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Studying the feasibility and safety of gene therapy to treat limb girdle muscular dystrophy (LGMD) type 2C

Submission date	Recruitment status	[ ] Prospectively registered
17/03/2011	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
08/04/2011	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
08/04/2011	Musculoskeletal Diseases	[ ] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Prof Serge Herson

Contact details
Service de Médecine Interne
Groupe Hospitalier Pitié-Salpêtrière
47 boulevard de l'Hôpital
Paris
France
75013

Additional identifiers

Protocol serial number
GTG001.06

Study information

Scientific Title
Phase I clinical study of AAV1-gamma-sarcoglycan gene therapy for limb girdle muscular dystrophy type 2C

Study objectives
Evaluation of clinical safety and feasibility of gene therapy in patients with limb girdle muscular dystrophy type 2C (gamma-sarcoglycanopathy)

Ethics approval required
Old ethics approval format

Ethics approval(s)
Committee for the Protection of Persons (CPP) Ile de France VI [Comité de Protection des Personnes (CPP) Ile de France VI] approved on 10/10/2006

Primary study design
Interventional

Study design
Phase I open-label dose escalation three cohort single institutional clinical trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Limb girdle muscular dystrophy (LGMD), type 2C (gamma-sarcoglycanopathy)

Interventions
1. No placebo arm
2. Six month follow-up on AAV1 γ-sarcoglycan, AAV1 replication-defective vector expressing the human γ-sarcoglycan gene under the control of the desmin promoter, prepared for clinical use under cGMP conditions for biologics to be used in clinical trials
3. Three dose levels: 3x109 vg/100µl, 1,5x1010 vg/100µl and three concomitant injections of 1.5 x1010 vg/100µl into the same site (i.e. a dose of 4.5x1010 vg/300µl)
4. Single intramuscular injection of product into carpi radialis muscle under open procedure
5. Enrolment of subjects on a sequential mode
6. Muscular evaluation is made periodically during the 6 following months after enrolment 7. Muscular biopsy is made on day 30 after enrolment

Intervention Type
Other

Phase
Phase I

Primary outcome(s)
Assessment of clinical tolerance by standard clinical examination

Key secondary outcome(s)
1. Assessment of biological, immunological, histological and functional tolerance by laboratory monitoring, evaluation of humoral and cellular immune response to both transgene and vector as well as non-specific immune response, evaluation of histological changes on muscle biopsy and evaluation of changes in muscle function
2. Assessment of efficacy through studies of transduction efficiency, distribution, expression

and fiber type specificity and muscle biopsy histological changes (based on immunohistochemistry and Western blot studies and analysis of sarcoglycan labelling)

Completion date
01/06/2010

Eligibility

Key inclusion criteria
1. Confirmed diagnosis of LGMD 2C including:
1.1. Molecular analysis proving del525T mutation on γ-sarcoglycan gene (chromosome 13) at homozygous state
1.2. Muscle biopsy with immunohistochemical and/or Western blot analysis showing marked decrease or absence of γ-sarcoglycan staining in muscle, as well as a fibrosis assessment should be available. If not, an initial muscular biopsy may be performed during the pre-enrolment period
2. Minimum age of 15 years
3. Males and females may be equally enrolled
4. Adequate carpi radialis muscle bulk for muscle biopsy as assessed by examination
5. Subjects should be able to communicate with the investigation staff
6. Subjects should be able to understand, to comply with and to perform all needed evaluations during the trial period including muscle strength tests
7. Forearm muscle strength should be of at least 3+ as assessed through the British Medical Research Council (MRC) Manual Muscle Testing (MMT) scale
8. Subjects should also have already lost ambulation
9. Subjects should be able and willing to return for follow up
10. Subjects should be able and willing to give signed informed consent
11. For minor subjects, a signed informed consent will be given by a legally authorised representative
12. Eligible subjects belonging to a multiplex family should not be enrolled in the same cohort

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Severity of disease and presence of ill-prognosis complications:
1.1. Severe respiratory dysfunction such as subjects with tracheostomy or forced vital capacity (FVC) < 1000ml and/or < 30%
1.2. Uncompensated heart failure
1.3. An ejection fraction (EF) < 30% as measured on either echocardiography or scintigraphy
1.4. Severe rhythm disturbances and/or high degree conduction defect in the absence of a pacemaker insertion
2. Underlying conditions, diseases or active viral infections likely to increase risk of complications

or to interfere with the investigational treatment:
2.1. Contraindications for injections and muscle biopsies
2.2. Platelet count < 100,000/mm3
2.3. Total bilirubin > 10 mg/l (> 17 µmol/l)
2.4. Serum creatinine > 110 µmol/l
2.5. Lymphocytes CD4+ < 250/mm3 (< 15%)
2.6. History of diabetes mellitus
2.7. Current infectious diseases, including known positive human immunodeficiency virus (HIV) serology, hepatitis B and C
2.8. Abnormal profile on protein immunoelectrophoresis
2.9. Immunisations of any kind within the past month
2.10. Receipt of another investigational agent within 4 weeks of study enrolment
2.11. History of or current steroid medication for indications other than muscular dystrophy, chemotherapy, radiotherapy or other immunosuppressive therapy
2.12. Steroid medication, if any, should be discontinued at least 3 months before entering the protocol and not received during the study
2.13. Pregnant or lactating women
2.14. Females or males of childbearing age must be willing to employ adequate contraception, that is to use condoms during the 3 months following the administration of the product
2.15. Pre-injection neutralising anti-AAV1 antibodies titer (on pre-enrolment / D-30 visit) superior or equal to 1/800

Date of first enrolment
21/11/2006

Date of final enrolment
01/06/2010

Locations

Countries of recruitment
France

Study participating centre
Service de Médecine Interne
Paris
France
75013

Sponsor information

Organisation
Genethon (France)

ROR
https://ror.org/03fj96t64

Funder(s)

Funder type
Research organisation

Funder Name
Genethon (France)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration