A double-blind, randomized, placebo-controlled, clinical trial to test the efficacy of Epoetin alfa on physical performance of Friedreich Ataxia patients (FriEMax).

Friedreich ataxia (FRDA) is a rare genetic disorder characterised by severe neurological disability and cardiomyopathy. FRDA is the consequence of frataxin deficiency. Although several drugs have been proposed, there is no available treatment. Several trials recently demonstrated that erythropoietin can increase the intracellular levels of frataxin. The present project is aimed at testing a long term therapeutic approach using erythropoietin, which is an already available and commercialised drug. The study will test its effect on exercise capacity, which is reduced in patients with FRDA.

The trial will take place in three Italian centers (Naples, Rome, Bari), and will involve 56 FRDA patients. The trial will be randomized, placebo-controlled, double-blind.

The study was supported by the “Friedreich’s Ataxia Research Alliance (FARA)” through the Keith Michael Andrus Award and the Italian “Associazione Italiana per la lotta alle Sindromi Atassiche (AISA)” through an unrestricted grant and an additional special contribution for a dedicated arm ergometer.
Study objectives

Primary Objective
Primary objective of the study will be the effect of a one-year treatment with single and very high doses of EPO on a functional marker of FRDA. The trial will be focused on the efficacy of EPO on exercise capacity in patients with FRDA. This is a relatively new approach to a trial in FRDA. Usual primary endpoints in phase II trials are either frataxin measurements, clinical scales, or safety and tolerability measures. Safety and tolerability have already been addressed in our previous trial and should not be considered as a primary endpoint. Clinical progression is difficult to assess in a relatively small phase II trial and requires different sample size and budget.

Primary endpoint of the study is the effect EPO on peak oxygen uptake (VO\(_2\) max) at the cardiopulmonary exercise test (CPET). Patients will undergo a complete CPET at baseline (Visit 2), at 24 weeks (Visit 5), and at 48 weeks (Visit 7).

Secondary Objective
Secondary objectives of the study will be: frataxin, cardiomyopathy, vascular reactivity, clinical progression, and safety. Frataxin will be measured every three months, before each EPO administration. Cardiomyopathy progression will be measured using echocardiography. Neurological deterioration will be monitored three times during the clinical trial in order to assess the effect of EPO on disease progression, using ataxia scales and upper limbs functional tests. Safety and tolerability will be measured recording adverse events and monitoring laboratory parameters. Quality of life will be assessed using different clinical scales.

Study Plan
The trial will start with a screening visit that will assess the patient’s eligibility. At this visit, informed consent will be obtained from all patients, then inclusion/exclusion criteria will be checked, and several activities and evaluations will take place. After one to two weeks, patients will return to the study center for Visit 2. Patients will be randomized to receive the study drug or placebo. A total of 56 patients will be randomized. After 48 hours, patients will return to the study center for Visit 3 for blood sampling. Patients will then return for Visit 4 (12 weeks) for safety assessments and for study drug administration. At Visit 5 (24 weeks) for a re-assessment, and study drug administration. Visit 6 (36 weeks) will be the same as Visit 4. The study will end at Visit 7 (48 weeks) with final endpoint assessment.
FRDA is an autosomal recessive ataxia caused by a trinucleotide GAA expansion in the first intron of the FXN gene. The gene encodes for a 210aa mitochondrial protein called frataxin, whose mRNA and protein levels are severely reduced in FRDA. Clinically, the age of onset is generally around puberty and, as the disease progresses, there is increasing ataxia of the limbs, and eventually most patients are wheelchair bound by the twenties. Cardiomyopathy with myocardial hypertrophy occurs very often and is the predominant cause of death. Type II diabetes, scoliosis, foot deformities, optic atrophy, and deafness are other relatively frequent symptoms.

Erythropoietin (EPO) is a glycoprotein that acts as a main regulator for erythropoiesis. EPO increases frataxin levels in cultured human lymphocytes from FRDA patients. Six trials have tested the effect of EPO in FRDA. Five trials showed a positive effect of the drug in increasing frataxin level in peripheral cells. In our trial we used single high doses of EPO, which proved to be the best compromise between frataxin increase, side effects, and patient comfort. It consisted of one subcutaneous injection of 1200 IU/Kg of Epoietin alfa every 12 weeks, and was able to increase frataxin up to 54% of baseline levels.

The cardiopulmonary exercise test with VO2 max measurement is considered as a “gold standard” to assess cardiorespiratory fitness. Since cardiomiopathy is the most important and life threatening condition associated with FRDA, the use of VO2 max is an appropriate surrogate marker of disease progression and disability. EPO proved to be effective in increasing VO2 max, and exercise duration in patients with chronic heart failure, and in patients with chronic kidney disease. The cardiopulmonary test consists of a ten minute arm ergometer test with increasing effort. During the test oxygen consumption and cardiological parameters are measured.
Arm ergometer

Special AISA contribution for a new arm ergometer for wheelchair bound patients

Inclusion criteria:
• Molecular diagnosis of Friedreich Ataxia, with a homozygote GAA expansion in the pathological range in both alleles
• Age ≥12 years
• Body weight ≥30, ≤90 Kg
• SARA score ≤30
• Patient able to read and sign the informed consent
• Patients able to perform a cardiopulmonary test

Exclusion criteria:
• Any clinically relevant ECG abnormality that may interfere with the study
• Any abnormal and clinically relevant laboratory exams at screening visit that may interfere with the trial
• Anemia with Hemoglobin <10 g/dL
• Positive history for venous and/or arterial thrombosis
• Drug-resistant arterial hypertension or epilepsy
• Any acute/chronic disease that might interfere with the clinical trial, as judged by the investigator
• Hypersensitivity to Epoetin alfa or any other component of the study drug
• Patients not able to comply to the study
• For female patients: pregnancy and/or breastfeeding and/or inadequate contraception.
Contacts and Institution

Federico II University
The University of Naples Federico II is a university located in Naples, Italy. It was founded in 1224 and is organized into 13 faculties. It is the world's oldest state university and one of the oldest academic institutions in continuous operation. The university is named after its founder Frederick II. One of the most famous students of this university was Roman Catholic theologian and philosopher Thomas Aquinas. Fredrick II had precise objectives when he founded the university in Naples: first, to train administrative and skilled bureaucratic professionals for the "curia regis", also it was necessary to prepare lawyers and judges who would help the sovereign to draft laws and administer justice.

Secondly, he wanted to facilitate the cultural development of promising young students and scholars, avoiding any unnecessary and expensive trips abroad.

Federico II University Hospital
The Federico II Hospital serves as a hub and third level hospital for southern Italy. It consists of 24 buildings, 1100 inpatients, 24 departments, 1062 Medical Doctors, and 1200 nurses. The following regional referral centers are active in the neurology department: multiple sclerosis, epilepsy, Parkinson's disease and movement disorders, regional network for rare diseases.

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