Tamoxifen in Duchenne muscular dystrophy - TAMDMD:
A multicentre, randomised, double-blind, placebo-controlled, phase 3 safety and efficacy 48-week trial
The study will be extended to an open label study with the following title (OLE: Open Label Extension):
Tamoxifen in Duchenne muscular dystrophy - TAMDMD:
A 48 week open label extension of a multi centre, randomised, double-blind, placebo-controlled, phase 3 safety and efficacy trial

Published: 02-10-2018
Last updated: 11-04-2024

To test if tamoxifen treatment, compared to placebo, reduces the progression of the disease in 6.5-12 years old ambulant DMD patients by at least 50% (using the MFM D1 subscore as primary clinical endpoint in group A patients).To test if tamoxifen...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON52599

Source
ToetsingOnline

Brief title
TAMDMD

Condition

- Musculoskeletal and connective tissue disorders congenital

Synonym
muscle degeneration and muscle weakness

Research involving
Human

Sponsors and support

Primary sponsor: UKBB University of Basel Children's Hospital/Division of Neuropediatrics
Source(s) of monetary or material Support: Dit project wordt ondersteunt door het Schweizerischen Nationalfonds zur Förderung der wissenschaftlichen Forschung (SNF);Scientific and Technological Research Council of Turkey (TÜB□TAK);French National Research Agency (ANF) in het kader van E-Rare-3;the ERA-Net for Research on Rare Diseases. Verdere financiering wordt verkregen via Duchenne UK;Duchenne Parent Project Netherlands;en la Association Monegasque contre les myopathies.

Intervention

Keyword: Degeneration (muscle), Duchenne (muscular dystrophie, Pediatric, Tamoxifen

Outcome measures

Primary outcome

Primary Outcome

Group A: The primary efficacy outcome will be the change of motor function

under TAM treatment compared to placebo. This will be assessed by the motor

function measure (MFM) D1 subscore (standing and transfers) in ambulant

patients.

For the MFM D1 subscore several exercises that will be scored have to be done by the patients such as:- to sit up on a mat (without support of upper limbs),

- to stand up from sitting on a mat,

- to sit down on the chair from standing,

- to walk forward 10 steps on both heels,

- to walk forward 10 steps on a straight line,

- torun10m,

- and to hop 10 times on one foot,

The MFM is a validated assessment tool used to measure proximal and distal motor function in both ambulant and non-ambulant patients with neuromuscular disorders as recommended by the EMA in trials for DMD (Bérard et al. 2005). The instruction manual, validation examinations and other publications using the MFM can be downloaded from the MFM- website (www.mfm-nmd.org). This score also seems to be particularly interesting because of its relation to loss of ambulation and its responsiveness to short-term changes. Therefore, the results suggest to use the MFM D1 subscore as the primary endpoint for the selected population of ambulant DMD patients. Ambulant DMD patients show a rapid decline of about -17.2% per year of the D1 subscore and a D1 subscore of 40% is predictive for loss of ambulation 1 year later (Bushby & Connor 2011).

Recently, Bonati et al, (2015) demonstrated that among all analysed clinical measures, the MFM D1 subscore showed the most significant decline in ambulant DMD patients older than 7 years, resulting in the highest effect size and power (Bonati et al. 2015).

Group B: The primary efficacy outcome in this group will be the motor function

from baseline to week 48 under TAM treatment compared to placebo. This will be assessed by the motor function measure (MFM) D2 subscore in non-ambulant patients allowing a partial extrapolation and comparison of MFM D2 values between group A and group B. Note that the MFM D1 subscore in non-ambulant patients is usually 0%; therefore the MFM D1 subscore is not suitable for this population.

For the MFM D2 subscore several exercises that will be scored have to be done by the patients such as:

- from supine on a mat to raise the head and maintain the raised position
- from supine on a mat to raise one hand and move it to the opposite shoulder
- from seated on the chair to raise the head from fully flexed position and maintain the raised position
- from seated on the chair to place the two forearms and/or the hands on the table at the same time without moving the trunk.

Secondary outcome

Secondary clinical outcomes to assess muscle function:

- MFM total score, the D2, and D3 MFM subscores, North Star Ambulatory Assessment, proximal upper limb function from baseline to week 48 under tamoxifen treatment compared to placebo.
- Timed function tests (6 minute walking distance in meter, 10 meter walking time in seconds, time to rise from lying on the floor / supine up in seconds,) from baseline to week 48 under tamoxifen treatment compared to placebo.

