ISRCTN37815869 https://doi.org/10.1186/ISRCTN37815869

Repurposing carbamazepine for treatment of skeletal dysplasia in children

Submission date
28/01/2019

Recruitment status
No longer recruiting

Registration date
23/05/2019

Overall study status
Completed

Last Edited
15/11/2024

Condition category
Musculoskeletal Diseases

[_] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Metaphyseal chondrodysplasia type Schmid (MCDS) is an ultra-rare inherited disorder. It is associated with curvature of leg bones, flaring at the end of long bones, and joint problems. These symptoms can make movement difficult by impairing walking and causing pain in the joints and legs throughout life. Current treatment focuses on pain relief and surgery. This study aims to find a treatment for the cause of MCDS and test whether the drug carbamazepine (CBZ) can improve the health of patients with MCDS.

Who can participate?
Children who have MCDS and have not yet reached bone maturity

What does the study involve?
The study comprises two stages.
Stage 1 is open to UK participants only. The study involves an initial period of 12 months of observation during which participants do not receive CBZ treatment. This observation period includes up to five visits to hospital that involve collecting demographic and medical history, physical examinations, laboratory safety assessments, measurement of growth and bone alignment (including x-rays) and multiple questionnaires.
Participants then enter a dose titration and tolerability stage for the next 12 months. In this stage, participants receive CBZ treatment, with the aim of finding the best dose for them. The drug is given in either tablet or liquid form, depending on the child's preference. The safety and tolerability of CBZ are assessed. For this part of the study, participants visit the hospital up to six times and receive weekly phone calls while the best dose is found for the individual (up to 11 calls). Ad hoc safety visits can also be performed, if clinically indicated. Similar data is collected to the data collected in the observation year. Once a dose is selected, the participant receives treatment at that dose until they have been treated with CBZ for a total of 24 months.
Additionally, eligible Stage 1 participants may opt to continue treatment for further 12 months (treatment with CBZ up to 36 months) subject to a separate informed consent at visit 2.5.
Participants are required to visit hospital at 3-monthly intervals throughout their CBZ treatment to assess the impact of the treatment. Similar data to that collected in the observation year is collected throughout the CBZ treatment phase.
Stage 2 is open to both UK and International participants. The study involves an initial period of

6 months of observation during which participants do not receive CBZ treatment. This observation period includes up to four visits to hospital that involve collecting demographic and medical history, physical examinations, laboratory safety assessments, measurement of growth and bone alignment (including x-rays) and multiple questionnaires.
Participants then enter a 12-month CBZ treatment stage during which they are required to visit hospital 3-monthly to assess the impact of the treatment. Ad hoc safety visits can also be performed, if clinically indicated. Again, similar data is collected in the treatment stage to the data collected in the observational stage.

What are the possible benefits and risks of participating?
The potential benefit is that CBZ could improve the treatment of MCDS. If CBZ is taken during pregnancy, there is a risk that it will harm the unborn child. There is a potential risk that people treated with CBZ could develop common side effects such as dizziness and tiredness; feeling unsteady or finding it difficult to control movements; feeling or being sick; changes in liver enzyme levels (usually without any symptoms); skin reactions which may be severe; or leucopenia (a reduced number of the cells which fight infection making it easier to catch infections).

Where is the study run from?
Stage 1 is run from:
1. The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
2. Guy's and St. Thomas' NHS Foundation Trust, London, UK

Stage 2 is run from:
1. The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
2. Guy's and St. Thomas' NHS Foundation Trust, London, UK
3. Murdoch Children Research Institute, Melbourne, Australia
4. Rizzoli Orthopaedic Institute, Bologna, Italy

When is the study starting and how long is it expected to run for?
December 2017 to May 2024

Who is funding the study?
European Commission: Horizon 2020

Who is the main contact?
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3. Dr Dean Allerton
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Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2018-002633-38

Integrated Research Application System (IRAS)
244715

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 40280

Study information

Scientific Title
An open label phase I/IIa trial repurposing carbamazepine (CBZ) for the treatment of skeletal dysplasia in children

Acronym
MCDS-Therapy

Study objectives
The aim of the trial is to evaluate the effect of carbamazepine on children with a diagnosis of MCDS with confirmed COL10A1 pathogenic mutation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 19/11/2018, Yorkshire & The Humber - Sheffield Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Newcastle upon Tyne, NE2 4NQ; Tel: +44 (0)207 104 8082; Email: nrescommittee.yorkandhumber-sheffield@nhs.net), ref: 18/YH/0428

Study design
Non-randomized; Both; Design type: Treatment, Drug, Health Economic

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Skeletal dysplasia

Interventions
Current interventions as of 16/05/2024:
This is a two-stage open-label, single-arm phase I/IIa trial of carbamazepine in children with skeletal dysplasia who are outpatients.

