations between phenotypes and genotypes, for each type of MPS using multivariate models

Exploratory objectives

- Predictive analysis of treatment responders versus non-responders according to biomarkers (rate of urinary GAG, predicted pulmonary forced vital capacity (FVC), distance walked in the 6-min walk test, etc.) following the TRIPOD statement and a propensity score approach.

Biollections

- Prospective standardised urine and plasma biocollection for future biomarkers studies, centralised in Necker (Paris) and HCL (Lyon) CRBs. Samples to be collected at inclusion and once a year when patient is under treatment

Number of recruiting sites	Inclusion targets vs current status	
13 in France, through the network of reference and recognised expert centres for rare metabolic inherited diseases	Year 1	Year 2
	500	1000
	0	-

Public-Private Partnerships valorising the cohort resources

- Specific Research Project negotiated with **Shire**: Real life impact of Elaprase treatment in MPS-II patients (**2,02 millions €**)
- Specific Research Project under discussion with **Sanofi Genzyme**: Real life benefit of Aldurazyme treatment in MPS-I patients
- Specific Research Project under discussion with **Ultragenyx**: enzymotherapy of MPS-VII (Sly disease)

European valorisation / extension of the cohort

- None at present