Secondary clinical outcomes to assess muscle force:

- Quantitative muscle testing (using Grip force) from baseline to week 48 under

tamoxifen treatment compared to placebo.

Secondary surrogate marker to assess muscle degeneration:

- Quantitative muscle MRI including muscle fat fraction (MFF) and T2 times of thigh muscles visualised by MRI from baseline to week 48 under tamoxifen treatment compared to placebo.

Outcomes and endpoints of the OLE part are the same as in the RCT (Randomized Controlled Trial) part of the trial

Study description

Background summary

Duchenne muscular dystrophy (DMD) is a rare disease and the most common hereditary muscular dystrophy. It is characterized by progressive muscle wasting, respiratory and cardiac impairments and premature death. This disease only affects boys since the defective gene is located on the X chromosome. The incidence is 1 in 3*500 to 6*000 male live births (Ricotti et al. 2016). In Europe there are about 30*000 affected patients. About one third of the boys affected by DMD do not have a family history of the disease because the DMD gene has undergone a spontaneous mutation. Symptoms usually begin before the age of six years. Children with DMD have difficulties in standing up, walking and climbing stairs. Most boys need a wheelchair at about age 12. Moreover, muscle wasting continues and affects other muscles including the diaphragm and the heart, leading to reduced respiratory and cardiac functions; patients often die in their 20ies. Adequate care and support prolong life expectancy to the early 30ies but quality of life is severely reduced due to an evolving pathology including cardiomyopathy and artificial respiration in the late stages of the disease (Verheart et al. 2011). With the exception of glucocorticoids, there is no treatment that improves quality of life and long-term survival time of DMD patients. Glucocorticoids (mainly prednisolone or deflazacort) are prescribed to most DMD patients; they reduce inflammation

and excessive Ca2+ influx in dystrophic muscle fibres (Ruegg et al. 2012). At the therapeutic level, glucocorticoids prolong the age of ambulation and slightly increase quality and duration of life (Manzur et al. 2008). However, glucocorticoids have many undesirable effects, notably retarding growth, which

can lead to drug cessation in some patients. Therefore, an alternative therapy is urgently needed that efficiently counteracts the disease symptoms, possibly by interfering with the pathological signalling cascade, and causes fewer undesirable effects.
The DMD gene codes for a protein called dystrophin that links a transmembrane protein complex with the extracellular matrix with enzymes mediating intracellular signalling, such as nitric oxide synthase, kinases and phosphatases on one hand, and with numerous ion channels, pumps and exchangers on the other hand. Through a not yet fully understood mechanism of action, dystrophin affects ion channels and participates in regulating the influx of Ca2+ ions into the cell. When dystrophin is absent, Ca2+ influx is increased leading to cell death via necrosis or apoptosis. Increased cytosolic Ca2+ levels were reported in muscle biopsies from DMD patients and in the muscles of mdx mice, a mouse model for DMD, implicating it as a main driver of the pathology. Increased Ca2+ influx through either store- operated channels or stretch-activated channels was reported to be involved in such an increment. Therapies targeting these subsets of channels have shown clear benefits in mdx mice; however, proof of principle in DMD patients has yet to be established (Ruegg et al. 2012).

Study objective

To test if tamoxifen treatment, compared to placebo, reduces the progression of the disease in 6.5-12 years old ambulant DMD patients by at least 50% (using the MFM D1 subscore as primary clinical endpoint in group A patients).
To test if tamoxifen treatment, compared to placebo, reduces the progression of the disease in 10-16 years old non-ambulant DMD patients not treated with glucocorticoids (using the MFM D2 subscore as primary endpoint.)

Open Label Extension study:
The main objective of the OLE part of this study is to test if earlier initiation compared to delayed start of tamoxifen treatment reduces the progression of the disease and to evaluate long-term efficacy and safety.

Post OLE Observation: During the Post OLE Observation it will be investigated whether disease progression increases after discontinuation of TAM

Study design

This is a 48-week multicentre, parallel, randomised, double-blind, placebo controlled phase 3 safety and efficacy trial. There are two treatment arms: Tamoxifen (verum) and placebo (control), with treatment allocation of 1:1.
We plan to screen at least 79 and to enroll at least 71 ambulant DMD patients aged between 6.5 and 12 years (group A) and 16 * 20 non-ambulant DMD patients aged between 10 and 16 years (group B). In order to reach statistical power, 60 ambulant patients (group A) need to complete the trial. Treatment with 20 mg

Tamoxifen once daily will be given for the total trial duration of 48 weeks. Only patients with glucocorticoids (standard treatment of care) will be included in group A (ambulant patients) and only non-glucocorticoid users in group B. At baseline as well as at the end of the study clinical, laboratory, and MRI measurements will be performed. These include the MFM scale, timed function tests, the 6 minute walking distance, quantitative muscle testing (QMT), quantitative thigh muscle MRI and questionnaires. A physical examination, an ECG, vital signs as well as safety laboratory blood analyses will be performed at every visit. Furthermore, an x-ray of the hand and a DEXA-scan will be performed at baseline and at the end of the study.

The Open label extension study will be extended for 48 weeks. All subjects will receive 20mg of Tamoxifen on a daily base.
Week 48 from the RCT (Randomized Controlled Trial) will be the first visit (V1) for the OLE trial. The study design is similar as the RCT trial, subjects on site visits (from V1 to V5, V2 will be a phone visit, similar to the previous trial) will occur every 12 weeks up to Week 96, a FU visit (V6) will take place at V108

Post OLE Observation:
The Open label Extension study will be extended with 2 years with an Observational non interventional phase, during this phase the subjects will receive the medication the local physician is prescribing, the subject will not receive tamoxifen from the sponsor. During the observation phase, data will be collected from examinations that are routinely performed by the subjects physician.

Intervention

Procedures at each visit
A pre-screening form has to be completed for each patient and sent to sponsor by fax for approval at least 20 days before the planned screening visit.
During the study visits asessments according to the study flow chart will be performed and data collected is captured in the patients* source documents. After the visit this data is entered in the eCRF by a study nurse/study coordinator.The PARS III questionnaire has to be completed by a parent/legal representative during the study visit.
Basically, the physical as well as the physiotherapeutical examinations are part of the standard medical care in DMD patients. Usually, the MRI, the completion of the questionnaire and the DEXA and x-ray bone age determination (if applicable, in selected sites) are study specific examinations and not routine treatment in this disease.

1. Screening visit (Visit 0, Week -4, ±16 days)
After signing the informed consent form, the inclusion and exclusion criteria are verified. If the criteria are fulfilled the patient will be enrolled in the study. During this visit the following procedures will be performed.

- Informed consent
- Demographics
- Medical history
- Check inclusion/exclusion criteria
- Concomitant therapy
- Physical examination, incl. anthropometric measurements
- Vital signs, ECG
- Physiotherapeutical evaluation
- Safety blood analyses
In case of screening failure due to exclusion criteria the patient can be re-screened once for this study.

2. Baseline visit (Visit 1, Week 0)
During this visit the following procedures will be performed:
- Check inclusion/exclusion criteria
- Capture adverse events
- Concomitant therapy
- Physical examination, incl. anthropometric measurements and Tanner staging
- Vital signs, ECG
- Ophthalmological examination (visual acuity and slit-lamp examination)
- DEXA scan and x-ray bone age determination (in selected sites only)
- Wells score for DVT
- Physiotherapeutical evaluation
- MRI
- Patient reported outcome measures
- Safety blood analyses and biomarkers I
- Randomisation (if the patient still qualifies for the study, he will be randomised and receive study medication)
- Dispense study medication
- Raven's Coloured Progressive Matrices test

3. Telephone call (Week 6, ±7 days)
The patient will be contacted by phone and asked about his health, according to the questionnaire in appendix 6.

4 .Visit 2, 3 and 4 (Week 12, ±16 days; Week 24, ±16 days; Week 36, ±16 days)
During these visits the following procedures will be performed:
- Capture adverse events
- Concomitant therapy
- Physical examination, incl. anthropometric measurements (and Tanner staging at visit 3)
- Vital signs, ECG
- Ophthalmological examination at visit 3
- Wells score for DVT
- Physiotherapeutical evaluation
- (MRI and patient reported outcome measures at visit 3)
- Safety blood analyses (and biomarkers I at visit 3)

- Collection of study medication
- Dispense of study medication

5. End of Study visit (Visit 5, Week 48, ±16 days)
- Capture adverse events
- Concomitant therapy
- Physical examination, incl. anthropometric measurements and Tanner staging
- Vital signs, ECG
- Ophthalmological examination
- DEXA scan and x-ray bone age determination (in selected sites only)
- Wells score for DVT
- Physiotherapeutical evaluation
- MRI
- Safety blood analyses and biomarkers I and II
- Collection of study medication
- Raven's Coloured Progressive Matrices

6. Follow-up Telephone call (Week 52, ±7 days)
The patient will be contacted by phone and asked about his health, according to the questionnaire in appendix 11. In case an adverse event has occurred in the time from visit 5 to the follow-up phone call, the patient will be asked to come to the site to undergo physical and if applicable further additional examination within one week, respectively as soon as possible (in case of hospitalization etc.).
Ophthalmological examination, physiotherapeutical examination, MRI, X-ray bone age determination and DEXA have to be performed within one week following the visit date.

1.Start of Open Label Extension visit (Visit 1OLE, Week 48)
- Concomitant therapy*
- Physical examination, incl. anthropometric measurements and Tanner staging*
- Vital signs, ECG*
- Ophthalmological examination*
- DEXA scan and x-ray bone age determination (in selected sites only)*
- Wells score for DVT*
- Physiotherapeutical evaluation*
- MRI
- Safety blood analyses and biomarkers I and II*
- Raven's Coloured Progressive Matrices*
- Check inclusion/exclusion criteria
- Dispense study medication

*will be assessed in the context of the end of study visit (visit 5)

2. Visits 2OLE and 4OLE (Week 60, ±16 days, Week 84, ±16 days)
- Capture adverse events
- Concomitant therapy

- Physical examination, incl. anthropometric measurements
- Vital signs, ECG
- Wells score for DVT
- Safety blood analyses I (total amount of blood taken 7.4 ml)
- -Collection of study medication
- Dispense study medication
- Physiotherapeutical evaluation

3.Visit 3OLE (Week 72, ±16 days)
- Capture adverse events
- Concomitant therapy
- Physical examination, incl. anthropometric measurements and Tanner staging
- Vital signs, ECG
- Ophthalmological examination at visit 3
- Wells score for DVT
- Physiotherapeutical evaluation
- MRI and patient reported outcome measures
- Safety blood analyses (total amount of blood taken 7.4 ml)
- Collection of study medication
- Dispense of study medication

4. End of Open label extension visit (Visit 5OLE, Week 96, ±16 days)
- Capture adverse events
- Concomitant therapy
- Physical examination, incl. anthropometric measurements and Tanner staging
- Vital signs, ECG
- Ophthalmological examination
- DEXA scan and x-ray bone age determination (in selected sites only)
- Wells score for DVT
- Physiotherapeutical evaluation
- MRI
- Safety blood analyses (total amount of blood taken 7.4 ml)
- Collection of study medication
- Raven's Coloured Progressive Matrices

5. Follow-up visit (Visit 6OLE, Week 108, ±14 days)
- Capture adverse events
- Concomitant therapy
- Physical examination, incl. anthropometric measurements
- Vital signs, ECG
- Wells score for DVT
- Safety blood analyses (total amount of blood taken 7.4 ml

Post OLE Observation: the data will be generated from routine examinations performed by the local physician.
The following data will be generated:

- Further intake of Tamoxifen
- Concomitant therapy
- Participation in other clinical trials
- Physiotherapeutic Evaluations: results of 6-minutes walk test, North Star Ambulatory Assessment (NSAA) or Motor Function Measurement (MFM if NSAA is not applicable)

Study burden and risks

Tamoxifen (TAM) is a selective estrogen receptor modulator and has been used for more than 35 years to treat estrogen receptor positive breast cancer. In adults it is usually given at a dose of 20mg per day. There is abundant safety information on the use of TAM in adults and adolescents but less on pre-pubertal children. TAM therapy has been used for decades for the management of pubertal gynecomastia using doses of 10 * 20 mg per day (Dermann et al 2008, Eugster et al 2003, Kreher et al 2005, Pollack et al 1997). Even though randomised controlled trials were not included and some studies had methodological flaws, a systematic review on a total of 164 publications showed some promising results. No clinical side-effects were reported or observed (Lapid et al 2013). Importantly, in these studies, TAM did not alter the acquisition of male sexual traits. Therefore, it appears that a trial on boys of the age group 6.5-12 years and older can be carried out with a low risk of undesirable effects. DMD patients under steroid medication exhibit reduced growth and altered bone quality, which correlates with more frequent fractures. It should be noted that this reduction in stature might be counted among the effects of glucocorticoids. In contrast, TAM prevents bone loss (Starnes et al 2007, Vogel et al 2006) and has shown to increase the height of short boys through decreasing the rate of bone maturation (Kreher et al 2005). Dorchies et al (2013) demonstrated that very low levels of TAM and TAM metabolites (10-30 nM) are sufficient to cause major therapeutic effects on the dystrophic mouse, which is encouraging in the perspective of this clinical application. It is possible that therapeutic TAM concentrations might be reached using lower than standard TAM regimen. The benefits elicited by the Eisomers of TAM metabolites, which were produced in substantial amounts in dystrophic mice (Dahmane et al. 2010), but are barely detectable in humans (Murdter et al 2011), deserve attention. This could result in lower than expected benefits in DMD-patients.Undesirable effects:

Only the very common (>1/10) and the common (>1/100 to <1/10) and to boys relevant undesirable effects will be reported in the study protocol. For more information please refer to the SmPC.
Very common: fluid retention, hot flushes, nausea, skin rash, and fatigue.
Common: anemia, increase in serum triglycerides, vomiting, diarrhea, constipation, light-headedness, headache, ischemic cerebro-vascular events, sensory disturbances including paresthesia and dysgeusia, cataracts, retinopathy, changes in liver enzyme levels, fatty liver, alopecia, myalgia, leg cramp, hypersensitivity reactions, thromboembolic events including deep

vein thrombosis, microvascular thrombosis and pulmonary embolism.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Children (2-11 years)

Inclusion criteria

Group A (ambulant patients)
- Documented diagnosis of DMD by mutation analysis in the dystrophin gene or by substantially reduced levels of dystrophin protein (i.e. absent or <5% of normal) on Western blot or immunostaining
- Stable treatment with glucocorticoids >6 months (no significant change in dosage (>0.2mg/kg)) at screening; dosing adaptations according to weight change are allowed
- Male gender
- 6.5 to 12 years of age at time of screening

- weight >20kg
- ambulant patients
- able to walk at least 350 meters in 6 minute walking distance test without assistance at screening
- MFM D1 subdomain of the MFM scale >40% at screening
- Ability to provide informed consent and to comply with study requirements
- Patients harbouring a nonsense mutation treatable with the approved drug ataluren should be under stable ataluren treatment for at least 3 months or in case of non tolerance being off ataluren treatment for at least 3 months before screening Group B (non-ambulant patients)
- Documented diagnosis of DMD by mutation analysis in the dystrophin gene or by substantially reduced levels of dystrophin protein (i.e. absent or <5% of normal) on Western blot or immunostaining
- not using glucocorticoids for >6 months
- Male gender
- non-ambulant patients (walking distance less than 10 meters)
- 10 to 16 years of age at time of screening
- Ability to provide informed consent and to comply with study requirements7S8S9S

Open label Extension: Recent participation and completion of TAMDMD study

Exclusion criteria

- Known individual hypersensitivity or allergy to tamoxifen or other ingredients /excipients of IMP
- Female gender
- Use of tamoxifen or testosterone within the last 3 months
- Known or suspected malignancy
- Other chronic disease or clinically relevant limitation of renal, liver or heart function (as judged by the Investigator)
- Known or suspected non-compliance
- Any injury which may impact functional testing, e.g. upper or lower limb fracture
- Planned or expected spinal fusion surgery during the study period (as judged by the Investigator; i.e. due to rapid progressing scoliosis), previous spinal fusion surgery is allowed if it took place more than 6 month prior to screening.
- Inability to follow the procedures of the study, e.g. due to language problems, psychological disorders of the participant/parents (as judged by the investigator)
- Concomitant participation in any other interventional trial (and up to 3 months prior to screening)
- Use of CYP2D6 inhibitors or of CYP3A4 inducers (apart from glucocorticoids), platelet aggregation inhibitors and coumarin-type anti-coagulants
- Use of drugs metabolized by CYP2C9, such as phenprocoumon, phenytoin,

warfarin, celecobix, fluvastatin, ginko biloba, st. John's wort and sulfamethoxazol.
- Galactosemia (lack of galactose-1-phosphat-uridylyltransferase or UDP-galactose-4-epimerase or galactokinase; Fanconi-Bickel-syndrome); congenital lack of lactase; glucose-galactose malabsorption.
- Presence of one or more of the following eye disorders: cataract, retinopathia, optic neuropathy, alteration of the cornea.
Presence of one or more of the following laboratory abnormalities: anaemia, thrombocytopenia, leukopenia, neutropenia or agranulocytosis.Group A:
- Glucocorticoid naïve patients
- Start of glucocorticoid treatment or change in dosage <6 month prior to screening (dosing adaptations according to weight change are allowed)Group B:
- Glucocorticoid treated patients or patients that stopped steroid treatment <6 month prior to screening
- Participation in any other interventional trial

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-11-2019
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tamox
Generic name:	Tamoxifen

Ethics review

Approved WMO Date:	02-10-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-01-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-07-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-08-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-05-2022

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-004554-42-NL
ClinicalTrials.gov	NCT03354039
CCMO	NL66050.091.18