Stage 1 of the trial includes:
1. 12 months baseline observation
2. 12 months dose titration and tolerability

3. 12-month treatment phase + additional optional 12 months of treatment for eligible participants

Stage 2 of the trial includes:
1. 6 months baseline observation
2. 12-month treatment phase

Previous interventions:
This is a two-stage open-label, single-arm phase I/IIa trial of carbamazepine in children with skeletal dysplasia who are outpatients. The trial includes a 12-month baseline observation period and a 12-month initial dose determination stage (Stage 1) followed by long-term assessment of efficacy and safety at the chosen dose (Stage 2).

Intervention Type
Drug

Phase
Phase I/II

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

Primary outcome(s)
Current primary outcome measures as of 16/05/2024:
1. Laboratory safety assessments, adverse events and physical examinations collected post IMP administration
2. Outcome of dose-titration safety review at 6 months post IMP treatment initiation

Stage 2:
1. Alteration from baseline in growth velocity over 12 months
2. Growth velocity follow-up data at 12 months post treatment initiation

Previous primary outcome measures:
Stage 1:
1. Laboratory safety assessments at screening, month 0, month 6 and month 12
2. Adverse events and physical examinations collected over a 12-month period post IMP administration
3. Outcome of dose-titration safety review at 3 and 12 months post IMP treatment initiation

Stage 2:
1. Growth velocity at baseline and over 24 months
2. Growth velocity follow-up data at 24 months post treatment initiation

Key secondary outcome(s))
Current secondary outcome measures as of 16/05/2024:
Stage 1:
1. Pain perception measured by PEDSQL Pain Coping Inventory and PEDSQL Pain Questionnaire over 24 months

Stage 2:
1. Height percentile at baseline and over 12 months

2. Long bone alignment and configuration measured by X-ray analysis at baseline and over 12 months
3. Pain perception measured by PEDSQL Pain Coping Inventory and PEDSQL Pain Questionnaire at baseline and over 12 months
4. Health-related quality of life measured by Paediatric Quality of Life Inventory (PedsQL) and EQ-5D-Y at baseline and over 12 months

Previous secondary outcome measures:
Stage 1:
1. Pain perception measured by PEDSQL Pain Coping Inventory and PEDSQL Pain Questionnaire at baseline and 12 months

Stage 2:
1. Height percentile at baseline and over 24 months
2. Long bone alignment and configuration measured by X-ray analysis at baseline and over 24 months
3. Pain perception measured by PEDSQL Pain Coping Inventory and PEDSQL Pain Questionnaire at baseline and over 24 months
4. Health-related quality of life measured by Paediatric Quality of Life Inventory (PedsQL) and EQ-5D-Y at baseline and over 24 months
5. MCDS biomarker signatures (+/- CBZ treatment) measured using blood samples

Completion date
31/05/2024

Eligibility

Key inclusion criteria
Current inclusion criteria as of 16/05/2024:
1. Participants where a pathogenic mutation in the gene encoding the COL10A1 protein has been identified by sequence analysis
2. Ambulant at the time of consent/assent, with open epiphyses
3. Willing and able to attend for safety monitoring assessments
4. Willing and able to adhere to the trial visit schedule and other protocol requirements
5. Capable of giving informed consent, or if appropriate, participants having an acceptable individual capable of giving consent on the participant's behalf (e.g. parent or legal guardian of a child under 16 years of age)
6. Written informed consent signed (by parent(s)/legal guardian and/or the subject, according to the local regulations)
7. If female and of childbearing potential, the participant must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)] at baseline and agree to regular pregnancy testing during the trial
8. Sexually active female participants of childbearing potential must practice true abstinence in line with their preferred and usual lifestyle, or use two acceptable effective methods of contraception whilst on treatment and for a period of 28 days after discontinuation: a barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository and an established non-barrier method such as oral, injected, or implanted hormonal methods (hormonal preparations must contain not less than 50µg oestrogen). Use of some alternative non-hormonal method of contraception should be considered: an intrauterine device or intrauterine system for the entire duration of the treatment period and for a period of 28 days after discontinuation.

Previous inclusion criteria:
1. Pathogenic mutation in the gene encoding the COL10A1 protein has been identified by sequence analysis
2. Ambulant at the time of consent/assent, with open epiphyses
3. Willing to attend for safety monitoring assessments
4. Willing and able to adhere to the trial visit schedule and other protocol requirements
5. Capable of giving informed consent, or if appropriate, participants having an acceptable individual capable of giving consent on the participant's behalf (e.g. parent or legal guardian of a child under 16 years of age)
6. Written informed consent signed (by parent(s)/legal guardian and/or the subject, according to the local regulations)
7. The patient, if female and of childbearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)] at baseline and agree to regular pregnancy testing during the trial
8. Sexually active female patients of childbearing potential are required to practice true abstinence in line with their preferred and usual lifestyle or use two acceptable effective methods of contraception, a barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository and an established non-barrier method such as oral, injected, or implanted hormonal methods (hormonal preparations must contain not less than 50 µg oestrogen) use of some alternative non-hormonal method of contraception should be considered, an intrauterine device or intrauterine system for the entire duration of the treatment period

