

Research Study Protocol

Full Title: Clinical and genetic determinants of disease progression and response to lifestyle and pharmacological interventions in patients with hypertrophic cardiomyopathy

Short Title: Lifestyle and Pharmacological Interventions in Hypertrophic Cardiomyopathy

Research Protocol: Version 2.0 14th September 2018

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Abstract

The overall aim of this project is to establish potential benefits of a novel lifestyle (physical activity and dietary nitrate) and pharmacological (angiotensin receptor neprilysin inhibitor) intervention in patients with hypertrophic cardiomyopathy (HCM). HCM is the most common genetic cardiovascular disease with a broad spectrum of disease severity. Exercise training is associated with a significant increase in exercise tolerance, but appear to have limited effect on measures of cardiac morphology or function in patients with hypertrophic cardiomyopathy. Dietary supplementation with inorganic nitrate (i.e. concentrated nitrate-rich beetroot juice) improves exercise capacity, vasodilatation and cardiac output reserves while reduces arterial wave reflections, which are linked to left ventricular diastolic dysfunction and remodelling. Angiotensin receptor neprilysin inhibitor reduces death, hospitalisation, and may improve cardiac function and exercise tolerance in heart failure. Using a five-centre, open label, three-arm, pilot design, the present study will evaluate the effect of lifestyle intervention (physical activity and dietary supplementation with inorganic nitrate) and pharmacological (angiotensin receptor neprilysin inhibitor sacubitril / valsartan) in patients with hypertrophic cardiomyopathy. The Aim is to examine whether these interventions improve functional capacity, clinical phenotypic characteristics, and quality of life in patients with HCM.

Background and Rationale for the Study

Hypertrophic cardiomyopathy (HCM) is the most common hereditary cardiac disease, affecting one in 500 individuals.[1] The predominant cause is mutation of genes that encode protein components of the cardiac sarcomere.[2] The mechanisms that lead from a sarcomere gene mutation to phenotypic expression of HCM are poorly understood, which impedes the search for a treatment that can disrupt the pathophysiological process.[3]

The clinical diagnosis of HCM is based on hypertrophy of the left ventricle that cannot be explained by extrinsic factors such as increased afterload.[4] The course of the disease is highly variable, ranging from an asymptomatic, benign course with a normal life expectancy to a progressive disease characterised by angina, heart failure, atrial fibrillation, stroke, malignant arrhythmia, syncope, or sudden cardiac death. Disease progression can relate to increasing left ventricular hypertrophy and fibrosis leading to worsening of diastolic (and

occasionally systolic) function, increased left ventricular end-diastolic pressure, and left atrial enlargement.[5]

No medical treatment has been reliably shown to halt or reverse disease progression.[6] Clinical trials demonstrated limited or no effect of angiotensin receptor blockers or late sodium current inhibitor on disease progression, cardiac structure and function, exercise tolerance and quality of life in patients with HCM.[7 8] Accordingly, treatment recommendations are focused on the alleviation of symptoms, prevention of thromboembolic events, and implantation of prophylactic implantable cardioverter defibrillators in patients at high risk of sudden cardiac death.[4]

Lifestyle interventions including physical activity and dietary nitrate supplementation are safe and can improve symptoms and signs in patients with heart failure. Exercise training is associated with a significant increase in exercise tolerance, but appear to have limited effect on measures of cardiac morphology or function in patients with HCM.[15] Dietary supplementation with inorganic nitrate (i.e. concentrated nitrate-rich beetroot juice) improves exercise capacity, vasodilatation and cardiac output reserves while reduces arterial wave reflections, which are linked to a left ventricular diastolic dysfunction and remodelling.[16-18]

Angiotensin receptor neprilysin inhibitor (ARNI) is a novel treatment shown to reduce mortality and hospitalisation in heart failure with reduced ejection fraction, [9] while there is an ongoing trial to evaluate its effect on heart failure with preserved ejection fraction.[10] Recent preliminary data suggest that ARNI improves left ventricular wall motion and exercise tolerance, while reduces markers of left ventricular wall stress.[11-13] The impact of ARNI on parameters of cardiac function and remodeling has not been previously described in heart failure. Several trials are ongoing aiming provide mechanistic insight on the effect of ARNI in heart failure.[14] The effect of ARNI has not been evaluated in patients with HCM.

Despite both lifestyle and ARNI interventions may have potential positive effect, no study so far has evaluated their effect on exercise tolerance, cardiac remodelling and quality of life in patients with HCM.

Aim and Objectives:

The aim of the project is to identify clinical and genetic markers of disease progression and response to lifestyle and pharmacological interventions in patients with hypertrophic cardiomyopathy. Specifically, the project will examine whether i) Lifestyle intervention incorporating physical activity and dietary supplementation with inorganic nitrate, and ii) Angiotensin receptor neprilysin inhibitor will improve functional capacity, clinical phenotypic characteristics, and quality of life in patients with HCM. This aim will be achieved through the following objectives:

- (1) Review of the genetic testing and medical history of eligible patients.
- (2) Perform detailed clinical assessments and phenotyping before and after four months of pharmacological and lifestyle interventions i.e.:
 - Compare peak oxygen consumption by cardiopulmonary exercise testing before and after the interventions;
 - Quantitatively determine effects of the interventions on hypertrophy, left ventricular obstruction, left ventricular mass and fibrosis using echocardiography and cardiac magnetic resonance imaging.
 - Administer quality of life questionnaires before and after exercise intervention.

Main Hypotheses:

1. Lifestyle intervention incorporating physical activity and dietary supplementation will significantly improve exercise tolerance, clinical phenotype and quality of life in HCM patients.
2. Angiotensin receptor neprilysin inhibitor will significantly improve exercise tolerance, clinical phenotype and quality of life in HCM patients.

Primary outcome:

Change in exercise tolerance i.e. peak oxygen consumption and anaerobic threshold.

Secondary outcomes will include changes in:

1. Magnitude or distribution of cardiac hypertrophy or left ventricular chamber dimensions.
2. Degree of left ventricular outflow obstruction.
3. Systolic or diastolic function.
4. Cardiac energetic and left ventricular wall motion.
5. Injury and stretch activation markers.

6. Quality of life indicators.

Research Design and Methods

Overall study design

We propose to study at least 225 patients across five centres using an open label, three-arm pilot trial designed to evaluate the effect of lifestyle intervention (physical activity and dietary supplementation with inorganic nitrate) and pharmacological (angiotensin receptor neprilysin inhibitor sacubitril / valsartan) in patients with HCM, who are currently not participating in any drug trial or a regular exercise regimen (i.e. \leq minutes of exercise, \leq 1 day per week for the previous 3 months). All patients will be administered a pre-screening questionnaire in order to determine eligibility and will be randomized into a intervention or a standard (control) care group in the 2:1 ratio. This will be a collaborative effort with investigators from University Hospital Regensburg, Assistance Publique - Hôpitaux de Paris (France), Azienda Ospedaliero Universitaria Careggi Florence (Italy), Institute of Cardiovascular Diseases of Vojvodina (Serbia), and University of Newcastle (United Kingdom) who will secure their own Institutional Review Board approvals. Target number is at least 45 patients at each centre. The study will be performed at the Clinical Research Facilities, Cardiac Genetics Departments, and Magnetic Resonance Centres in participating institutions, three of which will evaluate the effect of pharmacological intervention, and two will evaluate lifestyle intervention.

Eligibility criteria

In accordance with clinical guidelines, patients diagnosed with hypertrophic cardiomyopathy are eligible for inclusion if they had a history of unexplained left ventricular hypertrophy with either a maximum wall thickness of 15 mm or more on echocardiography or borderline hypertrophy (maximum wall thickness 13–14 mm) on echocardiography and at least one first-degree relative with hypertrophic cardiomyopathy.[4]

Inclusion criteria:

1. Adults (\geq 18 years of age) with confirmed diagnosis of obstructive and/or non-obstructive hypertrophic cardiomyopathy.
2. Confirmed diagnosis of hypertrophic cardiomyopathy.
3. Agreement to be a participant in the study protocol and willing/able to return for follow-up.
4. Able to provide written informed consent.

Exclusion criteria:

1. Less than 3 months post septal reduction therapy (surgery or catheter based intervention)
2. Clinical decompensation in the previous 3 months, defined as New York Heart Association class IV congestive heart failure symptoms.
3. Resting blood pressure greater than 180/100 mm Hg.
4. Systolic blood pressure lower than 100 mmHg
5. Hypotensive response to exercise testing (≥ 20 mmHg decrease of systolic blood pressure from baseline blood pressure or an initial increase in systolic blood pressure followed by a decrease of systolic blood pressure ≥ 20 mmHg).
6. Use of angiotensin converting inhibitors or angiotensin receptor blockers.
7. Resting left ventricular outflow tract gradient > 50 mm Hg.
8. Left ventricular ejection fraction of less than 50% by echocardiography.
9. Implanted pacemaker or cardio defibrillator in the last 3 months or scheduled.
10. Renal insufficiency with an glomerular filtration rate of less than 30 mL/min per 1.73m².
11. Present or planned pregnancy.
12. Life expectancy less than 12 months.
13. Body mass index > 40 kg/m².
14. A history of exercise induced syncope or ventricular arrhythmias.
15. Inability to exercise due to orthopaedic or other non-cardiovascular limitations.
16. Use of other investigational drugs at the time of enrolment.
17. Any surgical or medical condition that in the opinion of the investigator may place the patient at higher risk from his/her participation in the study or is likely to prevent the patient from complying with the requirements of the study or completing the study.
18. History or presence of any other disease with a life expectancy of < 3 years
19. History of noncompliance to medical regimens and patients who are considered potentially unreliable.
20. History or evidence of drug or alcohol abuse within the past 12 months.
21. History of malignancy of any organ system (other than localized basal or squamous cell carcinoma of the skin or localized prostate cancer), treated or untreated, within the past 2 years, regardless of whether there is evidence of local recurrence or metastases.
22. Life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained ventricular tachycardia and AF or atrial flutter with a resting ventricular rate > 110 beats per minute.

23. Participation in competitive or organized sport activities (such as football, basketball, rugby, hockey, etc), burst activity (such as sprinting, racket sports, etc) or heavy isometric exercise (such as body building or bench-pressing) or opposition of refraining from the same for the duration of the study.

Recruitment procedures

Potentially eligible patients will be identified through the Cardiology clinics of the participating centres. Patients will be identified and contacted by the member of the study research team. An information sheet will be mailed out upon request. Consent forms will be signed by the participant and countersigned by a member of the study team during the first research visit.

Interventions

Duration of lifestyle and pharmacological interventions is proposed to be 4 months.

Lifestyle Intervention

The lifestyle intervention will consist of two integrated components i.e. physical activity and dietary supplementation with inorganic nitrate.

The first component of the lifestyle intervention is physical activity component which is a validated home-based exercise intervention aiming to increase daily physical activity level by at least 2000 steps/day from baseline (e.g. walking for approximately 30 minutes), at least 5-7 days per week, as this increment in daily physical activity was associated with a 10% lower risk of a cardiovascular events in high risk patients.[19]

The previous study confirmed the feasibility and acceptability of such physical activity intervention in patients with chronic heart failure.[20] This increase can be divided into several bouts of shorter activity duration throughout the day (e.g. 3 x 10 min or similar). To control for exercise intensity patients will be instructed to use standardised Borg Scale (0-20) to rate perceived exertion aiming for achieving the levels between 11 – 13 (easy-light-to somewhat hard). The exercise prescription will be progressed individually as conditioning takes place, with the emphasis placed on volume of activity i.e. duration before intensity. Targets will be set by participants, but we will present potential health benefits of increasing physical activity by 2000 steps per day at least five days per week (≥ 150 minutes per week). No strength training or burst activity will be prescribed and all activities will fall well within the recommended national guidelines for recreational exercise. Participants will be counselled to hydrate adequately during exercise, and to be alert to warning signs and symptoms that should prompt them to stop exercising and contact the research team. All patients will be provided with

pedometers and asked to complete a daily physical activity diary which will be reviewed and discussed on a weekly basis (telephone call) with the member of the research team. All study participants will keep an exercise log and be provided with pedometers.

The second component of the lifestyle intervention is a dietary supplementation with inorganic nitrate. A single dose of inorganic nitrate given in the form of concentrated nitrate-rich beetroot juice (NO₃⁻, BEET IT Sport, James White Drinks Ltd., Ipswich, UK) containing 6 mmol of NO₃⁻ in 70 ml bottle versus an otherwise identical nitrate-depleted placebo (James White Drinks, LTD., Ipswich, UK). Instructions will be provided for self-administration of the nutritional intervention and patients will be asked to consume beetroot juice each morning with the breakfast for 4 months.

The EPIC Food Frequency Questionnaire (FFQ) will be administered at baseline and the FETA software used to extract dietary (energy and nutrient) information.[21] Adherence to the intervention will be tracked by completion of activity logs, weekly telephone follow-ups, pedometers, and self-reported diaries.

Pharmacological Intervention

(Angiotensin receptor neprilysin inhibitor sacubitril / valsartan)

Patients who meet the study inclusion/exclusion criteria, after signing the informed consent, will be invited to the screening visit. Patients previously receiving angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy will require a 36-hour washout period before initiation of sacubitril/valsartan to reduce the risk of angioedema.[14]

The treatment period begins on day 1 with initial dosing of sacubitril/valsartan, followed by uptitration every 2 to 4 weeks, according to the prescribing information, to the target dose of 97/103 mg twice daily. The 3 doses of sacubitril/valsartan available throughout the study are 24/26 mg (dose level 1), 49/51 mg (dose Level 2), and 97/103 mg (dose Level 3), each taken by mouth twice daily.

Doses may be adjusted based on overall safety and tolerability. If necessary, dose adjustments or elimination of concomitant medications is made to alleviate adverse effects. If adverse effects are not alleviated or it is not possible to adjust concomitant medications, the study treatment may be down-titrated by 1 dose level—or, at the lowest dose, temporarily withdrawn—for 1 to 4 weeks. The patient may then be reassessed and the study treatment further down-titrated every 1 to 4 weeks until the patient is deemed stable. Once stability is

achieved, the patient is re-challenged with up-titration to the target dose. If the patient discontinues the study medication, the patient is advised to return to the clinic for an end-of-study visit. Patients undergo treatment for four months.

Control group / Usual Care

Patients with HCM typically do not receive exercise and/or nutritional therapies. The choice of a usual care (no intervention) comparator in this pilot study is therefore reflective of the situation for the vast majority of patients with HCM. In this study, the intervention and control group will receive usual medical management for HCM according to national and local guidelines. Participants in the control group will also be provided with activity logs, weekly telephone follow-ups, pedometers, and self-reported diaries but will be asked not to change their physical activity and dietary habits during the study.

Research Visits

Eligible participants will attend the Clinical Research Facilities of five participating centres for the total of 5 visits i.e. two at baseline (Visit 1 and Visit 2), and two at 4-month (Visit 3 and Visit 4) when the assessments performed during Visits 1 and 2 (detailed below) will be repeated. Patients will be given new activity logs at the end of 4-month protocol period and these logs will be reviewed 3 months later (7 months after study initiation) during the follow-up visit (Visit 5). During this visit, patients will be asked to complete quality of life questionnaires. Additionally, physical activity will be reviewed and patients will be asked to repeat cardiopulmonary exercise test.

Participants will be contacted via email, telephone or spoken to in person to discuss the project and will be taken through the information sheet to ensure they understand the nature of the study.

The following testing will be performed at study initiation and termination, as detailed below:

1. Bloods, body composition, electrocardiography, cardiac autonomic function, arterial stiffness.
2. Cardiopulmonary exercise testing in combination with echocardiography.
3. Cardiac magnetic resonance imaging in patients without implantable devices.
4. Quality of life, Anxiety and Depression, and Food Frequency questionnaires.

Mandatory procedures: Medical history review; Physical examination and anthropometry; Fasting bloods; Resting ECG; Echocardiography (rest and Valsava); Cardiopulmonary exercise stress testing; Magnetic Resonance Imaging (standard cine imaging + LGE, spectroscopy, tagging as available) for 20 randomly selected patients (at each centre) i.e. 10 intervention and 10 control; 24hr Holter monitoring; Questionnaires (2 x Quality of Life and 1 x Anxiety and Depression); and 5-7 days physical activity (pedometer). Genetic testing only in patients without existing genetic testing.

Optional procedures: Body composition (% body fat, lean body mass etc) by air displacement plethysmography, bioimpedance, or DEXA; Stress echocardiography; Arterial stiffness; Heart Rate and Blood Pressure Variability.

Research Visit 1: will be performed at the Clinical Research Facility and will last 3.5-4 hours. It will include one-hour break for breakfast. The following clinical investigations will be performed during the Visit 1:

i) Consent and Screening Questionnaires (20 minutes).

- Patients will be provided with the opportunity to ask further questions and requested to provide written informed consent. Review of the medical history will be performed.

ii) Physical examination, anthropometric and body composition (30 min).

- Body weight and height will be measured using hospital based scale and stadiometer. The amount of fat and muscle in the body will be assessed using non-invasive air displacement plethysmography (BodPod), or bioimpedance methods, as appropriate. In case of contraindications only anthropometrics (weight, height, and waist circumference) will be measured.

iii) Blood Sample and Genetic Testing (15 min).

- After an overnight fast, the blood sample will be taken from the antecubital vein. The blood sample will be assessed for brain natriuretic peptides (NTproBNP), lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol), triglycerides, glucose, HbA1c, markers of renal function (urea, creatinine, eGFR), markers of inflammation (TNF α , CRP), endothelial progenitor cells, and circulating endothelial cells. Blood sample (25 ml) will be collected before and after the intervention. In patients who did not have genetic testing performed earlier, it will

the genetic analyses will include the following genes: MYH7, MYBPC3, TNNT2, TNNI3, ACTC1, ACTN2, ANKRD1, CSRP3, FHL1, GLA, LAMP2, MYL2, MYL3, PLN, PRKAG2 and TPM1.

iv) Breakfast (60 min)

- As participants are coming following an overnight fast, they will be provided with a light breakfast consisting of a toast and orange juice. Following breakfast patients will be asked to complete validated questionnaires: Quality of Life (Minnesota Living with Heart Failure and SF36), Hospital Anxiety and Depression Scale, and Food Frequency Questionnaires.

v) Electrocardiography (ECG) (10 min).

- The ECG will be performed using a standard 12-lead electrocardiogram in supine position.

vi) Arterial stiffness assessment (10 min).

- Arterial stiffness, as a measure of arterial function, will be assessed using non-invasive SphygmoCor device which allows for both pulse wave analysis and pulse wave velocity to be performed non-invasively using the gold standard techniques. The measurement is simple and painless, taking only a few minutes to perform. While the participant is in a comfortable supine position, the researcher will place a tonometer (pencil-like sensor) gently against the wrist and will record blood pressure signal from the pulse.

vii) Cardiac autonomic function (20 min).

- Cardiac autonomic function i.e. heart rate and blood pressure variability will be assessed using non-invasive methods integrated into the TaskForce device. Using electrocardiogram and continuous blood pressure monitoring with a finger cuff under resting supine condition computer will assess heart rate variability and blood pressure variability.

viii) Transthoracic Echocardiography (ultrasound of the heart) (30 min).

- An echocardiogram is an ultrasound scan of the heart which details structure and function of the heart. Participant will be undressed to the waist. A probe (e.g. thick blunt pen) is placed on the chest. Lubricating jelly is put on the chest to form good contact between the probe and skin. The probe is connected by a wire to the ultrasound machine and monitor. Pulses of ultrasound are sent from the probe through the skin towards the heart. The ultrasound waves then echo ('bounce back') from the heart and various structures in the heart. Transthoracic

echocardiography including color and tissue Doppler will be performed at rest, in response to Valsalva manoeuvre, and at the end of cardiopulmonary exercise test, detailed below. Real-time images acquired in the standard parasternal (long-axis) and apical (apical 4, apical 2, and apical long) views, and 3 cardiac cycles recorded. Parasternal short-axis views acquired at 3 levels: basal (at mitral valve level), midpapillary, and apical (minimum cavity distal to papillary muscle level). Parasternal long axis of the right ventricular and right ventricular outflow tract will be monitored. Peak velocity of the left ventricular outflow tract will be recorded from the apical 5 chamber view by pulse Doppler, used to calculate pressure gradient. Apical 4-chamber view will be used for right ventricular evaluation.

ix) Cardiopulmonary exercise test (30 min).

- A progressive exercise test using cycle ergometer will be undertaken to assess oxygen consumption and ventilation. Patients will be asked to wear facemask to collect and analyse expired gasses. An ECG, blood pressure, and cardiac output (using non-invasive bioimpedance method that utilise 4 dual electrodes placed on the back side of the thorax) will also be performed at resting and during the exercise. Additionally heart rate will be monitored using wireless smart cardia device at rest and during exercise. In brief, using a cycle ergometer the progressive exercise test involves maintaining a pedal frequency of 60-70 revolutions per minutes with work increasing at 1 minute intervals. The test will be terminated when the patient is unable to maintain pedal frequency above 60 rpm or the patient voluntary terminates the test.

x) Holter monitoring

A type of portable heart monitor that is a small electrocardiogram (ECG) device worn in a pouch around the neck or waist. A Holter monitor keeps a record of the heart rhythm, typically over a 24-hour period, and the patient keeps a diary of activities and symptoms. The ECG recording is then correlated with the person's activities and symptoms. This type of test is useful for identifying heart disturbances that are sporadic and not readily identified with a resting ECG.

xi) Physical activity monitoring (explanation 10 min).

- At the end of all investigations the patient will be provided with the small, unobtrusive accelerometry monitor (i.e. wrist-watch and/or pedometer for counting daily number of steps)

to assess physical activity level over a 7-day period. The monitor will be returned to the research team through the post in provided pre-paid envelope.

- Lunch will also be offered at the end of research Visit 1 to study participants.

Research Visit 2: will be performed at the Magnetic Resonance Centre on different day but during the same week as Research Visit 1 depending on availability of the scanner, and will last up to 2 hours. It is expected that some people will not be eligible for the scan, particularly if they have implanted a metal device, or if they feel claustrophobic (fear of being enclosed in a small space). Cardiac magnetic resonance imaging assessment will include the following:

i) Magnetic Resonance Imaging (MRI) Screening Questionnaire (15 min).

The subject is taken through a MRI screening questionnaire (Version 1-1 April 2008) to ascertain that they have no contraindications to MRI studies by an experienced MR radiographer. They have the opportunity to ask questions about the MR studies.

ii) Cardiac MRI Examination (90 min):

Selected participants (20 per centre) without MRI examination over the previous 6 months will undergo a standard cardiac cine imaging, to evaluate cardiac morphology, systolic and diastolic function, (ii) cardiac tagging to evaluate wall motion and torsion. These measurements will be taken with the participants laying supine within a Philips 3T MRI scanner. After a short break, participants will lie in the scanner prone for phosphorus magnetic resonance spectroscopy, to measure the ratio of PCr/ATP, a measure of steady state metabolite use. Perfusion imaging performed to assess first pass perfusion during bolus injection of 0.1 mmol/kg of gadolinium contrast agent. Phase sensitive 2D inversion recovery prepared Gradient Echo imaging will be performed 15-20 minutes post injection to evaluate for delayed enhancement of the myocardium.

Research Visit 3: will be performed within 3 days after the intervention i.e. 4 months after Research Visit 1 and will include assessments undertaken during Research Visit 1.

Research Visit 4: will be performed within 7 days after the intervention i.e. 4 months after Research Visit 2 and will include assessments of the cardiac MRI undertaken during Research Visit 2.

Research Visit 5 (3-month follow-up): will be performed 7 months after study initiation when quality of life questionnaires and cardiopulmonary exercise testing will be completed, and physical activity reviewed.

End of the Study

At the end of the study all participants will be provided with information about study's major findings. This will be communicated by letter mailed to the participants home address and will

also include an invitation to attend a volunteer feedback evening at the Clinical Research Facility where the overall results of the study will be presented. The study will be completed when study participants completed the proposed research visit.

Statistical Analyses

Clinical data will be collected, coded and entered into database generated and managed by the research team. Descriptive statistics will be reported as mean \pm SD. All major treatment comparisons between the randomized groups will be performed according to the intention-to-treat principle: that is, patients will be analysed – and end points will be attributed – according to the treatment arm to which patients are randomized regardless of non-adherence. Comparisons between groups will be performed by unpaired *t* tests for continuous variables and χ^2 or Fisher's exact test for categorical variables. Changes in continuous variables over time within each group, and between groups, will be assessed by paired *t*-tests. The bivariate correlations procedure will be used to compute Pearson's correlation coefficients with the significance levels. For all subjects, multiple linear regression analysis will be performed for changes in primary and secondary outcome measures at month 6 from baseline as the dependent variable, with baseline demographic and clinical characteristics (age, sex, and genetic status) as independent variables. Results will be reported as means with 95% confidence intervals. Two-sided *P* values will be calculated for all statistical analyses. Significance will be defined as *P* less than 0.05.

Funding

This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement no. 777204.

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