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Safety and efficacy of tamoxifen therapy for myotubular myopathy

Submission date
11/03/2021

Recruitment status
No longer recruiting

Registration date
21/04/2021

Overall study status
Completed

Last Edited
08/11/2024

Condition category
Nervous System Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
X-linked myotubular myopathy (XLMTM) is a rare genetic disorder that mainly affects the muscles used for movement (skeletal muscles) and occurs almost exclusively in males. It causes muscle weakness (myopathy) and decreased muscle tone (hypotonia). The aim of this study is to test the effectiveness and safety of tamoxifen to improve motor (movement) and respiratory (breathing) function in males with XLMTM.

Who can participate?
Males aged 2 and over with myotubular myopathy resulting from a confirmed mutation in the MTM1 gene

What does the study involve?
All participants will receive tamoxifen for about 6 months (6 months +/-1 week) and placebo (dummy drug) for about 6 months (6 months +/- 1 week). Depending on random allocation, the drug or placebo will be dispensed at the end of the first study visit (Phase 1). At the end of Phase 1, participants will enter a 'washout' period when they will stop treatment. After about 3 months of washout, participants will cross over to the other treatment for the final 6 months of their study participation (Phase 2).

What are the possible benefits and risks of participating?
Known potential benefits are based on pre-clinical studies in mice treated with tamoxifen which have shown that tamoxifen treatment extends their lifespan, increases grip strength, and improves muscle disease. The most common associated adverse events in adult males were gastrointestinal (digestive) and cardiovascular (heart), but otherwise tamoxifen treatment was well-tolerated. Males treated for infertility and gynaecomastia (generally younger and prescribed tamoxifen for shorter durations) reported minimal or no side effects. The risk of these adverse events will be assessed at every clinic visit and monthly phone calls. The number of assessments at study visits may be difficult for some participants. These assessments will be completed during their routine hospital appointments if possible to avoid multiple visits. As the assessments undertaken during the study visits may be strenuous for the participants, separate appointments may have to be made to the routine hospital visits. This will be discussed with the participants, their families and the study team prior to any study visits being booked.

Where is the study run from?
Great Ormond Street Hospital for Children NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
January 2021 to October 2024

Who is funding the study?
1. Great Ormond Street Hospital Children's Charity (UK)
2. Sparks (UK)
3. Myotubular Trust (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2020-004443-86

IRAS number
286790

ClinicalTrials.gov number
NCT04915846

Secondary identifying numbers
CPMS 47284, IRAS 286790

Study information

Scientific Title
A Phase 1/2 randomized, placebo-controlled, double-blinded, single crossover study to determine the safety and efficacy of tamoxifen therapy for myotubular myopathy (XLMTM)

Acronym
TAM4MTM

Study objectives
Pre-clinical studies in MTM knockout mice demonstrated increased longevity and strength and improvement of muscle histopathology with tamoxifen treatment; it is hypothesized that tamoxifen treatment will improve motor and respiratory function in myotubular myopathy (MTM) patients. This is a randomized, double-blinded, single crossover clinical trial to determine the safety and efficacy of tamoxifen in improving motor and respiratory function in MTM

patients. Each subject will serve as his own control during the placebo phase of the study. As treatments for MTM are not available, there is a need for primary or adjunct therapies to gene therapy and enzyme replacement therapy, which are in development.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/12/2020, London - Central Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8221; londoncentral.rec@hra.nhs.uk), ref: 20/LO/1145

Study design
Interventional randomized cross over trial

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Myotubular myopathy

Interventions
Method of randomisation:
Once a patient has been confirmed as eligible for the study, the Enrollment section of the Patient Enrollment application will be completed and submitted to Ozmosis Research. No patient can receive the investigational drug/placebo treatment until the Patient Enrollment application has been submitted to Ozmosis Research and a Confirmation of Registration has been returned to the site with kit allocation details. TAM4MTM is a double-blinded clinical trial. All participants will receive tamoxifen for approximately 6 months and placebo for approximately 6 months. Neither the study team nor the participant will know which treatment regimen the participant begins with.

Methodology of treatment arms:
All participants will be taking tamoxifen and placebo for approximately 6 months each:
Phase 1 – 6 months taking either tamoxifen or placebo.
Washout period - at month 6, all participants cease the Phase 1 regimen and enter the washout

phase.
At month 9, all participants cross over to the Phase 2 regimen taking either tamoxifen or placebo.

Generic drug name, dosage and frequency:
Apo-Tamox or placebo. 10 mg tablet taken twice daily i.e. 20 mg. The dosage for the TAM4MTM clinical trial is 10 mg b.i.d (twice a day) of tamoxifen or placebo. One tablet (10 mg Apo-Tamox or placebo) should be taken in the morning and one tablet in the evening. The participant should record in the Patient Diary the time and number of tablets taken.

Duration of treatment:
The participant duration is 18 months. Screening begins at Month -3, Phase 1 is 6 months i.e. Month 1-6, washout period is 3 months i.e. Month 7-9, phase 2 is 6 months i.e. Month 10-15.

The following assessments will be completed during the course of the study:

Screening eligibility visit (Month -3):
The Principal Investigator will verify the eligibility of the participant and obtain written informed consent or written informed assent and consent from the parent or legal guardian. Written informed consent will also be obtained from one parent or legal guardian for parental participation.
Complete medical history and concomitant medications will be recorded at screening. In addition, the assessments below will also be performed at screening:
1. Demographics
2. Physical examination
3. Growth and vital signs
4. Standard safety lab tests (haematology (WBC, RBC, HBC, platelets and haematocrit), serum chemistry (CPK, AST, ALT, bilirubin, -GGT, calcium levels), hormone levels, and lipid profiles)
5. ECG
6. Abdominal ultrasound
7. Ophthalmological exam
8. Motor function measurement
9. 10-Metre Walk Test (10MWT) if ambulant
10. Pulmonary function test for subjects without tracheostomies
11. Time off vent for subjects with tracheostomies
12. Quality of life survey
13. PedsQL NMM
14. TAM4MTM survey

Subsequent study visits after the screening visit (if eligible) comprise of the following:

Clinic (in-person) study visits are month 0 (baseline), month 3, month 6, month 9, month 12 & month 15 (+/- 1 week).

Telephone study visits are month 1, month 2, month 4, month 5, month 7, month 8, month 10, month 11, month 13 and month 14 (+/- 1 week) for IMP compliance and TAM4MTM survey.

Washout period - at month 6, all participants cease the Phase 1 regimen and enter the washout phase. At month 9, all participants cross over to the Phase 2 regimen.
Safety blood draws are every 6 weeks during the drug trial phase (Months 0-15).

At each clinic (in-person) study visit, the following assessments will be performed:
1. A complete physical examination of all the organs and systems
2. Ophthalmological exam
3. Measurement of the participant's weight, and length or height
4. Growth and vital signs measurements: body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure, oxygen saturation levels, height (or length) and weight
5. ECG with Q-T measurement
6. Abdominal ultrasound
7. All adverse events (whether IMP related or not) that occurred between study visits or monthly phone calls. All adverse events prior to the screening study visit will be deemed 'medical history'. All adverse disease-related events will be recorded.
8. Use of concomitant medications and supplements
9. Motor function measurements. If the participant is ambulant, the 10MWT will also be performed
10. Pulmonary function test subject without tracheostomies; time off vent for subjects with tracheostomies
11. PedsQL Neuromuscular Module (PedsQL NMM)
12. TAM4MTM monthly survey and every month in-between clinic study visits
13. Standard safety lab tests (every 6 weeks during drug trial phase, Month 0-15). Haematology (WBC, RBC, HBC, platelets and haematocrit), serum chemistry (CPK, AST, ALT, bilirubin, -GGT, calcium levels), hormone levels, and lipid profiles will be performed at each study visit, and midway between study visits in Phase 1 and 2
14. Drug safety monitoring - in addition to the standard safety labs, sex hormone levels (LH, FSH, testosterone, estradiol) will be monitored for all study subjects
15. Tamoxifen pharmacokinetics - at each clinic study visit and every 6 weeks during Phase 1 and 2 (in between study visits i.e. only the research blood sample will be collected)
16. MTM biomarker - at months 0, 3, 6, 9, 12, and 15 months for analysis of the MTM biomarker miR-133a
At each study visit, concomitant medications and adverse events will be recorded.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Tamoxifen

Primary outcome measure
Measured at screening (month -3), months 0, 3, 6, 9, 12, 15:
1. The safety and tolerability of tamoxifen therapy in males with XLMTM. This will be done by monitoring participants closely once they start IP dosing from Month 0-6 (phase 1), Washout Month 7-9 and Month 10-15 (phase 2)
2.1. Motor function measured using Motor Function Measure 32; if the participant is under the age of 4 years, both Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-Intend) and MFM32 will be performed
2.2. For ambulant patients: 10-metre walk test (10MWT) in addition to MFM32

Secondary outcome measures

Measured at screening (month -3), months 0, 3, 6, 9, 12, 15. TAM4MTM Survey will be conducted over the telephone monthly between clinic visits:
1. Respiratory function measured using:
1.1. Standardized pulmonary function tests (PFTs):
1.1.1. Patients not completely dependent on mechanical ventilation, without a tracheostomy: forced expiratory volume in the first second exhalation (FEV1), forced vital capacity (FVC), peak cough flow (PCF), maximum expiratory pressure (MEP), maximum inspiratory pressure (MIP) or sniff nasal inspiratory pressure (SNIP)
1.1.2. Patients with tracheostomy and dependent on mechanical ventilation: time off ventilation before oxygen saturation reaches 94%, or when participant shows distress
1.2. Type of respiratory support (non-invasive or invasive), and length of time used per day
1.3. Length of time (minutes or hours) off mechanical respiratory support per day
2. Vital signs: body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure and oxygen saturation will be measured, as well as weight and length/height. Performed by qualified site staff.
3. Physical Exam: includes range of eye motion (horizontal and vertical) and ptosis. Performed by the PI or qualified site staff.
4. Blood collection/sampling by venepuncture and results analysed by the local labs. Sex-hormone lab results will be sent to the study coordinator at SickKids for review. Sera will be aliquoted and sent to Sickkids for pharmacokinetic and biomarker analysis.
5. Ophthalmological assessment performed by an ophthalmologist or optometrist) for Healthy Eye Check. Any abnormalities should be noted. Participants' eyes will also be checked for cataracts.
6. Electrocardiogram (ECG): as a safety measure, ECGs with Q-T measurement will be conducted at every study visit. ECG will be taken using an ECG machine to check the electrical activity of the heart.
7. Abdominal ultrasound performed by qualified site staff using an ultrasound machine. Any abnormal hepatic peliosis should be noted and reviewed by qualified persons.
8. PedsQL NMM - The PedsQL NMM is a validated measure of quality of life for neuromuscular conditions and has been successfully used for other neuromuscular diseases such as DMD and SMA. SMA (Davis et al., 2010; Iannaccone et al., 2009). It encompasses three scales and is comprised of parallel self-reporting and parent-proxy report formats for age ranges 2-4 years, 5-7 years, 8-12 years, 13-18 years, and 18-25 years.
9. TAM4MTM monthly survey - Monthly participant self-evaluation (or parental evaluation) of any changes in strength, endurance, pain, range of motion, ventilator requirement, feeding, and ability to perform daily activities. Adverse events, Wells Score and adherence to drug schedule will be monitored.

Exploratory objectives:
1. Tamoxifen and tamoxifen metabolite levels measured using liquid chromatography with tandem mass spectrometry (LC-MS/MS) on serum collected every 6 weeks during Phase 1 and 2 starting at t = 0
2. miR-133a as a biomarker for MTM, measured using blood collected at t = 0, 3, 6, 9, 12, and 15 months

Overall study start date
01/01/2021

Completion date
31/10/2024

Eligibility

Key inclusion criteria
In order to be eligible to participate in this study, an individual must meet all of the following criteria:
1. Male
2. Patients aged 2 years and older may participate
3. MTM resulting from a confirmed mutation in the MTM1 gene
4. Patients over 18 years of age and parent(s)/legal guardian(s) of patients < 18 years of age must provide written informed consent prior to participating in the study and informed assent will be obtained from minors, or at least 7 years of age when required by regulation
5. Willing and able to comply with all protocol requirements and procedures

Participant type(s)
Patient

Age group
Mixed

Lower age limit
2 Years

Sex
Male

Target number of participants
Planned Sample Size: 16; UK Sample Size: 4

Total final enrolment
4

Key exclusion criteria
An individual who meets any of the following criteria will be excluded from participation in this study:
1. Other disease which may significantly interfere with the assessment of MTM and is clearly not related to the disease, at the discretion of the qualified investigator
2. Has undergone surgery or hospitalisation < 3 months before starting TAM4MTM (at t = -3 months), or has surgery scheduled during the 18 months of participation in TAM4MTM, which will impede motor assessments in the opinion of the Investigator
3. Has a history of thromboembolic events
4. Has severe liver dysfunction
5. Currently enrolled in a treatment study for XLMTM or receiving treatment with an experimental therapy other than pyridostigmine
6. Treatment with pyridostigmine for < 6 weeks duration (must be greater than 6 weeks to be included in TAM4MTM)
7. Use of concomitant medication known to inhibit CYP2D6 and/or CYP3A4, including clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal and grapefruit, paroxetine, troleandomycin, rifampin, phenobarbital,

aminoglutethimidine, medroxyprogesterone, amiodarone, haloperidol, indinavir, ritonavir, quinidine, rifampicin, or any selective serotonin reuptake inhibitor (SSRI)
8. Subject has a contraindication to tamoxifen or its ingredients

Date of first enrolment
01/10/2022

Date of final enrolment
31/07/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Great Ormond Street Hospital for Children
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Sponsor information

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Hospital for Sick Children

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etsuko.tsuchiya@sickkids.ca

Sponsor type
Hospital/treatment centre

Website
http://www.sickkids.ca/

ROR

https://ror.org/057q4rt57

Funder(s)

Funder type
Charity

Funder Name
Great Ormond Street Hospital Charity; Grant Codes: V4220

Alternative Name(s)
Great Ormond Street Hospital Children's Charity, GOSH Charity, GOSH

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
Sparks

Alternative Name(s)
Sparks Charity

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
Myotubular Trust

Alternative Name(s)

Funding Body Type

Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in journals and conferences once all trial sites and participants have concluded the study and the data have been reviewed.

Intention to publish date
31/10/2024

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No