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Sex
All

Total final enrolment
27

Key exclusion criteria
Current exclusion criteria as of 16/05/2024:
1. Patients who have reached skeletal maturity*
2. Patients who have a planned surgery or planned osteotomy (which in the opinion of the Chief Investigator, Principal Investigator and/or the clinical members of the TMG deems the patient unsuitable for the trial)**
3. Patients who have had a prior adverse reaction to carbamazepine or similar drugs such as oxcarbazepine, or to any related tricyclic antidepressants.
4. Patients known to have atrioventricular block
5. Patients who have a history of bone marrow suppression/depression
6. Patients who have evidence of chronic hepatic or renal impairment
7. Patients who have acute intermittent porphyria
8. Patients who have received a monoamine oxidase inhibitor within 14 days of commencing

therapy
9. Patients who have abnormal blood screening results at the time of treatment initiation will be excluded unless the Investigator believes the abnormality to be non-significant clinically
10. Patients of Han Chinese, Thai and other Asian origins who carry the HLA-B*1502 allele

*Skeletal maturity will be assessed as part of the eligibility criteria. Individuals who may reach skeletal maturity before the end of the study should not be included. Patients will be assessed clinically on a case-by-case basis through discussion of the site PI with the CI and/or the clinical members of the TMG during the screening process.
If a participant reaches skeletal maturity during the treatment phase of the trial, they will be asked to continue on the trial for an additional 6 months from the point of skeletal maturity. Patients will stay on their medication and attend study visits, to evaluate if CBZ may have any effect on MCDS patients after they reach skeletal maturity.

**Patients who have planned surgery or planned osteotomy will not automatically be ineligible for the trial. Every potential participant with planned surgery or osteotomy will be assessed clinically on a case-by-case basis through discussion of the site PI, with the CI and/or the clinical members of the TMG during the screening process.

Previous exclusion criteria:
1. Reached skeletal maturity
2. Prior adverse reaction to carbamazepine or similar drugs such as oxcarbazepine, or to any related tricyclic antidepressants.
3. Have atrioventricular block
4. History of bone marrow suppression/depression
5. Evidence of chronic hepatic or renal impairment
6. Acute intermittent porphyria
7. Received a monoamine oxidase inhibitor within 14 days of commencing therapy
8. Abnormal blood screening results at the time of treatment initiation will be excluded unless the Investigator believes the abnormality to be non-significant clinically
9. Patients of Han Chinese, Thai and other Asian origins who carry the HLA-B*1502 allele

Date of first enrolment
01/04/2019

Date of final enrolment
31/05/2022

Locations

Countries of recruitment
United Kingdom

England

Australia

Belgium

France

Germany

Italy

Study participating centre
Freeman Hospital (lead centre)
Institute of Genetic Medicine
International Centre for Life
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Newcastle-upon-Tyne
United Kingdom
NE7 7DN

Study participating centre
Evelina Children's Hospital
Guy's and St Thomas' NHS Foundation Trust
London
United Kingdom
SE1 9RT

Study participating centre
The Institut national de la santé et de la recherche médicale (INSERM)
Paris
France
-

Study participating centre
University of Antwerp
Antwerp
Belgium
-

Study participating centre
Rizzoli Orthopaedic Institute
Bologna
Italy
-

Study participating centre

Murdoch Children Research Institute
Melbourne
Australia
-

Sponsor information

Organisation
The Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
European Commission; Grant Codes: 754825

Alternative Name(s)
European Union, Comisión Europea, Europäische Kommission, EU-Kommissionen, Euroopa Komisjoni, EC, EU

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan
Until publication of the trial results, access to the full dataset will be restricted to the Trial Management Group and to authors of the publication. The data generated within the MCDS-Therapy trial will be made available beyond the project for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of EU relevant policies. Hence, in line with these principles, investigators affiliated with bona fide research organisations that seek to answer important research questions related to drug repurposing and MCDS will be able to

request access to experimental data and biological samples. The data will be anonymised and consent will be obtained for sharing of data and biological samples for ethically approved future research, which is not yet certain but will be relevant to skeletal dysplasias, bone disease or ER stress biomarkers. The custodian of the data generated by the trial is the CI, Dr Michael Wright (Michael.Wright@nuth.nhs.uk).

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results			15/11/2024	No	No
HRA research summary			28/06/2023	No	No
Other files	version 1.0	13/03/2023	24/10/2024	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 9.0	16/10/2023	15/11/2024	No	No
Statistical Analysis Plan	Stage 1 version 1.0	28/05/2021	24/10/2024	No	No
Statistical Analysis Plan	Stage 2 version 1.0	09/02/2024	24/10/2024	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes