MCDS-Therapy

Clinical Trial Protocol

Full Title:	**An open label phase I/IIa trial repurposing carbamazepine (CBZ) for the treatment of skeletal dysplasia in children**
Short Title/Acronym:	**MCDS-Therapy**
Protocol Version Number & Date:	**V9.0**
	16 October 2023

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V4.0 27th August 2020

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V8.0 21 October 2022

Statement:

This protocol has regard for the HRA guidance.

RESEARCH REFERENCE NUMBERS

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RESEARCH SPONSOR (UK only)

Sponsor Name:	**The Newcastle upon Tyne Hospitals NHS Foundation Trust**
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Funder Name:	**European Commission: Horizon 2020**
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PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Representative of the UK Research Sponsor

Name:

Position:

Signature: Date:

Chief Investigator

Name: Michael Wright

Position:

Signature: Date:

Statistician

Name: James Wason

Position:

Signature: Date:

Newcastle Clinical Trials Unit (NCTU)

Name: Helen Hancock

Position:

Signature: Date:

PROTOCOL ACCEPTANCE SIGNATURE PAGE

Short Trial Title: **MCDS-Therapy**

Principal Investigator

I have carefully read and understood protocol version 9.0, dated 16 of October 2023. I agree to conduct the trial in compliance with Good Clinical Practice and all required regulatory requirements.

Name:

Position:

Signature: Date:

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Out of Hours Contacts

For UK trial sites please contact the respective Switchboard, either Newcastle upon Tyne Hospitals NHS Foundation Trust Switchboard on +44 (0)191 233 6161 or Guy's & St Thomas' NHS Foundation Trust (Evelina London Children's Hospital) Switchboard on +44 (0) 191 020 7188 7188 and request to speak to the clinician on call for the Clinical Genetics team.

For non-UK trial sites, please follow local out of hours processes.

Committees

Chair of Independent Data Monitoring Committee (IDMC)

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Chair of Trial Steering Committee (TSC)

Prof. James Betts
Professor of Metabolic Physiology, Centre for Nutrition, Exercise & Metabolism, Department for Health, Bath University
Email: J.Betts@bath.ac.uk

Trial Website

http://www.mcds-therapy.eu

TRIAL SUMMARY

Trial Title	**An open label phase I/IIa trial repurposing carbamazepine (CBZ) for the treatment of skeletal dysplasia in children**	
Acronym	**MCDS-Therapy**	
Clinical Phase	Phase I/IIa	
Summary of Trial Design	A two-stage open-label, single arm phase I/IIa trial of carbamazepine in children with skeletal dysplasia who are outpatients. The trial includes an initial dose determination stage (Stage 1) followed by long-term assessment of efficacy and safety at the chosen dose (Stage 2).	
Summary of Participant Population	Children with a diagnosis of Metaphyseal chondrodysplasia, type Schmid (MCDS) with confirmed COL10A1 pathogenic mutation.	
Planned Sample Size	40 participants (11 participants Stage 1 dose titration; 29 participants Stage 2 treatment)	
Baseline Observation Duration	Stage 1 participants: 12-18 months (dependent on covid-19 impact) Stage 2 participants : 6 months	
Treatment Duration	Stage 1 participants: 24 months + additional optional 12 months* Stage 2 participants: 12 months* *LPLV must occur no later than 31st January 2024	
Planned Trial Period	70 months	
	Objectives	**Outcome Measures**
STAGE 1 – DOSE TITRATION & TOLERABILITY		
Primary	To assess the safety and tolerability of carbamazepine (CBZ) in the treatment of children with MCDS who are ambulant but have not yet reached skeletal maturity (open epiphyses)	Laboratory safety assessments, adverse events and physical examinations collected post IMP administration.
	To determine an appropriate dose of CBZ to inform the treatment of children with metaphyseal chondrodysplasia, type Schmid in Stage 2.	Outcome of dose-titration safety review at 6 months post IMP treatment initiation.
Secondary	To evaluate the effect of CBZ on pain in children with MCDS over 24 months	Alteration from baseline in pain perception over 24 months as measured by: • PEDSQL Pain Coping Inventory • PEDSQL Pain Questionnaire

STAGE 2 – TREATMENT		
Primary	To evaluate efficacy of CBZ for the treatment of children with MCDS who are ambulant but have not yet reached skeletal maturity (open epiphyses)	Alteration from baseline in growth velocity over 12 months
	To determine if efficacy of CBZ warrants a subsequent formal development programme for carbamazepine in this indication	Growth velocity follow-up data at 12 months post treatment initiation
Secondary	To evaluate the effect of CBZ on height in children with MCDS over 12 months	Alteration from baseline in height percentile over 12months
	To evaluate the effect of CBZ on bone conformation in children with MCDS over 12 months	Alteration from baseline in long bone alignment and configuration over 12 months as measured by X-ray analysis
	To evaluate the effect of CBZ on pain in children with MCDS over 12months	Alteration from baseline in pain perception over 12 months as measured by: • PEDSQL Pain Coping Inventory • PEDSQL Pain Questionnaire
	To evaluate the effect of CBZ on health-related quality of life of children with MCDS over 12 months	Alteration from baseline in HRQOL scores over 12 months as measured by: • Paediatric Quality of Life Inventory (PedsQL) • EQ-5D-Y
Exploratory	To identify novel biomarkers relevant to CBZ treatment of MCDS which can be used to monitor therapy and disease progression.	Use of samples (blood) from the cell, and mouse models, patients enrolled into this trial and control samples to identify MCDS biomarker signatures (+/- CBZ treatment)
Investigational Medicinal Product	Carbamazepine (CBZ), brand name Tegretol®	
Formulation, Dose & Route of Administration	Tegretol® 100mg, 200mg and 400mg Immediate release tablets OR Tegretol® 100mg/5ml liquid (oral suspension) Tegretol® to be given orally, dose to be used during Stage 2 (treatment) to be confirmed during Stage 1 (dose titration & tolerability). Anticipated dosage expected to be between 5-20mg/kg bodyweight daily. To be administered in two divided doses.	

Vitamin D	Vitamin D, preferred brand name Fultium (Sites will use suitable alternatives according to local policies and guidelines)
Formulation, Dose & Route of Administration	Preferred brand/formulation Fultium D3 800 IU capsules OR Fultium D3 drops Vitamin D dosing and treatment duration will be appropriate to the need of the patient, following local guidance for vitamin D insufficiency or deficiency as appropriate. Dosing will be prescribed/administered in line with local policies and guidelines and where possible, using the Fultium SmPC (or PI[b] for Australia). Only participants identified as having vitamin D deficiency or insufficiency will be prescribed vitamin D as determined by 3 monthly blood testing during IMP administration stages (1 & 2).

GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
ADR	Adverse Drug Reaction
AE	Adverse Event
AGEP	Acute Generalised Exanthematous Pustulosis
AP	Anterior-Posterior
AR	Adverse Reaction
BNF	British National Formulary
CA	Competent Authority
CNS	Central Nervous System
CESP	Common European Submission Portal system
CBZ	Carbamazepine
CDMS	Clinical data management system
CI	Chief Investigator
CRF	Case Report Form
CRL	Crown-rump length
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
DIBD	Development International Birth Date
DLT	Dose Limiting Toxicity
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ER	Endoplasmic reticulum (ER stress)
EQ-5D-Y	EuroQoL 5 Dimension Youth Questionnaire
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
GSDs	Genetic Skeletal Diseases
HRQOL	Health Related Quality of Life
HRA	Health Research Authority
HTA	Human Tissue Authority
HTAct	Human Tissue Act
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration
IDMC	Independent Data Monitoring Committee
IGM	Institute of Genetic Medicine
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IRMER	Ionising Radiation (Medical Exposure) Regulations
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LPLV	Last Patient Last Visit
MA	Marketing Authorisation
MAOIs	Monoamine-Oxidase Inhibitors

MCDS	Metaphyseal chondrodysplasia type Schmid
MedRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MTA	Material Transfer Agreement
MTD	Maximum Tolerated Dose
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
NUTH	The Newcastle upon Tyne Hospitals NHS Foundation Trust
PAC	Patient Advisory Committee
PEDSQL	Paediatric Quality of Life Inventory Pain coping inventory/questionnaire
PI[a]	Principal Investigator
PI[b]	Product Information
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
R&D	Research & Development
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SJS	Stevens-Johnson syndrome
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
UNEW	Newcastle University
UPR	Unfolded protein response
USM	Urgent Safety Measure

1 Contents

2 BACKGROUND

2.1 Metaphyseal Chondrodysplasia Type Schmid (MCDS)

Metaphyseal chondrodysplasia type Schmid (MCDS) is a rare autosomal dominant skeletal dysplasia affecting <1/100,000 of the population. It can affect both male and females. It was initially described as *'dysostosis enchondralis metaphysarea'* by Schmid in 1949 and subsequently by Maroteaux and Lamy in 1958 and is a very rare form of short-limbed dwarfism that is characterised by disproportionate short stature and long bone deformities.

MCDS is characterized by an abnormal bone formation at the end of the metaphyses that results in short stature with short limbs (short-limbed dwarfism). The knowledge on the course of the disease is based on clinical expertise and the available literature describing case reports of affected patients. Patients usually come to medical attention after 2 years of age with short stature, waddling gait and varus or valgus deformity of the knees. The greatest disability stems from the tendency to develop hip (coxa vara) and knee deformity, which causes chronic pain and the need for long-term analgesia. Coxa vara is a deformity of the hip with an abnormal decreased angle between the head and the shaft of the femur; it causes malalignment of the femur and the hip resulting in an altered function of the joint.

Even though there is no evidence of decreasing life expectancy, MCDS is a condition that has a debilitating effect on the patient's whole life, as it limits normal everyday activities. The available data in the literature suggest that height deficit usually exceed -3SD below the normal average, and it can be very variable with a reported range form -7SD to -3.6SD, in a single case height was at -1.2 SD (Lachman et al., 1988)(Mäkitie et al., 2005). Adult height in patients with MCDS varies between 135cm and 160 cm.

MCDS is caused by heterozygous mutations in the *COL10A1* gene (Warman et al., 1993)(Wallis et al., 1994). Collagens are structural proteins of connective tissues (i.e. bone, tendons, cartilage), and collagen type X is produced in the cartilage by chondrocytes in the hypertrophic stage (Schmid and Linsenmayer, 1985). In patients with MCDS, mutant collagen X proteins misfold and are retained within the endoplasmic reticulum (ER) of hypertrophic chondrocytes, causing an increase in ER stress, which is the main cause of the pathology in this condition.

2.2 ER stress – the primary disease mechanism in MCDS

Type X collagen, a protein encoded by *COL10A1* and expressed exclusively by hypertrophic chondrocytes in the cartilage growth plate of growing bones, was first described in 1985 by researchers in Manchester (Kielty et al., 1985). Mutations in *COL10A1* were subsequently shown to cause the autosomal dominant skeletal dysplasia, metaphyseal chondrodysplasia type Schmid (MCDS) by several research groups across the world (Warman et al., 1993)(Wallis et al., 1994).

Since 1993 over 50 different mutations in *COL10A1* have been identified globally; however, it has only been in the last decade that considerable progress has been made in identifying the underlying disease mechanism of MCDS, primarily driven through the generation and in-depth analysis of genetically relevant mouse models of MCDS (Table 1).

Table 1 - Relevant mouse models used to dissect tissue pathology and identify disease mechanisms in MCDS

COL10A1 MCDS Mutation	Research Group	Reference
Asn617Lys	Manchester/Melbourne	(Rajpar et al., 2009)Rajpar *et al.,*
Tyr632Stop	Manchester/Newcastle	Unpublished
Y663X	Hong Kong	(Ho et al., 2007)Ho *et al.,* 2007
13bp del	Hong Kong	(Tsang et al., 2007)Tsang *et al.,* 2007

Mutant type X collagen molecules mis-fold during protein synthesis and are retained as aggregates within the endoplasmic reticulum (ER) of hypertrophic chondrocytes, thereby causing ER stress and activation of the unfolded protein response (UPR) [See references in Table 1.1].

It has been unequivocally demonstrated that increased ER stress in hypertrophic chondrocytes is the primary cause of the MCDS phenotype seen in patients with MCDS (Rajpar et al., 2009).

The occurrence of increased ER stress causes the cells to disengage their normal differentiation programme in an attempt to reduce ER stress and survive. This altered differentiation program results in decreased levels of vascular endothelial growth factor, produced by hypertrophic chondrocytes, delaying vascular invasion and causing a characteristic expansion of the hypertrophic zone in MCDS. Ultimately, this results in a significant reduction in bone growth, with associated severe skeletal abnormalities [See references in Table 1.1].

Pharmacologically targeting the misfolding of mutant type X collagen and/or the resulting ER stress is therefore an attractive therapeutic avenue for MCDS, because it does not involve restoration of the cartilage extracellular matrix (e.g. by cell therapy) or correction of the underlying genetic mutation (e.g. by gene therapy). Moreover, MCDS is an exemplar of an extensive class of extracellular matrix pathologies in which the expression of a mutant structural protein has a profound cellular consequence and is an underlying 'core disease mechanism' in a diverse spectrum of human connective tissues diseases [(Briggs et al., 2015a); (Briggs et al., 2015b); (Bateman et al., 2009).

Thus, the targeting of ER stress as a common 'core disease mechanism' through drug repurposing represents a paradigm shift in the treatment of rare diseases.

2.3 Carbamazepine in patients with MCDS

Preclinical studies strongly support the potential efficacy of CBZ in MCDS both *in vitro*, improving the cellular phenotype of MCDS cells, and *in vivo*, in improving the phenotype of MCDS in the mouse model (Mullan *et al*., 2017).

In addition, CBZ was previously used to treat myotonia in four patients (aged 7 months to 11 years) with the genetic skeletal disease Schwartz-Jampel Syndrome and as a secondary consequence it was noted that their height had increased from the <3rd to 5th percentile (Squires and Prangley, 1996) (Topaloğlu *et al*., 1993).

Preclinical repurposing of CBZ for MCDS underwent a thorough scientific assessment by the Commission for Orphan Medicinal Products (COMP) during the recent evaluations for ODD designation in September 2016. COMP approved CBZ for the treatment of MCDS on 13th September 2016 (EMA/OD/148/16). Furthermore, Newcastle University (UNEW) has filed an International Patent Application (No PCT/GB2017/050710; Filing date 15 March 2017) on the use of CBZ to treat a broad group of human connective tissue disorders that are caused by inappropriate intracellular mutant protein aggregation. This will provide the consortium with the required freedom to operate.

There are no previous studies of CBZ in patients with MCDS. This trial is designed to provide initial data on safety, tolerability and efficacy. Assessing the effect of CBZ on growth, bone alignment and quality of life in patients with MCDS, we aim to evaluate if the data supports the planning of a phase II long term randomised controlled trial.

3 RATIONALE

The aim of the MCDS therapy trial is to evaluate the effect of carbamazepine on children with a diagnosis of MCDS with confirmed COL10A1 pathogenic mutation. There is currently no specific treatment for patients with MCDS, and patient care is based only on the management of symptoms.

The trial is based on the results of preclinical studies detailed in section 2.2, which support the efficacy of carbamazepine on cells and in mice with a COL10A1 mutation, both at a molecular level on the pathogenic mechanism reducing ER stress, and on growth and bone alignment in mice.

Carbamazepine (CBZ) is a well-established drug, which has been widely marketed throughout Europe since the 1960s and is routinely used in paediatric care for the treatment of epilepsy and neuropathic pain. It has a well-known safety profile. Based on clinical experience of the MCDS patient population, there is no clinical reason to expect a different safety profile of CBZ on patients with MCDS, compared to patients of similar ages treated with CBZ for epilepsy. Its effects on patients with MCDS have never been investigated.

The trial will include children with MCDS; to evaluate the effect of CBZ on growth and bone alignment it is necessary to evaluate this on patients who have not reached bone maturity.

MCDS is a very rare disease for which there are no existing natural history studies. Baseline data will be collected in the first year of the trial for all patients before starting administration of CBZ, to allow for the comparison of pre and post treatment characteristics in each individual.

The trial aims to recruit 40 patients, and is divided into an initial dose titration and tolerability stage (Stage 1 – UK only), followed by a treatment stage (Stage 2 – All partners). The choice of route of administration and dose and dosage regimen have been developed based on the use of CBZ in the treatment of epilepsy in children, for which CBZ is currently licenced.

The optimum dosing will be established during Stage 1. A cohort of 11 patients will be evaluated through a review of safety and tolerability using laboratory safety assessments, adverse events and physical examination data collected via telephone calls conducted weekly during the initial dose titrations, as well as at clinic visits at week 2 then at 3 months and 6 months.

The efficacy of CBZ in the treatment of children with MCDS will be evaluated in full at the end of Stage 2 (29 patients), based on growth velocity, bone alignment, quality of life and pain using data collected every 3 months for 12 months. Participants who have completed stage 1 of the trial will be given the opportunity to continue for a maximum of an additional 12 months of treatment. During this, additional data on the same variables as have been assessed during stage 1 will be collected.

3.1 Risk Assessment

This trial is categorised as:-

- **Type B** = somewhat higher than the risk of standard clinical care

There is currently no standard drug treatment for patients with MCDS. This trial involves the use of a medicinal product licensed for the treatment of a different disease group. It has an established side effect and adverse reaction profile. It is not anticipated that the trial will require substantial dosage

modifications compared to the licensed indication of the IMP. Based on clinical experience of the paediatric MCDS patient population, there is no reason to believe that the side effect or adverse reaction profile will be different in the subjects of this trial to those found in the general paediatric population. Type X collagen is not expressed in the kidney or liver and as such the COL10A1 mutation does not cause an abnormality in liver or renal function, the mechanism by which the body metabolises CBZ.

CBZ is a long established drug that has been licenced in the UK and in the countries of all trial sites for the treatment of seizure disorders and trigeminal neuralgia in children of the age range proposed for this trial. There is extensive clinical experience with CBZ and there is no reason to suspect a different safety profile in the trial population.

4 OBJECTIVES AND OUTCOME MEASURES

Trial objectives and outcomes are detailed in Table 2

Table 2 – Trial primary and secondary objectives and corresponding outcome measures

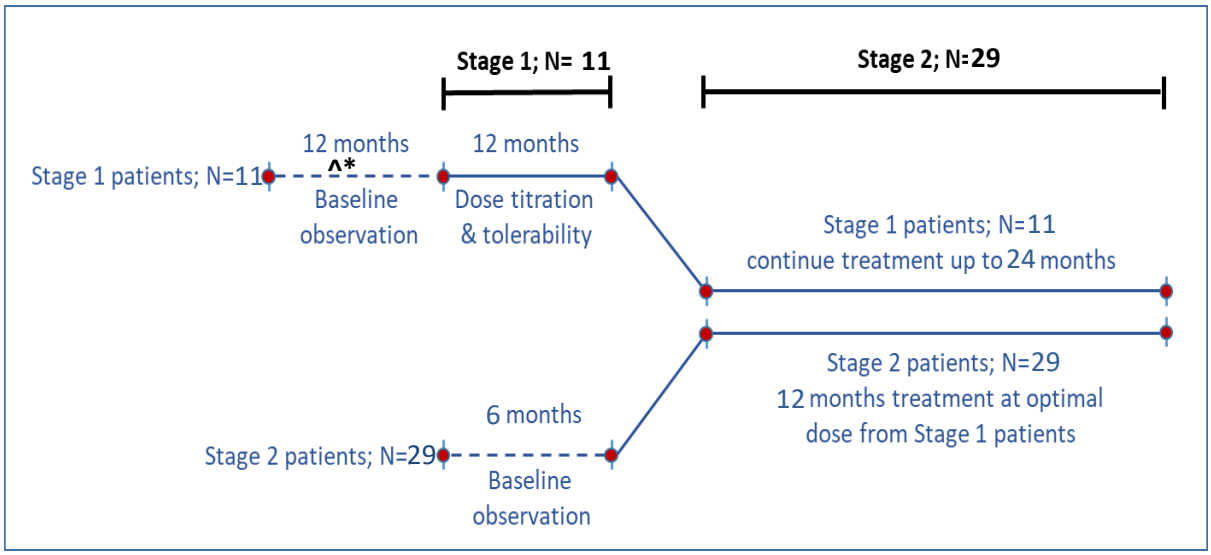
	OBJECTIVE	OUTCOME
Stage 1 – Dose titration and tolerability		
Primary	To assess the safety and tolerability of carbamazepine (CBZ) in the treatment of children with MCDS who are ambulant but have not yet reached skeletal maturity (open epiphyses)	Laboratory safety assessments (section 8.7.5), adverse events (section 8.7.12) and physical examinations (section 8.7.2) collected post IMP administration.
	To determine an appropriate dose of CBZ to inform the treatment of children with metaphyseal chondrodysplasia type Schmid in Stage 2.	Outcome of dose-titration safety review at 6 months post IMP treatment initiation.
Secondary	To evaluate the effect of CBZ on pain in children with MCDS over 12 months	Alteration from baseline in pain perception over 12 months as measured by: • PEDSQL Pain Coping Inventory (section 8.7.9) • PEDSQL Pain Questionnaire (section 8.7.9)
Stage 2 – Treatment		
Primary	To evaluate efficacy of CBZ for the treatment of children with MCDS who are ambulant but have not yet reached skeletal maturity (open epiphyses)	Alteration from baseline in growth velocity over 12 months
	To determine if the level of efficacy warrants a subsequent formal development programme for CBZ in this indication	Growth velocity follow-up data at 12 months post treatment initiation

Secondary	To evaluate the effect of CBZ on height in children with MCDS over 12 months	Alteration from baseline in height percentile over 12 months
	To evaluate the effect of CBZ on bone conformation in children with MCDS over 12 months	Alteration from baseline in long bone alignment and configuration over 12 months as measured by X-ray analysis (section 8.7.8)
	To evaluate the effect of CBZ on pain in children with MCDS over 12 months	Alteration from baseline in pain perception over 12 months as measured by: • PEDSQL Pain Coping Inventory • PEDSQL Pain Questionnaire
	To evaluate the effect of CBZ on health related quality of life of children with MCDS over 12 months	Alteration from baseline in HRQOL scores over 12 months as measured by: • Paediatric Quality of Life Inventory (PedsQL) • EQ-5D-Y
Exploratory	To identify novel biomarkers relevant to CBZ treatment of MCDS which can be used to monitor therapy and disease progression.	Use of samples (blood) from the cell, and mouse models, patients enrolled into this trial and control samples to identify MCDS biomarker signatures (+/- CBZ treatment)

5 TRIAL DESIGN

This is a two stage open label phase I/IIa trial to assess repurposing of carbamazepine (CBZ) for the treatment of children with Metaphyseal Chondrodysplasia Type Schmid (MCDS). The trial includes an initial dose determination stage, followed by long-term assessment of efficacy and safety at the chosen dose. The trial was initially designed to have a cohort of 12 participants in the dose determination stage, and a cohort of 28 participants in the treatment stage. However due to the COVID-19 pandemic delays, this has been amended to stage 1; N=11 and stage 2; N=29. The overall sample size remains the same (N=40) (Figure 1).

Figure 1 - Overview of MCDS-Therapy Clinical Trial



*The 12 month baseline observational visit may be rescheduled to a 18 month visit for participants who have missed the 12 month visit due to COVID-19 (Stage 1 UK participants only).

^ To aid with study participant retention due to COVID 19, with discussion with the CI, the 12 month baseline observational visit window can be up to 12 months and 8 weeks. This will be assessed on a case by case basis through discussion with the site PI[a] with approval from the CI and the NCTU team notified.

Eligible Stage 1 participants may continue treatment for further 12 months (up to 36 months) subject to a separate informed consent at visit 2.5.

Last Patient Last Visits in Stage 1 and Stage 2 must be completed by 31st January 2024.

5.1 Baseline observation

Participants will undergo an observational phase (12-18 months for Stage 1 participants dependent on covid-19 impact; 6 months for Stage 2 particpants) prior to drug administration during which baseline observation data will be collected post confirmation of eligibility (see Table 5 & 8). This will include data on height, weight and calculated growth velocity, baseline haematology and biochemistry indices in blood, radiographic appearances of relevant bones and baseline measurement of health related quality of life (HRQOL) including pain (see section 8.7 for full description of trial assessments).

<u>Stage 1 (UK only) Baseline Observation period and COVID-19</u>

The baseline observation period for some participants may have been affected by the study being temporarily halted due to COVID -19. For these participants, the following timelines will be used for their baseline observation period:

- For participants who have attended a baseline and 6 month visit but their 12 month visit has been missed due to the COVID-19 halt, they will attend a visit at 18 months (the 12 month visit will be rescheduled as an 18 month visit).
- For participants who have attended a baseline visit and have missed their 6 month visit due to COVID-19, they will attend their 12 month visit^. They will have no data available for their 6 month visit.

^To aid with study participant retention due to COVID-19, with discussion with the CI, the 12 month visit window can be up to 12 months and 8 weeks. This will be assessed on a case by case basis through discussion with the site PI[a] with approval from the CI and the NCTU team notified.

For the stage 1 participants affected by COVID-19, this will ensure that participants have two height calculations for their baseline observation period over a 12 month period. Some participants for stage 1 may attend more visits over their baseline period, and it is expected for Stage 2, that the participants will attend 3 visits over their 6 month baseline observation period. This will not impact the number of measurements taken during the dose titration and treatment phase: this will continue as per schedule.

Participants will be assessed for eligibility once they complete their 12 month or 18 month visit and if still eligible to continue on the trial, participants will continue onto Stage 1.

5.2 Stage 1 (UK only) – Dose titration and tolerability & treatment

Stage 1 is a dose titration of carbamazepine in 5mg/kg increments to a preselected maximum dose of 20mg/kg, with review of safety and tolerability in a population of 11 participants from two UK trial sites over a 12 month period (See Table 6). A safety review will be conducted, once the 11th patient has reached the 6 month time point. For a detailed description of the Stage 1 dose titration, see section 8.8. Once a suitable dose is agreed, Stage 1 participants will continue CBZ treatment at this agreed dose until they reach 24 months treatment (See Table 7). There will also be an opportunity to continue CBZ treatment for an additional 12 months for participants who wish to do so. This optional CBZ treatment will be a subject to an additional informed consent at visit 2.5. Their 12/24 month data will be included in the final analysis following Stage 2, subject to IDMC consultation.

5.3 Stage 2 - Treatment

During Stage 1, the additional 29 Stage 2 participants will be recruited and will commence the 6-month observation period in preparation for the start of Stage 2. Stage 2 is a 12-month CBZ treatment stage in a population of 29 participants from multiple trial sites across the UK, and self sponsored trial sites across Europe and Australia(See Table 3. Stage 2 patients will only begin treatment after the Stage 1 safety review is completed and when an agreed safe and tolerable dose has been identified (section 8.8.6). In the case that the dosing regimen remains the same, Stage 1 participants will be included in Stage 2 analysis. In the case that the dosing regimen changes, the IDMC will be consulted about whether inclusion is appropriate. Participants who are in the Stage 2 treatment phase may be on a lower dosing regimen if they are unable to tolerate the maximum dose of 20mg/kg. The titration will need to be recorded in the patient's notes and documented in the trial MACRO database. Clinical judgement alongside clinical assessments will be used to determine if the dose must be lowered.

6 TRIAL SETTING

This is a multicentre international clinical trial. UK trial sites will be sponsored by the Newcastle upon Tyne Hospitals NHS Foundation Trust. However, International trial sites will be sponsored by a local, country specific Sponsor.

The clinical centres have been selected based on:

- Established track record at an international, or at least national level in the diagnosis and management of patients with Genetic Skeletal Diseases (GSDs) including MCDS
- Previous experience within the centre of participation in clinical trials

- Projected ability to recruit patients with MCDS within proposed timescales

All clinical centres are, or have previously been involved in the routine care and follow up of patients with MCDS and are secondary or tertiary care centres. All trial sites have the services needed for MCDS clinical care, including radiology. MCDS is a very rare disease, and in most cases, the diagnosis is reached at the specialised centres following referrals from primary care or other specialist services. A list of the participating countries can be found in section 6.1 below.

When a patient is diagnosed elsewhere, they are usually referred to the selected specialist centres for the follow up of their rare disease. It is expected that most patients involved in the trial will be identified amongst the patients in the care of the specialised centres that have been selected as trial sites. Some patients may be referred to the trial sites by selected Participant Identification Centres (PICs), which are secondary or tertiary centres with expertise in rare diseases who might identify newly diagnosed patients not yet known to the trial sites.

6.1 Trial sites

6.1.1 Stage 1 – Dose titration

- The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK (NuTH)
- Guy's and St. Thomas' Hospital, London, UK (GSTFT)

6.1.2 Stage 2 – Treatment

The two UK sites will continue recruitment in to Stage 2:

- The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK (NuTH)
- Guy's and St. Thomas' Hospital, London, UK (GSTFT)

The following international sites will recruit in to Stage 2:

- Murdoch Children Research Institute - Melbourne, Australia (MCRI)
- Rizzoli Orthopaedic Institute - Bologna, Italy (IOR)

The following international sites have been identified as possible recruiting sites, however a feasibility assessment will be completed prior to site confirmation:

- Assistance Publique – Hôpitaux de Paris – Paris, France (AP-HP)
- University of Antwerp - Antwerp, Belgium (UZA)
- University of Freiburg- Freiburg Germany (UKL-FR)

All clinical centres are regional or national referral centres for the diagnosis and management of patients with GSDs including MCDS.

7 ELIGIBILITY CRITERIA

7.1 Inclusion Criteria

- Participants where a pathogenic mutation in the gene encoding the COL10A1 protein has been identified by sequence analysis
- Ambulant at the time of consent/assent, with open epiphyses
- Willing and able to attend for safety monitoring assessments
- Willing and able to adhere to the trial visit schedule and other protocol requirements

- Capable of giving informed consent, or if appropriate, have 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)
- Written informed consent signed by parent(s)/legal guardian(s) and/or the subject, according to the local regulations
- 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 throughout the trial
- Sexually active female particpants 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.

7.2 Exclusion Criteria

- Patients who have reached skeletal maturity*
- 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)**
- Patients who have had a prior adverse reaction to carbamazepine or similar drugs such as oxcarbazepine, or to any related tricyclic antidepressants.
- Patients known to have atrioventricular block
- Patients who have a history of bone marrow suppression/depression
- Patients who have evidence of chronic hepatic or renal impairment
- Patients who have acute intermittent porphyria
- Patients who have received a monoamine oxidase inhibitor within 14 days of commencing therapy
- 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
- 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[a] 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[a], with the CI and/or the clinical members of the TMG during the screening process.

NB: Please ensure that patients fulfil the full eligibility criteria prior to enrolling them on to the trial and ensure eligibility is re-assessed after the baseline observation period is complete, and before the participant begins treatment with CBZ. If a patient is deemed unsuitable at the end of the baseline observation period re-assessment time point, further reassessment of eligibility is possible if the Site PI[a] and CI are in agreement that the exclusionary results are subject to change. In such cases, eligibility can be re-assessed within a 3 month period. If a patient meets any of the exclusion criteria after the 3 month reassessment period, they will be withdrawn from the study.

Protocol waivers will not be permitted for this trial. Enrolling a patient who does not meet the inclusion/exclusion criteria is considered a protocol waiver and is in breach of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and EU Clinical Trial Directive 2001.

8 TRIAL PROCEDURES

8.1 Recruitment

8.1.1 Patient Identification

Participants will be recruited from the existing MCDS patient populations or newly diagnosed patients in the clinical centres involved in the trial. All clinical centres are regional or national referral centres for the diagnosis and management of patients with GSDs including MCDS.

Potential participants and their parent(s)/legal guardian(s) will be provided with trial information in the form of a Participant Information Sheet (PIS) given either via an invitation letter sent through the post or a copy of the PIS provided during a patient's routine clinic appointment.

As the trial will be recruiting from a paediatric population, age appropriate documentation will be used.

8.1.2 Participant Identification centres (PICs)

Due to the rare nature of the MCDS condition, some of the trial centres may use Participant Identification Centres to identify participants. The PICs will identify potential participants from existing MCDS patient populations or newly diagnosed patients based on trial eligibility criteria. The trial will be discussed with potentially eligible patients and their parent(s)/legal guardian(s) and a copy of the participant information sheet provided. If a potential participant is interested in taking part in the trial, they will be referred to the nearest or most appropriate trial site and will be contacted by the local trial team by their preferred method of contact.

8.2 Consent/Assent

Following provision of trial information, participants and their parent(s)/legal guardian(s) will be invited to attend a consent/assent visit with their local trial team, having been given a minimum of 24 hours to consider the information provided. At the visit, the trial will be explained and discussed with the patient, allowing sufficient time to go through the details of the trial and for the clinician to answer any questions the patient and their parent(s)/legal guardian(s) might have.

The consent/assent process will include sufficient time to discuss the aim of the trial, trial procedures and the commitment required from the family and the patient. It will also include sufficient time for patients and their parent(s)/legal guardian(s) to ask all questions they might have and clarify any doubts. Only after their questions and concerns have been adequately addressed will informed

consent/assent be sought. The patient will be given the opportunity to discuss any aspect of the trial, including risks of pregnancy and contraception, without their parent(s)/legal guardian(s) present if required.

If the patients and parent(s)/legal guardian(s) agree to take part in the trial, they will be asked to sign and initial consent and assent forms, which will be also signed by the member of the trial team delegated by the Principal Investigator (PI[a])to perform this task. Informed consent/ assent will only be sought by a member of the trial team who is medically qualified, appropriately trained and delegated to do so. Consent/assent will be obtained prior to trial screening. N.B Informed consent is ongoing process, if a participant moves age groups during the trial, the age appropriate PIS will be provided, and the participant will be re-consented.
The age requirements for parental consent for children's participation in research differs between EU Member States.

For UK based participants, consent will be sought from patients who are 16 and over and the parent(s)/legal guardian(s) of patients under the age of 16. Furthermore, assent will be taken from patients aged between 7-15 years. For non-UK based participants, local regulations concerning ethics approval and informed consent will be followed for defining the age ranges for subjects capable and not capable of giving written assent. Subjects will be re-consented with the appropriate age-related documents as needed, if required by local regulations.

For the purposes of the MCDS-Therapy trial, consent, assent and patient information documentation will be translated into the relevant languages of the participating European sites where required.

The original signed consent and assent forms will be retained in the Investigator Site File (ISF), with copies provided to the patient/parent(s)/legal guardian(s), a copy filed in the patients' clinical notes and a copy sent by secure methods to Newcastle Clinical Trials Unit (NCTU) (UK centres only). The copy sent to NCTU for monitoring purposes will be destroyed once reviewed. Following consent/assent, the site will allocate the participant their unique trial identification number. The unique trial ID number will be made up of a 2-digit site code and a 3-digit patient code, starting with 001 for the first patient at that site and continuing sequentially with each consenting patient (Table 3).

Table 3 – Site unique trial ID numbers

Site	Site code
The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne UK (NuTH)	10
Guy's and St. Thomas' Hospital, London UK (GSTFT)	11
Rizzoli Orthopaedic Institute, Bologna Italy (IOR)	12
University of Freiburg- Freiburg Germany (UKL-FR)	13
Assistance Publique – Hôpitaux de Paris – Paris France (AP-HP)	14
Murdoch Children Research Institute, Melbourne Australia (MCRI)	15
University of Antwerp, Antwerp Belgium (UZA)	16

8.3 Pregnancy discussion

Due to the teratogenic nature of the trial drug, discussions regarding pregnancy will take place during the informed consent/assent process to ensure all potential female participants of child bearing age are aware of the risks of becoming pregnant whilst taking part in the trial. The trial team member taking consent/assent will discuss pregnancy with both the potential participant and their parent(s)/legal guardian(s). Due to the sensitive nature of this topic, the participant will have the

opportunity to speak with the clinician without the parent(s)/legal guardian(s) present. Both potential participants and their parent(s)/legal guardian(s) will be required to provide consent/assent confirming, where appropriate, which contraception will be used for the duration of the trial and for 28 days after discountination of treatment and participants will commit to regular pregnancy testing for the duration of the trial.

8.4 Screening

Following consent and prior to entry into the trial, all subjects will be screened to assess eligibility ensuring compliance with the trial inclusion and exclusion criteria (sections 7.1, 7.2). Eligibility must be assessed by a medically qualified doctor and this assessment must be documented in the participant's medical notes. A copy of the site eligibility checklist must be filed in the participant's medical notes. The eligibility checklist must also be completed in the trial MACRO database for those patients who enter the trial. Only personnel formally delegated by the Principal Investigator to assess eligibility may perform this task.

Eligibility will be assessed following consent before the participant enters the trial and re-assessed after the baseline observation period is complete before the participant begins treatment with CBZ, to confirm they are still eligible for the trial.

To confirm the participant is eligible to take part in the MCDS-Therapy trial the following assessments will be conducted: -

- Review of past medical history and diagnosis of MCDS, including review of available previous radiographic assessments
- Physical examination including height, weight and sitting height
- Blood samples will be obtained for full blood count, Plasma biochemistry including renal function, bone biochemistry, vitamin D and liver function (max 2 ml total). Samples will be processed at the trial site local laboratories following standard local laboratory procedures.
- Urine based pregnancy test
- The local clinician will need to confirm the participant has a pathogenic mutation in the gene encoding the COL10A1 protein. If the participants medical notes do not indicate the appropriate genetic analysis has been conducted, a further blood sample will be taken during the screening visit to confirm presence of the COL10A1 mutation. In the UK, The blood sample may be sent to the Diagnostic Laboratory, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, if local testing is not feasible. International sites will be responsible for conducting their own genetic analysis. The potential outcomes of this test will be discussed with the participant, ensuring they are aware that if the COL10A1 mutation is not present they will not be eligible to take part in the trial. When the genetic analysis results are complete, the potential participant will be invited back for a second screening visit. If the COL10A1 mutation is present, eligibility will be confirmed. If the COL10A1 mutation is not present, the patient will not be eligible for the trial and the investigator/clinician will discuss the impact of this outcome with the participant
- For patients of Han Chinese, Thai or other Asian origins the local clinician will need to confirm if the patient carries the HLA-B*1502 allele. A blood sample will be taken (max 6 ml) and sent to the local blood transfusion service or equivalent for HLA typing following consent/assent. Any patients who are found to carry the HLA-B*1502 allele will be excluded from the trial. Carriage of the HLA-B*1502 allele has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS), a serious and sometimes fatal cutaneous reaction, when treated with carbamazepine. Sites will be responsible for conducting their own HLA typing.

8.5 Payment

Participants will not receive payment for participation in the trial. Payment of reasonable travel and accommodation expenses will be detailed in the local site agreements.

8.6 Participant visit schedule

Table 4– MCDS-Therapy participant visit schedule

	Visits participants require					
	Stage 1: Dose titration participants (UK only)			*Stage 2: Treatment phase participants (Europe,UK & Australia)*		
Stage of trial	***VISIT***	***TIMEPOINT***		***VISIT***	***TIMEPOINT***	
Consent/assent, screening & eligibility	**Consent/assent & screening visit 1***			**Consent/assent & screening visit**		
	Screening visit 2*	**Up to 28 days post consent**		**Screening visit 2***	**Up to 28 days post consent**	
Baseline Observation	**Visit 1***	**0**	**Months post initiation of baseline observation**	**Visit 1***	**0**	**Months post initiation of baseline observation**
	Visit 2	**6****		**Visit 2**	**6**	
	Visit 3*	**12*****				
Dose titration	**Visit 1.1***	**0**	**Months post initiation of CBZ dose titration**	**Not required**		
	Dose evaluation telephone calls	**1 -11**	**Weeks post initiation of CBZ dose titration**			
	Visit 1.2	**2**				
	Visit 1.3	**3**	**Months post initiation of CBZ dose titration**			
	Visit 1.4	**6**				
	Visit 1.5	**9**				
	Visit 1.6	**12**				
Treatment phase	**Visit 2.1***	**12***		**Visit 2.1***	**0**	**Months post initiation of CBZ treatment**
	Visit 2.2	**15**		**Visit 2.2**	**3**	
	Visit 2.3	**18**		**Visit 2.3**	**6**	
	Visit 2.4	**21**		**Visit 2.4**	**9**	
	Visit 2.5	**24**		**Visit 2.5[֍]**	**12**	
Optional extended treatment phase	**Visit 2.6 [Δ]**	**27**		**Not required**		
	Visit 2.7 [Δ]	**30**				
	Visit 2.8 [Δ]	**33**				
	Visit 2.9 [Δ] [֍]	**36**				

*Visits which may coincide with the preceding or proceeding visit: - Screening visit 1 and 2/Visit 1 baseline observation; Visit 3 baseline observation/ visit 1.1 dose titration; Visit 3 baseline observation/Visit 2.1 treatment phase

**6 month visit may be missed for participants who have experienced delays to their visit schedule due to COVID-19 halt to the trial

***12 month visit may be rescheduled to 18 month visit for participants who have missed the 12 month visit due to COVID-19

[Δ] This is an optional visit subject to an additional informed consent

[֍] Visit 2.5 in Stage 2 and visit 2.9 in Stage 1 must occur no later than 31st January 2024.

8.7 Trial assessments

The following trial assessments will be conducted during the baseline observation period, stage 1 dose titration and tolerability and stage 2 treatment as indicated in the schedule of events, Tables 5, 6,7, 8 and 9, and the visit schedule (Table 4).

8.7.1 Demographic and Medical History

The participant's demographic and medical history will be taken following consent/assent. Details of their medical history to be noted include: Any medications used at time of consent/assent; Any medications used to manage their MCDS symptoms in the last 6 months; Incidence of surgical intervention to manage MCDS symptoms.

8.7.2 Physical examination

A full physical examination will be conducted. It will include examination of hair and skin, lymph nodes; eyes; ears; nose; throat; respiratory; cardiovascular; abdomen; musculoskeletal; neurological assessment; mental status assessment. Bodyweight will also be measured. Physical examination to be performed at times specified in the schedule of events (Tables 5, 6, 7, 8 & 9).

8.7.3 Tanner stage

Pubertal stage will be assessed by the clinician using validated Tanner staging criteria, in children aged 5 and older, at times specified in the schedule of events (Tables 5, 6, 7, 8 & 9) [Rasmussen et al 2015] (see Appendix 3). This is to evaluate the possibility that childbearing age has been reached in females and that pregnancy testing is therefore required during the trial (to be performed at the times specified in the schedule of events if indicated (Tables 5, 6, 7, 8 & 9). The Tanner staging criteria is also validated to use as a self-assessment [Morris et al 1980]. Self-assessment will be offered as an option, if participants prefer.

8.7.4 Pregnancy testing

A urine sample based (or serum based if applicable) pregnancy test will be carried during the initial screening visit and at selected times specified in the schedule of events (Tables 5, 6, 7, 8 & 9). In the event the Tanner stage assessment (section 8.7.3) indicates female participants have reached childbearing age, females will be required to perform a pregnancy test at that visit and then according to the schedule of events from that point onwards (Tables 5, 6, 7, 8 & 9).

8.7.5 Laboratory safety assessments

A blood sample will be taken for full blood count (approximately 1ml), and for kidney function and liver function tests (maximum 1ml) at times specified in the schedule of events (Tables 5, 6, 7, 8 & 9). These tests are comprised of:

- Full blood count (haemoglobin, platelets & white cells – neutrophils & lymphocytes)
- Kidney function test: creatinine, serum electrolytes, eGFR
- Liver Function test: total bilirubin, ALP, ALT or AST (site dependent)

A urine sample will also be taken to measure proteinuria using a dipstick at times specified in the schedule of events (Tables 5, 6, 7, 8 & 9).

Samples will be processed at the trial site local or associated laboratories, following standard local laboratory procedures.

8.7.6 Bone Biochemistry

A blood sample will be taken for Bone biochemistry (approximately 1ml), at times specified in the schedule of events (Tables 5, 6, 7, 8 & 9).

These tests are comprised of total calcium and/or adjusted calcium*, 25-OHD (or total Vitamin D, depending on local reporting parameters), Phosphate and PTH.

* calcium results will vary by site, depending on what is reported locally.

Samples will be processed at the trial site local or associated laboratories following standard local laboratory procedures.

If following Vitamin D testing a participant is found to be Vitamin D insufficient or deficient, they will be prescribed Vitamin D medication according to local guidelines(preferred brand: Fultium).

8.7.7 Growth and Growth velocity

Growth will be recorded at times specified in the schedule of events (Tables 5, 6, 7, 8 & 9). The assessment to record growth will include:

- Total height (H) and length (L) if <2 years old
- Sitting height in children >=5 years old (SH)
- Crown-rump length (CRL) in children <5 years old
- Calculated sub ischial leg length (height/length – sitting height/CRL)

All growth measurements will be recorded as described in Hall *et al* (Hall, Judith G. Handbook of normal physical measurements (2nd ed.), Oxford University Press, New York, 2007) and will be taken in triplicate to ensure accuracy.

Growth velocity will be measured by a change in annualised growth velocity from baseline based on measurements made in the 12-month(Stage 1)/6-month (Stage 2) observational phase (measured in cm/year).

8.7.8 X-ray analysis & Bone alignment

Participants will have an X-ray of the hips/knees and left wrist during baseline observation (post confirmation of eligibility), stage 1 dose titration and tolerability (every 6-12 months) and stage 2 treatment (every 6-12 months), as specified in the schedule of events (Tables 5, 6, 7, 8 & 9). A maximum of 20 sets of X-rays will be conducted over a 48 month period. Participants will receive up to two wrist and two hip/knees X-rays during baseline observation period and up to six wrist and six hip/knees X-rays during the 12-24 month dose titration/treatment period. Participants who consent to additional visits in the optional Extended Treatment Phase would receive two additional wrist and two additional sets of hip/knee X-rays.

Imaging to be collected: -

- Long leg standing Anterior-Posterior (AP) views (hips & knees)
- Left wrist (to assess bone age)

Both entire lower extremities (including a full view of the anterior superior iliac crest and the ankle talus) will be imaged at the same time, in a weight-bearing position.

Anonymised X-ray images will be stored in the trial MACRO database, labelled with unique study ID only. X-ray images will be reviewed by at least two independent radiologists to ensure consistency across sites has been achieved.

Using X-ray images of the hip and knees, bone alignment will be evaluated based on the angle formed between the head and neck of the femur and its shaft (Mikulicz angle). To ensure consistency, angle measurements will be performed centrally by at least two independent radiologists . This will be

measured according to the standards described in Keats TE Atlas of Roentenographic measurement Mosby 1990 p.289 p.320.

8.7.9 Questionnaires

Quality of life questionnaires and pain questionnaires will be administered at times specified in the schedule of events (Tables 5, 6, 7, 8 & 9) to assess health related quality of life and measure pain perception and pain coping strategies. These include:

- **EQ-5D-Y** (EuroQoL 5 Dimension Youth Questionnaire), a child-friendly version of the standard EQ-5D-3L (**https://euroqol.org/eq-5d-instruments/**). The EQ-5D-Y descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems, and extreme problems. It also includes self-rated health on a vertical visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. The EQ-5D-Y can be self-completed by children and adolescents aged 8-15, and for children aged 7 years or younger a proxy version of the tool will be used. Validated versions of the instrument are available in over 40 languages
- **PEDSQL Quality of Life Inventory** - to measure health related quality of life in children and adolescents (Varni, Seid et al. 1999, Varni, Seid et al. 2001, Varni, Seid et al. 2002)
- **PEDSQL Pain Coping Inventory and PEDSQL Pain Questionnaire -** to measure pain perception and pain coping strategies. (Varni, J.W., Waldron, S.A., Gragg, R.A., Rapoff, M.A., Bernstein, B.H., Lindsley, C.B., & Newcomb, M.D. (1996). Development of the Waldron/Varni Pediatric Pain Coping Inventory. Pain, 67, 141-150).

Versions of the PedsQL for completion by the subject (for children aged 5 and over) and for the parent(s)/legal guardian(s) acting as a proxy for the child will be used. When the child is capable of self-completing an age-appropriate version, as assessed by parental & clinician judgement, they will do so. However, if the child is deemed incapable, the proxy version can be used alone. It is recommended where possible, the same parent/caregiver should complete the questionnaires at all visits.

To help with the completion of the trial questionnaires and to ensure that when needed, time spent in a hospital environment can be reduced, questionnaires may be sent to participants/parent(s)/legal guardian(s) to be completed at home to be given to site staff at their next trial visit.

8.7.10 Biomarker Sampling (UK only)

Blood sampling for exploratory biomarkers will only be performed at UK sites at times specified in the schedule of events (Tables 5, 6, 7, 8 & 9). For further details please consult section 8.11.

8.7.11 Concomitant Medication

The concomitant medications of participants will be collected and documented in patient's notes and in the electronic case report form (eCRF) within the trial MACRO database. Participants will be instructed to record concomitant medication including changes encountered during the trial in their MCDS-Therapy Patient Diary – in either their Baseline, Dose Titration or Stable Dose diary depending on which stage of the trial they are at. These will be assessed by the PI[a]/co-Investigators or delegated individual during trial telephone calls and/or trial visits at times specified in the schedule of events (Tables 5, 6, 7, 8 & 9). It is the responsibility of the prescribing clinician to check for interactions between the trial drug and other medications. For further guidance please refer to section 4.5 of the SmPC (PI[b] for Australia) for CBZ (Tegretol®).

8.7.12 Adverse Events

Participants will be asked at each trial visit and telephone call whether they have experienced any adverse events at times indicated in the schedule of events (Tables 5, 6, 7, 8 & 9). Any adverse events reported during trial visits, telephone calls or that come to the attention of the trial team by other means, will be recorded in the patient's medical notes and the eCRF, within the trial MACRO database. During the trial, participants will be instructed to record any adverse events in their MCDS-Therapy Patient Diary – in either their Baseline, Dose Titration or Stable Dose diary depending on which stage of the trial they are at, for use during trial telephone calls and trial visits. Adverse events will also include recording of any incidence of surgical intervention to manage MCDS-related symptoms.

If a reported adverse event is deemed to be serious, then a Serious Adverse Event form will also need to be completed (see protocol section 10.2 – Recording and reporting of AEs and SAEs) and sent to NCTU (UK only). For international sites sharing of safety information will be defined in the relevant country specific delegation agreement or equivalent.

8.7.13 Dose evaluation

For a detailed description of the dose titration evaluation please see section 8.8.

8.7.14 Drug Prescription

Medication will be dispensed at relevant trial visits as detailed in the schedule of events (Table 6, 7 & 9). Medication will be given to the participant/parent(s)/legal guardian(s) by an appropriately trained and delegated member of the trial team. The participant and their parent(s)/legal guardian(s) will receive medication counselling (section 8.7.15). Further details on medication dispensation and instructions will be detailed in the trial Pharmacy manual/IMP Management Guide.

8.7.15 Medication counselling

Medication counselling will be provided to participants and their parent(s)/legal guardian(s) at trial visits and during telephone calls as indicated in the schedule of events (Table 6, 7& 9). This will include information about the IMP, the strength of the prescribed formulation, the posology and how to use the Dosing Instructions document to ensure the correct dose is taken. Instructions will be given on how to complete the relevant sections of the Dose Titration Diary, what to do in the event of missed dose(s) and the importance of IMP compliance. Potential adverse reactions will be made clear and information will be provided about what to do in the event one (or more) of these occur, including seeking medical attention and provision of the trial patient card to medical professionals. Sites will be provided with a Pharmacy manual/IMP Management guide to assist with this process.

Table 5 - Schedule of Events, Stage 1 Baseline Observation (12 months duration)– (UK participants only)

Assessment*	Consent/Assent & Screening visit 1**	Screening visit 2** (up to 28 days post consent/assent)	Visit 1** 0 months (up to 28 days post consent/assent)	Visit 2 6 months (+/- 14 days)£	Visit 3** 12 months (+/- 14 days)^$
Informed consent/assent-	X				
Demographic and medical history	X				
Eligibility blood sample to confirm COL10A1 genetic mutation (if required)	X				
Physical examination	X		X	X	X
Confirmation of eligibility		X			
Tanner stage	X		X	X	X
Growth measurements	X		X	X	X
X-rays (left wrist for bone age and long leg standing AP)****			X		X
Laboratory safety assessments (including urine dipstick) %	X		X	X	X
Bone biochemistry %	X		X	X	X
Pregnancy testing (potentially child bearing females only)	X		X	X	X
EQ-5D-Y questionnaire			X	X	X
PEDSQL questionnaires (QoL Inventory, Pain coping Inventory & Pain questionnaire)			X	X	X
Adverse event recording			X	X	X
Concomitant medications	X		X	X	X
Biomarker blood sample (UK participants only)***			X	X	X

-Informed consent is ongoing process, if a participant moves age groups during the trial, the age appropriate PIS will be provided, and the participant will be re-consented

*All assessments to be performed as described in the protocol trial assessments section 8.7

**Screening visit 1 and 2 may coincide with baseline observation visit 1 and baseline observation visit 3 may coincide with dose titration visit 1.1 (Table 6) for stage 1 participants

*** A maximum of 2ml blood will be taken for exploratory biomarker analysis and a maximum of 2ml blood will be taken for the measurement of Bone markers (osteocalcine and CTX), if available at site.

****Clinical X-rays taken 3 months prior to participant consent/assent can be used for visit 1 as long as they meet the requirements for the trial and can be uploaded to the study database.

£This visit may be missed for some stage 1 participants due to the COVID-19 pandemic

^This visit may be rescheduled as an 18 month visit for some stage 1 participants due to the COVID-19 pandemic

$To aid with study participant retention due to COVID 19, with discussion with the CI, the 12 month visit window can be up to 12 months and 8 weeks. This will be assessed on a case by case basis through discussion of the site PI[a] with approval from the CI and the NCTU team notified.

% As this is a paediatric population, if there are difficulties in drawing blood or enough blood cannot be collected and to prevent multiple draws in one visit, it will be discussed with the PI[a] and the CI whether there is a clinical need to bring the participant back into clinic in the next 14 days for another blood draw attempt.

Table 6 - Schedule of Events, Stage 1 Dose titration & tolerability (UK participants only)

Assessment*	Visit 1.1** 0 months	Telephone call (Weeks 1-11 as required)	Visit 1.2 2 weeks (+/- 1 day)	Visit 1.3 3 months (+/- 14 days)	Visit 1.4 6 months (+/- 14 days)	Visit 1.5 9 months (+/- 14 days	Visit 1.6 12 months** (+/- 14 days)	Ad hoc visit***
Eligibility check	X							
Physical examination	X		X	X	X	X	X	
Confirmation of eligibility	X							
Tanner stage	X			X	X	X	X	
Growth measurements	X			X	X	X	X	
X-rays (left wrist for bone age and long leg standing AP)	X				X		X	
Laboratory safety assessments (including urine dipstick) %	X		X	X	X	X	X	
Bone biochemistry %	X		X	X	X	X	X	
Pregnancy testing (potentially child bearing females only)	X			X	X	X	X	X*****
EQ-5D-Y questionnaire	X			X	X	X	X	
PEDSQL questionnaires (Qol Inventory, Pain coping Inventory & Pain Questionnaire)	X			X	X	X	X	
Adverse event recording	X	X	X	X	X	X	X	X
Dose evaluation		X	X	X				X
Drug prescription	X		X	X	X	X	X	
Medication counselling	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Biomarker blood sample (UK participants only)******	X			X	X	X	X	

* All assessments to be performed as described in the protocol trial assessments section 8.7

**Visit 1.1 may coincide with baseline observation visit 3 (Table 5). If visit 1.1 does not coincide with baseline observational visit 3, it must be within 14 days of baseline observation visit 3. Visit 1.6 may coincide with stage 1 treatment visit 2.1.

*** Adhoc safety visit to be performed if clinically indicated

***** Pregnancy testing will only be performed if deemed necessary by clinical team
****** A maximum of 2ml blood will be taken for exploratory biomarker analysis and a maximum of 2ml blood will be taken for the measurement of Bone markers (osteocalcine and CTX), if available at site.
% As this is a paediatric population, if there are difficulties in drawing blood or enough blood cannot be collected and to prevent multiple draws in one visit, it will be discussed with the PI[a] and the CI whether there is a clinical need to bring the participant back into clinic in the next 14 days for another blood draw attempt.

Table 7 – Schedule of events - Stage 1, Treatment phase (UK participants only)

Assessment*	**Visit 2.1** 0 months (+/- 14 days)**	**Weekly Telephone call (as required)******	**Visit 2.2 3 months (+/- 14 days)**	**Visit 2.3 6 months (+/- 14 days)**	**Visit 2.4 9 months (+/- 14 days)**	**Visit 2.5 12 months (+/- 14 days)**	**Visit 2.6 15 months (+/- 14 days) Δ**	**Visit 2.7 18 months (+/- 14 days) Δ**	**Visit 2.8 21 months (+/- 14 days) Δ ∞**	**Visit 2.9 24 months (must be completed on/before 31/01/2024)Δ**
Informed consent/assent						X$^{\alpha}$				
Eligibility check	X					X$^{\alpha}$				
Physical examination	X		X	X	X	X	X	X	X	X
Confirmation of eligibility	X									
Tanner stage	X		X	X	X	X	X	X	X	X
Growth measurements	X		X	X	X	X	X	X	X	X
X-rays (left wrist for bone age and long leg standing AP)	X			X		X		X		X
Laboratory safety assessments (including urine dipstick) %	X			X		X		X		X
Bone biochemistry %	X			X		X		X		X
Pregnancy testing (potentially child bearing females only)	X		X	X	X	X	X	X	X	X
EQ-5D-Y questionnaire	X		X	X	X	X	X	X	X	X
PEDSQL questionnaires (QoL Inventory, Pain coping Inventory & Pain Questionnaire)	X		X	X	X	X	X	X	X	X
Dose Evaluation		X								
Drug prescription	X		X	X	X	X	X	X	X$^{\Phi}$	
Adverse event recording	X	X	X	X	X	X	X	X	X	X
Medication counselling	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Biomarker blood sample (UK participants only)*****	X		X	X	X	X	X	X	X	X

* All assessments to be performed as described in the protocol trial assessments section 8.7
**Visit 2.1 may coincide with Dose Titration and Tolerability visit 1.6 (Table 6). If visit 2.1 does not coincide with Dose titration and tolerability visit 1.6, it must be within 14 days of dose titration and tolerability visit 1.6
**** phone calls may be required, if patient is unable to tolerate 20mg/kg dose and requires dose titration
***** A maximum of 2ml blood will be taken for exploratory biomarker analysis and a maximum of 2ml blood will be taken for the measurement of Bone markers (osteocalcine and CTX), if available at site.% As this is a paediatric population, if there are difficulties in drawing blood or enough blood cannot be collected and to prevent multiple draws in one visit, it will be discussed with the PI[a] and the CI whether there is a clinical need to bring the participant back into clinic in the next 14 days for another blood draw attempt
[Δ] This is an optional visit for participants who re-consent to the Extended Treatment Phase only
[α] Informed consent/assent and Eligibility check at visit 2.5 is only applicable to participants who are eligible to continue in the optional Extended Treatment Phase
[ϞϞ] Visit 2.8 and 2.9 can be combined and all assessments can be done at one visit, if the Investigator feels this is appropriate.
[☼] If visit 2.8 is the final visit then Drug prescription is not applicable at this visit.

Table 8 - Schedule of Events, Stage 2 Baseline Observation (6 months duration) (UK, Europe & International sites)

Assessment*	Consent/Assent & Screening visit 1**	Screening visit 2** (up to 28 days post consent/assent)	Visit 1** 0 months (up to 28 days post consent/assent)	Visit 2** 6 months (+/- 14 days)
Informed consent/assent-	X			
Demographic and medical history	X			
Eligibility blood sample to confirm COL10A1 genetic mutation (if required)	X			
Physical examination	X		X	X
Confirmation of eligibility		X		
Tanner stage	X		X	X
Growth measurements	X		X	X
X-rays (left wrist for bone age and long leg standing AP)			X	
Laboratory safety assessments (including urine dipstick) %	X		X	X
Bone biochemistry %	X		X	X
Pregnancy testing (potentially child bearing females only)	X		X	X
EQ-5D-Y questionnaire			X	X
PEDSQL questionnaires (QoL Inventory, Pain coping Inventory & Pain questionnaire)			X	X
Adverse event recording			X	X
Concomitant medications	X		X	X
Biomarker blood sample (UK participants only)***			X	X

--Informed consent is ongoing process, if a participant moves age groups during the trial, the age appropriate PIS will be provided, and the participant will be re-consented
*All assessments to be performed as described in the protocol trial assessments section 8.7
**Screening visit 1 and 2 may coincide with baseline observation visit 1 and baseline observation visit 2 may coincide with treatment visit 2.1 (Table 9) for stage 2 participants.
*** A maximum of 2ml blood will be taken for exploratory biomarker analysis and a maximum of 2ml blood will be taken for the measurement of Bone markers (osteocalcine and CTX), if available at site.

Table 9 – Schedule of events - Stage 2, Treatment phase (UK, Europe & International sites)

Assessment*	**Visit 2.1** 0 months (+/- 14 days)**	**Weekly Telephone call (as required)******	**Visit 2.2 3 months (+/- 14 days)**	**Visit 2.3 6 months (+/- 14 days)**	**Visit 2.4 9 months (+/- 14 days) ∞**	**Visit 2.5 12 months (must be completed on/before 31/01/2024)**
Eligibility check	**X**					
Physical examination	**X**		**X**	**X**	**X**	**X**
Confirmation of eligibility	**X**					
Tanner stage	**X**		**X**	**X**	**X**	**X**
Growth measurements	**X**		**X**	**X**	**X**	**X**
X-rays (left wrist for bone age and long leg standing AP)	**X**			**X**		**X**
Laboratory safety assessments (including urine dipstick) %	**X**			**X**		**X**
Bone biochemistry %	**X**			**X**		**X**
Pregnancy testing (potentially child bearing females only)	**X**		**X**	**X**	**X**	**X**
EQ-5D-Y questionnaire	**X**		**X**	**X**	**X**	**X**
PEDSQL questionnaires (QoL Inventory, Pain coping Inventory & Pain Questionnaire)	**X**		**X**	**X**	**X**	**X**
Dose Evaluation		**X**				
Drug prescription	**X**		**X**	**X**	**X**✡	
Adverse event recording	**X**	**X**	**X**	**X**	**X**	**X**
Medication counselling	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant medications	**X**	**X**	**X**	**X**	**X**	**X**
Biomarker blood sample (UK participants only)*****	**X**		**X**	**X**	**X**	**X**

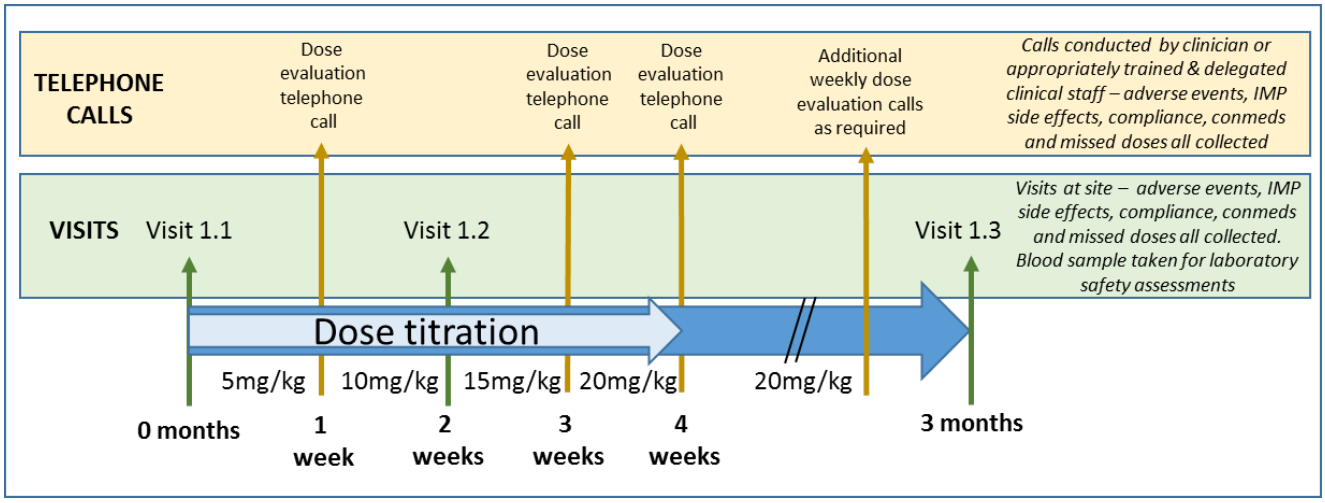
* All assessments to be performed as described in the protocol trial assessments section 8.7
**Visit 2.1 may coincide with stage 2 baseline observation visit 2 (Table 8). If visit 2.1 does not coincide with baseline observational visit 2, it must be within 14 days of baseline observation visit 2
**** phone calls may be required, if patient is unable to tolerate 20mg/kg dose and requires dose titration
***** A maximum of 2ml blood will be taken for exploratory biomarker analysis and a maximum of 2ml blood will be taken for the measurement of Bone markers (osteocalcine and CTX), if available at site.% As this is a paediatric population, if there are difficulties in drawing blood or enough blood cannot be collected and to prevent multiple draws in one visit, it will be discussed with the PI[a] and the CI whether there is a clinical need to bring the participant back into clinic in the next 14 days for another blood draw attempt.
ꝏ Visit 2.4 and visit 2.5 can be combined and all assessments can be done at one visit, if the Investigator feels this is appropriate.
☼ If visit 2.4 is the final visit then Drug prescription is not applicable at this visit.

8.8 Stage 1 – Dose titration and tolerability (UK only)

The dose titration stage of the trial will involve two recruiting UK sites. The trial follows a design that titrates the dose of carbamazepine (CBZ) to a pre-specified optimum, based on clinical considerations. The trial aims for all Stage 1 participants to reach a dose of 20mg/kg by the end of the 12 month stage 1 period. Clinical judgement alongside clinical assessments will be used to determine a stable dose for the patient. Stable dose will be confirmed when a participant reaches a dose of 20mg/kg or the maximum dose at which they are able to tolerate any CBZ-related side effects (their maximum tolerated dose (MTD) and has a period of at least 8 weeks with no significant IMP related adverse events/side effects).

Stage 1 participants will be treated according to the dose titration regimen outlined below and detailed in Figure 2, following the guidance stated in the Guy's and St Thomas' NHS foundation Trust's paediatric formulary and British National Formulary (BNF) for Children for use of CBZ in children with epilepsy.

Figure 2 – Overview of design of dose titration & tolerability period from month 0 to 3



- Participants will be initiated on a daily CBZ dose of 5mg/kg/day. This daily dose will be divided, and participants will be asked to take CBZ twice daily. Doses may be taken during, after or between meals, with a little liquid e.g. a glass of water. If the current dose is tolerated by participants following 7 days of treatment, patients will be instructed to increase their daily dose by 5mg/kg/day for a further seven days
- The dose level will be increased every seven days until a maximum dose of 20mg/kg/day or MTD is achieved

8.8.1 Weekly dose evaluation call

At weekly intervals (+/- 1 day) following initiation of IMP treatment participants and or their parent(s)/legal guardian(s) will receive dose evaluation telephone calls from a medically qualified clinician from their local trial team to determine if the current dose has been tolerated, and to decide if the dose requires up-titration or other appropriate modification. Calls will be conducted by the site clinician or appropriately trained and delegated clinical staff. The participant will be contacted on a weekly basis until they reach a dose they can tolerate (either 20mg/kg or the nearest maximum tolerated dose). Additional calls can be conducted if the patient requires additional support. During the call the participant will be asked to provide information regarding drug side effects, adverse events, any changes to concomitant medication, drug compliance and details of any missed doses.

Participants will be provided with a Diary to record this information in between calls/visits. Medication counselling will be provided if required. All dosage decisions, IMP side effects, adverse events and any changes to concomitant medication noted during the dose evaluation calls should be documented in the patient notes by the appropriately trained and delegated member of the research team and in the appropriate eCRF within the trial MACRO database.

Dose titration decisions made during the trial dose evaluation telephone calls will be based on the occurrence of known CBZ side effects listed within the approved CBZ (Tegretol®) SmPC (PI[b] for Australia) and accompanying Patient Information Leaflet. If the participant does not report any side effects of significant concern, their dose will be up titrated by 5mg/kg to the next dose level up to a maximum dose of 20mg/kg.

If the participant is experiencing side effects/adverse events not of significant concern but in the clinical opinion of the investigator/clinician, is unlikely to tolerate a higher dose at the time of the weekly telephone call, then the dose should remain the same or lowered to the previous dose tolerated by the participant. At the discretion of the investigator/clinician, a further assessment call may be made the following week to consider continuing up-titration of CBZ by 5mg/kg increments, with weekly review as described above, unless this coincides with visit 1.2 where the assessment would take place during the visit.

If the participant is reporting any side effects /adverse events of significant concern to the clinician which are suspected to be related to the IMP as listed within the approved CBZ (Tegretol®) SmPC (PI[b] for Australia) and/or accompanying Patient Information Leaflet, they will be asked to attend the trial site for laboratory safety blood assessments and further review. The results of the laboratory safety blood assessments, reported side effects/adverse events and clinical examination of the participant will be used to inform any changes to the participant's current dose.

If the participant is reporting any severe side effects as detailed in the CBZ (Tegretol®) SmPC (PI[b] for Australia) and/or Patient Information Leaflet which prevent the participant from adhering to the trial protocol or in the opinion of the investigator deem the participant not suitable to continue participation in the trial then CBZ should be permanently discontinued and the patient withdrawn from the trial. The patient will be contacted again within 7 days to ensure the reasons for withdrawal have been resolved to the satisfaction of the investigator. If the participant experiences any severe side effects beyond the dose titration and tolerability stage, the same approach will apply.

Participants who do not tolerate increased dosing will be kept on a lower dose or the dose will be reduced. The inclusion of such patients in the final efficacy analysis will be discussed and evaluated case by case by the TMG with input from the IDMC if required (see section 8.8.4 – Missed doses).

If an adverse event is deemed to be serious, then a Serious Adverse Event form will also need to be completed (see protocol section 10.2 – Recording and reporting of AEs and SAEs) and sent to NCTU (UK only).

8.8.2 Dose evaluation safety visits – Week 2

To ensure patient safety during the escalation of dose from 5mg/kg to 20mg/kg participants and their parent(s)/legal guardian(s) will attend a site trial visit at week 2 (+/- 1 day). Blood samples will be taken to conduct the laboratory safety assessments described in section 8.7.5. Medication counselling will be provided if required. Once the outcomes of the laboratory safety assessments have been received at the trial site, a follow-up phone call will be made to the participant and their parent(s)/legal guardian(s) to discuss any requirement to alter their dose regimen. Additional assessments including

adverse event reporting and recording of concomitant medication will also be conducted during this visit as indicated in Table 6.

8.8.3 Dose evaluation safety visits – Months 3, 6, 9 & 12

Participants will be further assessed at clinic visits scheduled at 3, 6, 9 and 12 months post dose titration commencing. Assessments will include physical examination, Tanner stage, growth measurements, X-rays (left wrist for bone age and long leg standing AP), laboratory safety assessments, pregnancy testing (potentially child bearing females only), EQ-5D-Y questionnaire, PEDSQL questionnaires, AE recording, drug prescription & medication counselling, recording of concomitant medications and biomarker blood sampling (UK participants only) as detailed in the schedule of events Table 6.

8.8.4 Missed doses

Participants will be provided with guidance regarding the management of their medication and what action to take if doses are missed in the form of the Diary. If a participant misses any doses, up titration decisions will require a participant to have demonstrated at least three consecutive days of 100% patient compliance immediately prior to up titration. If necessary, the treating clinician may instruct participants and their parent(s)/legal guardian(s) to remain at their current dose level for an appropriate amount of extra days before up titrating to the next dose level, if compliance is below this level to ensure compliance is met. Participants and their parent(s)/legal guardian(s) will be instructed to consult the research team for advice before up titrating under these circumstances if side effects/adverse events are experienced during the extra days. Any missed doses or variations in dose will be captured in the Diary and the eCRF.

8.8.5 Dose limiting toxicity (DLT)

For the purposes of this trial, a dose-limiting toxicity will be classed as an AE grade 3 or higher of the following

- anaemia
- haemolytic anaemia
- liver function impairment (increased alanine aminotransferase; increased alkaline phosphatase or increased blood bilirubin)
- kidney function impairment (increased creatinine or chronic kidney disease)

as defined by the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Published: November 27, 2017. See appendix 4 for grading details.

Participants will be monitored for occurrence of DLTs during the Stage 1 trial visits, which are known to be rare at the recognised CBZ dose for treatment of the licensed indications (epilepsy, the paroxysmal pain of trigeminal neuralgia and the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy).

If more than one participant experiences a DLT during the stage 1 dose titration and tolerability, the dose-regimen will be reviewed by the TMG, input from the IDMC will be sought and appropriate modifications made. These events are unlikely, as the trial does not plan to exceed the recognised dose for treatment of licensed indications for CBZ.

8.8.6 Dose finding review

An interim safety analysis will be conducted when at least six patients reach their MTD, which will allow modification of the regimen if required. The review will be led by the CI, Sponsor will be consulted and agreement from the trial IDMC will be sought. The review will be based on laboratory

safety assessments, adverse events and pain questionnaires. Treatment of the remaining stage 1 participants will not be delayed while this review is ongoing.

Once all 11 participants have reached 6 months (or those who are still continuing / not withdrawn), a safety review will be conducted to formally agree the IMP dose regimen to be implemented in Stage 2 of the study. Data to be reviewed includes laboratory safety assessments, adverse events, and pain questionnaires. The review will be led by the CI, Sponsor will be consulted and agreement from the trial IDMC will be sought.

Handling and review of data for both safety reviews will be performed in accordance with the trial Data Management Plan and Statistical Analysis Plan.

Participants who do not tolerate dosing will be kept on a lower dosing or dosing reduced. The inclusion of such patients in the final efficacy analysis will be discussed and evaluated case by case by the TMG with input from the IDMC if required.

Table 10 Timing and Frequency of reviews

Review	Time	Outcomes	IDMC agreement required
Interim safety analysis	First 6 patients reach MTD or 20mg/Kg	Primary outcome **(SAFETY):** Laboratory safety assessments, adverse events, pain scores and physical examinations collected post IMP administration.	Yes
Safety Review	11th patient reaches the 6 month time point (or those who are still continuing / not withdrawn),	Primary outcome **(DOSE):** Outcome of dose-titration safety review at 6 post IMP treatment initiation.	Yes, required to agree dose for Stage 2
Completion of Stage 1 safety analysis and Pain analysis	12 months from Baseline (when last patient recruited has reached 12 month time point) A further safety analysis will be presented to the IDMC on completion of Stage 1	Primary outcome (SAFETY): Laboratory safety assessments, adverse events, pain scores and physical examinations collected post IMP administration. Secondary outcome **(PAIN):** Alteration from baseline in pain perception over 12 months as measured by: • PEDSQL Pain Coping Inventory • PEDSQL Pain Questionnaire	No, to be presented at next IDMC meeting following analysis

8.8.7 Continuation of treatment with CBZ for Stage 1 participants

Assuming Stage 1 participants have achieved their MTD and no significant safety concerns arise from the dose titration 6 month safety review, participants from Stage 1 will continue treatment with CBZ. They will receive the dose approved by the trial IDMC until they have received 24 months of IMP treatment (post initiation of IMP treatment) to allow their data to be included in the Stage 2 final analysis. If a participant has not reached the dose approved by the trial IDMC, they will continue on the maximum dose they were able to tolerate until they have received 24 months of IMP. Stage 1 participants will continue to attend trial visits every three months as indicated in the schedule of events –treatment (Table 7) and the participant visit schedule (Table 4). Eligible Stage 1 participants in the UK, who commenced treatment before 2nd March 2021, will have the option to continue treatment with CBZ for an additional 12 months after they have completed 24 months of IMP treatment. All trial visits must be completed by 31st January 2024.

Assuming the dose regimen is sufficiently similar in stage 1 and 2, stage 1 patients will be included in the analysis at the end of the trial, using the primary endpoint measured at the end of the dose titration phase for stage 1 and at the end of 12 months of treatment for stage 2. If the dose regimen changes between stage 1 and stage 2, we will consult with the IDMC as to whether stage 1 and stage 2 patients should be combined in the final analysis.

8.9 Withdrawal Criteria

Participants have the right to withdraw from the trial at any time without having to give a reason. Investigator sites should try to ascertain the reason for withdrawal and document this reason on the eCRF within the trial MACRO database and in the participant's medical notes.

The Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Participant withdrawal of consent/assent
- Investigator's discretion that it is in the best interest of the participant to withdraw
- An adverse event that requires discontinuation of the trial medication or renders the participant unable to continue in the trial
- If a participant experiences unacceptable toxicity (more than one DLT)

If a trial participant withdraws from the trial all data collected to the point of withdrawal will be retained. Consent/assent will have been sought to allow this.

It should be noted that participants may also be given the option to withdraw from treatment only, but continue with follow-up as per the protocol schedule. This will be explicitly documented in the partcipants medical notes and within the eCRF.

8.10 Premature stopping of the trial

There are no formal stopping guidelines for the trial. However, if more than one participant experiences a DLT during the stage 1 dose titration and tolerability, the dose-regimen will be reviewed by the TMG, approval from the IDMC will be sought and appropriate modifications made. These events are unlikely, as the trial does not plan to exceed the recognised dose for treatment of licensed indications for CBZ.

8.11 Storage and Analysis of Biomarker Samples (UK sites only).

8.11.1 Collection

A maximum of 2ml blood will be taken for exploratory biomarker analysis at times specified in the schedule of events (Tables 5, 6, 7, 8 & 9). Additionally, a maximum of 2ml of blood will also be taken for the measurement of Bone markers (osteocalcine and CTX), if available at site.

Serum will be prepared at both UK clinical centres and will be collected in appropriate tubes to be supplied by the relevant clinical centres.

Serum samples will be shipped to the Newcastle MRC Centre Biobank for Rare and Neuromuscular Diseases based at the Institute of Genetic of Medicine, Newcastle University, on the day of collection if possible; otherwise, they will be stored locally (in a -80°C freezer) and shipped to the Newcastle MRC Biobank as soon as convenient and in accordance with the Trial Laboratory Manual.

For serum sample volumes, aliquoting and processing requirements please consult the trial Laboratory Manual.

8.11.2 Analysis

Proteomics and microRNAseq analysis of serum samples will take place in specialist facilities at Sciomics, Heidelberg and at the Skeletal Research Group, Institute for Genetic Medicine (IGM), Newcastle University respectively.

The Newcastle MRC Centre Biobank for Rare and Neuromuscular Diseases biobank manager or appointed delegate (technician) will be responsible for the appropriate shipping of samples to Sciomics. Serum samples for proteomics analysis will be shipped to Sciomics on dry ice in appropriate batches. Screening will be undertaken using the scioDiscover platform (semi-targeted affinity proteomics platform) to identify biomarker candidates during the course of the trial. Following an initial discovery phase (using cell and mouse model samples), serum samples will be collected from UK patients undergoing CBZ treatment in both Stage 1 and Stage 2. Patient samples will be profiled on custom microarrays containing selected proteins identified from the mouse and cell line analysis.

Serum samples destined for microRNAseq analysis at IGM will be collected from the biobank in person by an approved researcher. The Newcastle MRC Centre Biobank for Rare and Neuromuscular Diseases will also provide control samples for the microRNAseq analysis.

MicroRNA analysis (IGM Newcastle) will be performed on the HTG EdgeSeq microRNA Whole Transcriptome Assay system which measures the expression of 2,083 individual human microRNA transcripts in serum with minimal processing time by high-throughput sequencing. The novel technology employed avoids much of the bias in data generation to which other small RNA-seq methods are prone. Simply following sequencing DESeq2 is used for library size normalisation and differential expression analysis.

8.11.3 Storage

Serum samples will be sent for storage as soon after collection as possible within the Newcastle MRC Centre Biobank for Rare and Neuromuscular Diseases based at the Institute of Genetic of Medicine, Newcastle University.

Any samples remaining once the trial biomarker analysis has taken place will be banked for use in future bone disease or ER stress biomarker research, if the patient or their parent(s)/legal guardian(s) has consented to this.

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with trial procedures to comply with the applicable legislation (e.g. General Data Protection Regulation (GDPR)). Labelling requirements can be found in the trial Laboratory Manual. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and 2006 Human Tissue (Scotland) Act.

8.12 End of Trial

The end of trial will be defined as the date of last data collection for the last participant. As of protocol v9.0, all sites are requested to complete data collection by 31st January 2024. Some participant visits may need to be brought forward.

8.13 COVID-19

Additional site lockdowns

If additional local lockdowns occur during the trial, there are several changes that can be implemented (if required) to try and ensure participant safety and compliance with the trial protocol:

Study visits

It is expected that participant visits will take place as per protocol schedule. However, if a face to face visit is not taking place due to COVID-19 restrictions or lockdowns, the PI[a] will contact the patient at the time of the original scheduled visit (3 monthly), and carry out feasible assessments (i.e. SAE check, concomitant medication check, dose evaluation, medication counselling, remote completion of questionnaires and arrange laboratory safety assessments). Follow up calls will take place as per protocol for weeks 1-11.

Participant weight/dose calculation

To ensure participants and families spend the least amount of time in hospital, participants will not be required to have their weight taken at each of the dose titration visits. Participant weight will be mandatory every 6 months and this weight used to calculate the dosage for the next 6 months of study IMP.

Study medication

If required and where possible study medication will be prescribed in 6 month intervals. This will ensure that less time is required for the study visits. It will also be discussed with sites whether the study IMP can be couriered/posted to participants via recorded delivery.

Laboratory Safety Assessments

Participant safety bloods will still be required at the 3 monthly intervals. Sites can discuss whether these safety bloods can be taken by the participant's GP or local paediatrician, but only where these results are readily available to the study team. If sites wish to utilise local GPs/ local paediatricians for safety bloods, they must notify the central team in advance, where possible, so the appropriate set up processes can be completed.

Under extenuating circumstance, If safety bloods cannot be completed, it will be considered if it is appropriate for the participant to be withdrawn from IMP. Each case will be reviewed on an individual basis by the CI, Sponsor and the TMG, and it will be decided whether it would be appropriate to restart the participants IMP, once safety bloods become feasible. The IDMC may also be consulted.

COVID-19 Isolation
It is expected that participant visits will take place as per protocol schedule. However, if a participant or someone they live with has symptoms or has tested positive for COVID-19 and is required to self-isolate, the study visit window can be extended by 2 weeks.

9 TRIAL MEDICATION

9.1 Name and Description of IMP

For the purposes of this trial Tegretol® 100mg, 200mg and 400mg Immediate release tablets and Tegretol® 100mg/5ml liquid will be classed as IMP.

Tegretol® is a brand of carbamazepine licensed for use in the UK and in the countries of all participant sites for this trial. Tegretol®, rather than generic brands, will be used for consistency across all trial sites during both Stage 1 and Stage 2 of the trial. The use of of generic and controlled release formulations are not permitted for use in this trial. Non-UK sites should source the appropriate strengths available to them to accommodate the prescribed dose.

Tegretol® is currently licensed for the treatment of epilepsy, neuropathic pain and prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy.

Where possible, sites are to use sugar free formulations of the IMP.

UK Marketing Authorisation Holder for Tegretol®: - Novartis Pharmaceuticals UK Limited, Trading as Geigy Pharmaceuticals, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR England.

9.1.1 Reference Safety Information

Section 4.8 of the approved SmPCs (PI[b] for Australia) for Tegretol® 100mg, 200mg and 400mg tablets and Tegretol® 100mg/5ml liquid will be used as RSI for this trial. The manufacturer may update the SmPCs (PI[b] for Australia) for this IMP. The NCTU/Sponsor/CI will monitor and review changes to the SmPC (PI[b] for Australia) to consider the impact on the trial and will revise documentation if required.

Serious Adverse Reactions (SARs) that are thought to have a causal relationship to Tegretol® must be assessed for expectedness against the RSI outlined above only.

In the event of a SAR, which is thought to have occurred due to a reaction with the IMP, please also ensure to check section 4.5 'interaction with other medicinal products and other forms of interaction', of the SmPCs (PI[b] for Australia) for Tegretol® detailed above.

9.2 Drug Storage and Supply

All IMP will be stored as per SmPCs (PI[b] for Australia). Once dispensed, participants shall refer to the storage requirements specified on the product label and/or the Patient Information Leaflet provided.

Participating sites will source IMP as per their own local arrangements. Please refer to the current version of the MCDS-Therapy Pharmacy Manual/IMP Guidance document for further details.

9.3 Preparation and Labelling of IMP

Trial IMP will be taken from existing hospital stock and labelled for the trial in accordance with Annex 13 (EU labelling requirements). Participating sites must ensure that the labelling of the IMP is Annex 13 compliant or equivalent depending on country specific regulations. Please consult the MCDS-Therapy Pharmacy Manual/IMP Guidance document for further details.

9.4 Dosage Schedule & Modifications

Tegretol® 100mg, 200mg and 400mg tablets (immediate release) - Tegretol® is to be given orally, with the dose to be used during Stage 2 (treatment) confirmed during Stage 1 (dose titration & tolerability). Anticipated dosage is expected to be between 5-20mg/kg bodyweight daily, to be administered in two divided doses. Tegretol® may be taken during, after or between meals, with a little liquid e.g. a glass of water.

Tegretol® 100mg/5ml liquid (oral suspension) - Tegretol® liquid is to be given orally, with the dose to be used during Stage 2 (treatment) confirmed during Stage 1 (dose titration & tolerability). Anticipated dosage is expected to be between 5-20mg/kg bodyweight daily, to be administered in two divided doses. Tegretol® liquid should be shaken before use and may be taken during, after or between meals.

For stage 1 participants, dosing will be in accordance with the dose titration regimen outlined in section 8.8. CBZ dose to be used in Stage 2 treatment stage will be confirmed during Stage 1 (dose titration & tolerability) see section 8.8.

Participants and their parent(s)/legal guardian(s) will be able to discuss their preference regarding choice of tablet or liquid preparation with their clinician, choice will likely be influenced by participant age. The chosen preparation will be noted on the eCRF trial MACRO database. Stage 2 participants will receive Tegretol® for a 12 month period; with the last study visit occurring no later than 31st January 2024. Dosage will be calculated according to the participant's weight. As the trial is recruiting paediatric participants, participants will be weighed every 3 months during Stage 1 and Stage 2 as part of the physical examination and dose adjusted accordingly to ensure the appropriate dose is given to the participants as they grow. For Stage 2 participants CBZ will be titrated as indicated by the outcome of Stage 1.

For advice to be given regarding missed doses please see section 8.8.4.

9.5 Known Drug Reactions and Interactions

All relevant information relating to drug interactions can be found in section 4.5 of the Tegretol® SmPC (PI[b] for Australia).

Tegretol® may lower the plasma level, diminish or even abolish the activity of certain drugs. A list of drugs whose plasma levels may be affected by Tegretol® can be found in section 4.5 of the SmPC (PI[b] for Australia) for Tegretol®. Of particular note, Tegretol® may lower the plasma level, diminish or even abolish the activity of hormonal contraceptives. Therefore, alternative contraceptive methods should be considered.

9.5.1 Special warnings associated with Tegretol® use

Special warnings associated with Tegretol® use are described in section 4.4 of the Tegretol® SmPC (PI[b] for Australia). Participants and their parent(s)/legal guardian(s) will receive the Tegretol® Patient Information Leaflet outlining the IMP side effects as part of their medication counselling.

9.6 Concomitant Medications

A complete listing of all concomitant medication received during the trial, from Day 0 baseline observation through to last day IMP taken. will be recorded in the eCRF within the trial MACRO database, the Baseline, Dose Titration or Stable Dose Diary and the participant notes.

9.7 Assessment of Compliance

Participants will be taking trial IMP for up to 24 months (Stage 1: 24 months; Stage 2: 12 months). Eligible Stage 1 participants will also be offered an additional, optional, 12 months of treatment with CBZ after they complete 24 months of treatment. The last patient last visit must take place no later than 31st January 2024. Compliance regarding IMP will be checked weekly via telephone calls during the dose titration period (for up to 12 weeks) and at participant visits held every three months during the dose titration and treatment periods. IMP compliance will be recorded on the eCRF, within the trial MACRO database.

Participants will return all unused IMP and all IMP packaging to their trial team at site at every trial visit. The returned IMP and packaging will be held in the Pharmacy Department at site. Pharmacy will count and record all returns received from each participant on the trial accountability log. An accountability check will also be performed as part of on-site monitoring visits and during dose evaluation calls during the dose titration & tolerability stage.

9.8 Vitamin D

Vitamin D levels will be measured every three months during the dose titration and treatment period as specified in the schedule of events (Tables 6,7 & 9). In the event a participant displays signs of vitamin D insufficiency or deficiency, the participant will be prescribed vitamin D as required. Vitamin D dosing and treatment duration will be appropriate to the need of the patient, follow local guidance for vitamin D insufficiency and deficiency and will be in line with the Fultium SmPC (PI[b] for Australia). Only participants identified as having vitamin D deficiency or insufficiency will be prescribed vitamin D. Vitamin D will be sourced from existing hospital stock and stored as per SmPC (PI[b] for Australia). Participants and/or their parent(s)/legal guardian(s) will be able to discuss their preference regarding choice of capsules or drops with their clinician, choice will likely be influenced by participant age. The chosen preparation will be noted on the eCRF trial MACRO database.

The preferred brand/formulation for the trial is Fultium D3 800 IU capsules and Fultium D3 drops, However, sites can use suitable alternatives according to local policies and guidelines.

10 PHARMACOVIGILANCE

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward or unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

	The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions
Reference Safety Information (RSI)	The RSI is a list of medical terms detailing the ARs that are expected for an IMP and must be referred to when assessing a SAR for expectedness.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences * - life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the trial treatments, based upon the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the approved Reference Safety Information.

10.2 Recording and Reporting AEs and SAEs in the UK

AEs will be graded according to the CTCAE (Common Terminology Criteria for Adverse Events). The grading must be documented in the patient's medical notes.

Please see diagram in Appendix 1 Safety Reporting Diagrams for further guidance.

All AEs occurring from the point of consent to the end of trial participation must be recorded in the trial MACRO database eCRF as well as in the participant's medical notes.

All SAEs occurring from the point of consent to the end of trial participation must be reported to NCTU on the MCDS-Therapy SAE form via secure e-mail to nctu.mcds-therapy.sae@nhs.net or via secure transfer methods and also recorded on the trial MACRO database eCRF.

All SARs occurring from the first participant's dose of IMP to the last participant's end of follow-up must be reported to NCTU on the MCDS-Therapy SAE form and also recorded on the trial MACRO database eCRF.

Following this defined active monitoring period for SARs, investigators are still required to report any SARs or SUSARs they become aware of.

All UK SAEs/SARs must be reported to NCTU using the MCDS-Therapy SAE Form via secure e-mail to nctu.mcds-therapy.sae@nhs.net or via secure transfer methods within 24 hours of research staff becoming aware of the event. This will ensure that all the relevant individuals (CI, NCTU trial management and QA management staff and UK Sponsor) are informed of the event in a timely manner.

Preliminary reporting to NCTU via email or telephone is acceptable in order to meet the 24-hour reporting timeline, where circumstances do not allow for immediate completion of the SAE form. However, the SAE form should be completed and submitted as soon as possible after the initial notification in order to comply with reporting timelines.

For each SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator
- Whether the event is considered expected or unexpected in accordance with the approved RSI if a causal relationship is suspected

Any change of condition or other follow-up information should be submitted to the NCTU via secure e-mail to nctu.mcds-therapy.sae@nhs.net or via secure transfer methods as soon as it is available or at the latest within 24 hours of the information becoming available. Events will be followed up until the event is resolved or a final outcome has been reached.

10.3 Recording and Reporting SUSARs

All UK SUSARs occurring from first administration of IMP until the end of the trial must be reported to NCTU as soon as the research site become aware. NCTU will inform the trial UK Sponsor of all SUSARs within 24 hours of becoming aware of the event to ensure timely reporting to the MHRA and REC can be conducted. In the UK, the UK trial Sponsor is responsible for reporting SUSARs to the MHRA and REC.

For international sites the country specific Sponsors will be responsible for reporting SUSARs to their relevant competent authorities and ethics review organisations within each participating country, as per local requirements.

The assessment of expectedness will be performed by the trial CI with input from country specific Sponsor and the site PI[a] against the approved Reference Safety Information (RSI) for the trial. The RSI is contained within section 4.8 of the SmPC (PI[b] for Australia) for each of the Tegretol® 100mg, 200mg and 400mg tablets and Tegretol® 100mg/5ml liquid.

Fatal and life-threatening SUSARS in the UK must be reported to the MHRA no later than 7 calendar days after the UK Sponsor has first knowledge of the event. Any relevant follow-up information must be sought and reported within a further 8 calendar days.

Non-fatal SUSARs in the UK must be reported to the MHRA no later than 15 calendar days after the UK Sponsor has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report. For international sites the country specific Sponsor will also ensure that safety reporting timelines for competent authorities of participating countries outside of the UK will be adhered to following local requirements.

For UK SUSARs, as soon as a site suspects that a SAR may be a SUSAR they must contact the CI, sponsor representative and the trial manager immediately. Information should be submitted to the NCTU via secure e-mail to nctu.mcds-therapy.sae@nhs.net or via secure transfer methods (see Appendix 1 for details). The reporting timeframe starts at day 0 when the Sponsor is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)
- EudraCT number
- Patient trial number and date of birth
- Name of IMP(s)
- Date of notification of the event
- Medical description of the event
- Date and time of the onset of the event (including event end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g., Principal Investigator)

This information must be provided on the MCDS-Therapy SAE Form. The UK site is expected to fully cooperate with the NCTU and UK Sponsor in order that a full and detailed report can be submitted to the MHRA and REC within the required timelines. For international sites, the country specific Sponsor will also ensure that safety reporting submissions to competent authorities of participating countries outside of the UK will be adhered to following local requirements.

The Trial Manager will ensure all trial PI[a]s will be informed of any SUSARs that occur in relation to the trial IMP.

10.4 Responsibilities

10.4.1 Principal Investigator

- Checking for AEs and ARs when participants attend for treatment or follow-up
- Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness of events using the Reference Safety Information approved for the trial
- Ensuring that all SAEs and SARs, including SUSARs, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol
- Ensuring all AEs are recorded in the eCRF within the trial MACRO database

10.4.2 Chief Investigator

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment
- Using medical judgement in assigning expectedness to SARs in line with the RSI
- Immediate review of all SUSARs
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol
- Review/assignment of Medical Dictionary for Regulatory Activities (MedDRA) or body system coding for all SAEs and SARs

- Preparing the clinical sections and final sign off of the DSUR
- Reviewing RSI at least annually and the notification of PI[a]s of any required updates (may be delegated to NCTU)

10.4.3 UK Sponsor

- Data collection and verification of AEs, ARs, SAEs, SARs and SUSARs onto a database (may be delegated to NCTU)
- Reporting safety information to the independent oversight committees for the ongoing assessment of the risk/benefit ratio throughout the life of the trial (may be delegated to NCTU)
- Assessment of expectedness of any SUSARs (may be delegated to the CI)
- Expedited reporting of SUSARs to the relevant CA and REC within required timelines
- Notification of all investigator sites of any SUSAR that occurs (may be delegated to NCTU)
- Reviewing RSI at least annually and the notification of PI[a]s of any required updates (may be delegated to NCTU and CI)
- Preparing tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to all appropriate CAs (including MHRA) and RECs, as required (may be delegated to NCTU)

NB:Sponsors of the International sites may delegate specific responsibilities e.g. Data management to Newcastle University as outlined in the relevant delegation agreements or equivalent

10.4.4 Trial Steering Committee (TSC)

A TSC will be convened. The TSC will consist of up to 5 independent members including as a minimum an independent chairperson, an independent clinician, an independent patient representative and the Chief Investigator. In addition, representatives of the Trial Management Group, country specific Sponsors and Funder will be invited to attend or dial in via teleconference as needed but will not be voting members. Membership, responsibilities and quoracy requirements will be defined in the MCDS-Therapy TSC Charter, which will be reviewed at the first TSC meeting. At the first meeting, the TSC will also decide on the frequency of meetings, this is anticipated to be every 6-12 months throughout the trial. The role of the TSC will be to monitor progress and supervise the trial to ensure it is conducted to high standards in accordance with the protocol, the principles of GCP, relevant regulations and guidelines. The TSC will advise on whether to continue or discontinue the trial and make a recommendation to Sponsors and Funder. If the trial is prematurely discontinued, participants will be informed, and no further trial data will be collected. The TSC will be overarching and will review conduct at each individually sponsored site.

10.4.5 Independent Data Monitoring Committee (IDMC)

An IDMC will be convened. The purpose of this committee will be to independently monitor safety and data and will consist of at least three independent members including one independent clinician and an independent statistician. At the first meeting, the IDMC will agree on its charter of operation, how many times the IDMC should meet over the course of the trial, and possible adoption of formal stopping rules for safety. Membership, responsibilities and quoracy requirements will be defined in the MCDS-Therapy IDMC Charter. The IDMC will be overarching and will monitor safety and data for each individually sponsored site.

10.4.6 Trial Management Group

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the day-to-day progress of the trial. The day-to-day management of the trial within the UK will be co-ordinated by Newcastle Clinical Trials Unit (NCTU). The NCTU may also be delegated specific tasks from the international site Sponsors. The Trial Management Group will include the CI, Senior Trial Manager,

Trial Manager(s), Statistician, UK Sponsor Representative, Data Manager, Project Manager, Co-Investigator(s) and Pharmacist, as appropriate.

Quality control will be maintained through adherence to NCTU and UK Sponsor Standard Operating Procedures (SOPs) where applicable, the trial protocol, the principles of GCP, research governance framework and applicable clinical trial regulations.

In the UK, the following functions falling under the responsibility of the UK Sponsor will be delegated to the Chief Investigator and supported by NCTU:

- Reporting and notification to Medicines and Healthcare products Regulatory Agency (including obtaining clinical trial authorisation, notification of protocol amendments, submission of Development Safety Update Report (DSUR), notification of end of trial and submission of final trial report)
- Ethics Committee Opinion (including application for research ethics committee favourable opinion, notification of protocol amendments and end of trial, site specific assessment & local approval)
- HRA and Health and Care Research Wales (HCRW) Approval
- Adherence to Good Clinical Practice and Trial Conduct (including Good Clinical Practice (GCP) arrangements, data monitoring, emergency & safety procedures)

10.5 Notification of Deaths

All deaths will be reported as SAEs irrespective of the cause of death and reported to the Sponsor (NCTU should be notified) (see section 10.2).

10.6 Pregnancy Reporting

As the trial IMP CBZ (Tegretol®) is a known teratogen, the drug poses a significant risk to the foetus. The participants and their parent(s)/legal guardian(s) will be informed of the risks prior to taking part in the trial and will provide consent/assent to regular pregnancy testing and agreement to use contraception throughout the trial and for a period of 28 days after discontinuation of treatment (see section 8.3).

In the event of a UK trial participant becoming pregnant whilst receiving IMP, the participant must cease treatment immediately. The trial site must notify NCTU, the Chief Investigator and the UK Sponsor representative within 24 hours of becoming aware of the pregnancy.

10.6.1 Procedure for notification of pregnancy

The UK trial participant (if pregnant) or parent(s)/legal guardian(s) will need to sign a consent/assent form allowing the trial team to follow the pregnancy. The site will need to submit a completed pregnancy notification form to NCTU via secure e-mail to nctu.mcds-therapy.sae@nhs.net or using appropriate secure transfer methods.

10.6.2 Procedure for following pregnancy:

The pregnancy should be followed until completion (i.e. termination, miscarriage, stillbirth or live birth). This will comprise of regular telephone calls to the participant and documentation of the outcome of the pregnancy and any adverse events in the ISF and patient medical notes.

If the pregnancy results in a live birth, then the child will need to be followed up for 12 months to ensure there is no congenital abnormality. If a congenital abnormality is detected for either a live or stillbirth child, then this will need to be reported as an SAE (see section 10.2)

10.7 Overdose

Overdoses may be identified during trial calls or visits or by notification by the participant's GP. Overdoses will be recorded in the eCRF within the trial MACRO database and notified to the Sponsor following the NCTU deviation and violation SOP. If an SAE is associated with the overdose, trial sites must ensure that the overdose is reported in the appropriate manner (see section 10.2).

For signs and symptoms of CBZ (Tegretol®) overdose consult section 4.9 of the Tegretol® SmPC (PI[b] for Australia). Management of a Tegretol® overdose will be as per current Tegretol® SmPC (PI[b] for Australia) and guided by the patient's clinical condition.

10.8 Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. For UK sites, upon implementation of an USM by an investigator, the NCTU must be notified immediately (and within 24 hours of becoming aware) and details of the USM given. In the UK, the CI and NCTU must inform the MHRA and the REC in accordance with the Sponsor's standard operating procedures. All relevant competent authorities and ethics review organisations within participating sites outside of the UK will need to be informed of all relevant USMs, as per local procedures.Responsibility for this action will lie with the country specific Sponsor.

10.9 Development Safety Update Reports

In the UK, a Development Safety Update Report (DSUR) will be submitted to the MHRA and REC once a year on the anniversary of the Development International Birth Date (DIBD). The Trial Manager must ensure that the report is submitted within 60 days of the end of the reporting period. The Trial Management Group must contribute to the compilation of the DSUR and the CI must review and authorise the final report before it is ready for submission. The DSUR should also be reviewed by the NCTU QA Manager and UK sponsor Representative prior to submission via the Common European Submission Portal (CESP) system. NCTU staff will prepare and submit Development Safety Update Reports (DSURs) for the trial in the UK, in accordance with NCTU SOPs.

Country specific Sponsors will be responsible for submission of relevant safety reports equivalent to the DSUR for all non-UK competent authorities, e as per local reporting procedures..

11 STATISTICAL CONSIDERATIONS

11.1 Analysis Population

There will be two analysis populations:

- Patients who have completed the baseline observation period and have received at least one dose of CBZ
- Patients who have completed the baseline observation period and have received at least 75% of planned CBZ doses over the 12 -month treatment period

11.2 Statistical Analyses

11.2.1 Analysis of the Primary Outcome Measure

Two full statistical analysis plans (SAP) will be developed describing the Stage 1 (dose titration & tolerability) and Stage 2 (treatment) analysis. The Stage 1 SAP will be agreed prior to the IDMC

reviewing safety data from the first six patients. The Stage 2 SAP will be agreed prior to the final analysis. The growth velocity endpoint will be analysed using a suitable linear regression using actual height observed during treatment period and predicted height from the baseline period.

11.2.2 Analysis of Secondary Outcome Measures

The SAP will provide full details of the analysis of clinical secondary outcomes.

Responses to the EQ-5D-Y descriptive components will be reported in tabular form and responses will be converted into health state utilities using the recommended scoring algorithm available at the time of trial analysis for the UK. Currently, this is the scoring system for the UK general population. Changes in health related quality of life, based on responses to the EQ-5D-Y, will be compared across time points.

Responses to the PEDSQOL will be converted into scores using the recommended method. Scores will be reported for the Psychosocial Health and Physical Health sub-domains as well as the total score.

Use of surgical interventions to manage the condition will be captured on the eCRF over the whole follow up period. These will be reported descriptively as the type and proportion of participants experiencing an event per three month period from baseline until the end of trial follow up.

11.2.3 Interim Analyses and Criteria for the Premature Termination of the Trial

An interim safety analysis will be conducted after the first six patients in Stage 1 have reached their maximum tolerated dose or 20mg/kg. Data presented to the IDMC for review will include the number and reason for any DLTs, all laboratory safety assessments, pain scores and all adverse events. The IDMC will recommend or oppose continuation of the trial to the TSC.

A further, similar, safety analysis will be presented to the IDMC on completion of Stage 1. There are no formal stopping rules.

11.3 Statistical Sample Size Calculations

The sample size was chosen on the basis of the feasible number of patients that could be recruited to the trial in the specified time period. No statistical criteria were used to choose the sample size. The relative size of stage 1 and stage 2 were also based on feasibility, as stage 1 is recruiting from the UK only and stage 2 will be recruiting from the UK, European and Australian sites.

12 HEALTH ECONOMICS

This clinical trial is part of a multi work package research project. As part of the overall research project, an economic evaluation decision modelling exercise will be conducted. The precise form of model is being developed in parallel with the trial and is likely to take the form of a Markov-type state transition model, or should data allow, an individual patient (micro) simulation. The model will address the questions: “Is introducing carbamazepine cost-effective compared to surgical and pain management alone for the treatment of MCDS?” and, “What is the net budget impact of adopting carbamazepine for the management of MCDS?” The precise structure of the model will be developed during the project and will reflect the clinical decision question and the course of the condition. Data for this analysis will come from multiple sources including the literature, other extant cohorts and a cohort preference elicitation exercise that also runs concurrently with the trial. One source of data will be the analysis of quality of life questionnaires (EQ-5Q-Y scores) and use of health services completed by participants taking part in the trial and described in the statistical analysis section 11.

A separate health economics analysis plan will be drawn up for this modelling exercise, describing how the work will be conducted, where data used in the modelling will come from and how it will be

analysed. The PIS for this clinical trial will include information regarding the qualitative sub-study and the following link https://mcds-therapy.eu/get-involved/. This will allow participants or parent(s)/legal guardian(s) who are interested in getting involved a means of contacting the health economics research team.

13 DATA HANDLING

13.1 Data Collection Tools and Source Document Identification

All the data required will be recorded in patient clinical notes as part of routine clinical procedures. Data for individual patients will be transferred by each PI[a] or his/her delegated nominee to the eCRF on the trial database MACRO as soon as possible following each procedure. MACRO is a secure, online, validated clinical data management system. Patient identification on the eCRF will be via a unique trial identification number assigned to the patient at site once the patient has consented. A record linking the patient's name to the unique trial identification number will be held only in a locked room at the trial site and is the responsibility of the PI[a]. As such, patients cannot be identified from eCRFs. The CI, or nominated designee, will continually monitor completeness and quality of data recording in eCRFs and will correspond regularly with site PI[a]s (or their delegated assistants) to capture any missing data where possible, and ensure continuous high-quality data.

13.2 Data Handling and Record Keeping

Overall responsibility for data collection lies with the Chief Investigator. Data will be handled, computerised and stored in accordance with General Data Protection Regulations, 2018 and any relevant regulations for those sites residing outside of the European Union. Paper copies of trial-related documentation will be annotated, signed, dated and filed in the medical notes. The overall quality and retention of trial data is the responsibility of the Chief Investigator. All trial data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

The CDMS (Elsevier's MACRO) used for this trial is fully compliant with all regulatory frameworks for research of this nature. It uses a secure web-based interface for data entry; no research data is stored on computers at site. MACRO users are assigned role based permissions specific to their site and role. The system has an inbuilt back-up facility, through Elsevier's hosting partner (Rackspace)'s secure premises in London, and is managed and supported by the Rackspace team.

Business continuity and disaster recovery measures include; adequate inventories for hardware failure replacement; backup generators and electrical controls; periodic restoration and contingency testing of system dependencies; daily backups of all application and system data; full weekly backups of all application and system data; encrypted backups stored in secure offsite backup facilities which are connected by an independent private network to pass data to the Managed Backup infrastructure.

The trial specific Data Management Plan will include details of how the validity and quality of data will be monitored and managed. As far as possible, validations will be built into the trial specific database in MACRO and additional manual validations will be detailed in the Data Validation Plan.

13.3 Access to Data

Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, the Independent Data Monitoring Committee (IDMC) or the REC. Secure, anonymised, electronic data will be released to the Trial Statistician and Health Economist for analysis. The PI[a] and trial site staff may not disclose or use for any purpose other than performance of the trial, any data, record, or other

unpublished, confidential information to which they have access, in order to carry out the trial. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

Each person using MACRO will be issued with their own personal login credentials, which give them specific role based permissions. These typically include data entry permissions, read only permissions and monitor permissions and are limited to a site or sites as required. The PI[a] and nominated designees at each site will have full data entry access to trial data on the trial specific MACRO database for their site only. The NCTU team will have access to all the sites' data for data monitoring, data validity checks and raising data queries. At the end of the trial, following data lock and the production of the final report, each site will be provided with a copy of their data.

13.4 Archiving

UK Data will be archived in accordance with the NCTU Archiving SOP, European Commission Directive 2005/28/EC Article 17.. Essential data will be retained for a period of at least 25 years following close of trial in line with sponsor policy and the latest Directive on GCP (2005/28/EC). Archiving will be authorised by the UK Sponsor following submission of the end of trial report.

NCTU does not have its own archiving facility, therefore the archiving facility designated by the UK Sponsor will be used for storage of the UK Trial Master File (TMF), which contains the essential documents that individually and collectively permit the evaluation of the UK data produced.

Electronic data from the trial database will be provided for the Sponsors TMFs and to sites on read only, encrypted Compact Discs (CDs)/Digital Versatile Discs (DVDs).

Each International trial site will be responsible for archiving their trial Investigator Site File (ISF)/TMF according to their country specific Sponsor policy or equivalent archiving regulations

Authorisation will be requested from the UK Sponsor to destroy the UK documentation at the end of the UK defined archiving period.

14 MONITORING, AUDIT & INSPECTION

An MCDS-Therapy trial monitoring plan will be developed, based upon the trial risk assessment, and agreed by the Trial Management Group, NCTU QA representative and the UK Sponsor.

All UK monitoring activity will be detailed in the UK MCDS-Therapy monitoring plan. Monitoring of trial conduct and collected data will be performed by a combination of central review and off- and on-site monitoring visits to ensure the trial is conducted in accordance with GCP and appropriate regulations. UK trial site monitoring will be undertaken by NCTU Trial personnel.

For International sites monitoring responsibility will sit with the country specific Sponsor and conducted according to local regulations and policies. Sponsors will have access to the UK MCDS-Therapy monitoring plan to ensure across-trial consistency.

All UK monitoring findings will be reported and followed up with the appropriate personnel in a timely manner. UK Sites will be expected to assist the UK Sponsor in monitoring the trial e.g. hosting monitoring visits, providing information for on and off-site monitoring and responding to monitoring findings within the timeframes requested, wherever possible.

The trial may be subject to audit by representatives of the Sponsor or inspection by relevant competent authorities or the European Medicines Agency (EMA). Each investigator site will be required to permit trial-related monitoring, audits and regulatory inspection including access to all essential and source data relating to the trial.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Research Ethics Committee Review and Reports

In the UK, NCTU will obtain a favourable ethical opinion from an NRES Committee (REC) prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

The NCTU will notify the UK REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation (e.g. protocol or Participant Information Sheet). Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. The NCTU will notify the REC of any UK USMs that occur during the trial, notify the UK Sponsor and copy them into all correspondence. The UK Sponsor will notify the REC of any serious breaches of GCP or the protocol, or SUSARs that occur during the trial in the UK.

For non-UK sites, favourable ethical opinion will be sought from the relevant ethical review organisations by the local sponsor/trial site as per local requirements prior to the trial being initiated within each country. Similarly, submission and approval of substantial amendments in non-UK sites will be managed locally by the local sponsor/trial site as per local requirements. Sponsors will be expected to notify all ethics review boards within participating countries of any serious breaches/SUSARs as per local requirements.

An annual progress report will be submitted each year to the REC by NCTU until the end of the trial in the UK. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted. Reporting requirements for all non-UK ethics review boards will also be fulfilled by local sponsors as per local requirements.

The NCTU will notify the UK REC of the early termination or end of trial in accordance with the required timelines. Reporting requirements for all non-UK ethics review boards will also be fulfilled by local sponsors as per local requirements.

15.2 Peer Review

All relevant preclinical data was assessed by the EMA for Orphan Drug Designation and carbamazepine received orphan drug designation by the European Commission for the treatment of MCDS in September 2016 (EMA/OD/148/16 and EMA/COMP/513538/2016).

The trial is funded by European Commission Horizon 2020 and as part of the funding award has been subject to the funding peer review process. Post award, the trial was reviewed by the EMA protocol assistance panel.

The UK trial protocol has been reviewed and authorised by the UK Sponsor, Chief Investigator, Trial Statistician and NCTU Director.

15.3 Public and Patient Involvement

The rare disease charity Findacure is a co-applicant for the MCDS-Therapy trial. They are leading communication and outreach for the project and are working on patient engagement. Findacure have developed and are hosting the MCDS-Therapy website.

During the protocol development phase, Findacure assisted the production of patient information documents. They secured design assistance to develop the visual layout for these documents, making them more appealing and interesting for the trial's target paediatric population.

Findacure will work with clinicians within the team, as well as patient groups working in rare bone conditions, to connect with patients and their families. They will use these connections to better understand perceptions of research and obtain input into an ongoing communications, disseminations and engagement plan. The connections will also be invited to form an active Patient Advisory Committee (PAC) for the project. Findacure will work with this committee to provide ongoing guidance on patient-facing materials, the website, and approach to social media.

Findacure also hopes to work with patient groups to share recruitment materials and research updates, helping us to reach a wider audience.

Patient and parent(s)/legal guardian(s) of patient representatives have been consulted for development of trial related documentation. A patient representative will be invited to sit on the trial steering committee to ensure that the views of patients are represented as the study progresses.

15.4 Regulatory Compliance

The trial will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. All parties must abide by these regulations and the ICH GCP guidelines.

In the UK, the NCTU will obtain a Clinical Trial Authorisation (CTA) from the MHRA prior to the start of the trial and will notify the MHRA of any substantial amendments that require review by the competent authority. These substantial amendments will not be implemented until the MHRA have issued an acceptance of the amendment. For all non-UK competent authorities of participating countries, a CTA equivalent will be sought by the local sponsor/trial site within each participating country as per local requirements. Similarly, submission and approval of substantial amendments in non-UK sites will be managed locally by the local sponsor/trial site as per local requirements.

The UK Sponsor will notify the MHRA where required of any serious breaches of GCP or the protocol or SUSARs that occur during the trial in the UK.

The NCTU will notify the MHRA and all international site country specific Sponsors of any urgent safety measures that occur during the trial. It will be the responsibility of the country specific Sponsors to inform non-UK competent authorities of participating countries where required.

The Development Safety Update Report will be submitted each year to the MHRA by the NCTU until the end of the trial in the UK. Submission of relevant safety reports equivalent to the DSUR for all non-UK competent authorities will be the responsibility of the country specific Sponsors for each international siteas appropriate.

In the UK, the NCTU will notify the MHRA of the early termination or end of trial in accordance with the required timelines. Notification for all non-UK competent authorities will be the responsibility of the country specific Sponsors for each international site as appropriate.

Trial procedures are compliant with the Ionising Radiation (Medical Exposure) Regulations and appropriate review by a Medical Physics Expert and Clinical Radiation Expert will be undertaken.

15.5 Protocol Compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used. Unintentional protocol deviations will be documented and reported to the UK Sponsor in accordance with NCTU SOPs. Deviations that are found to frequently recur at a UK site are not acceptable and could be classified as a serious breach.

15.6 Notification of Serious Breaches to GCP and/or the Protocol

A serious breach is a breach which is likely to affect to a significant degree –

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial

The UK Sponsor must be notified immediately of any incident that may be classified as a serious breach. For UK serious breaches the UK Sponsor will notify the relevant ethics review organisation and/or competent authority as appropriate, within the required timelines in accordance with UK Sponsor and NCTU SOPs.

15.7 Data Protection and Patient Confidentiality

All investigators and trial site staff must comply with the requirements of the applicable legislation (e.g. GDPR) with regards to the collection, storage, processing and disclosure of personal information and will uphold the core principles of the legislation.

In line with the General Data Protection Regulations 2018 (GDPR) explicit consent/assent must be obtained via the informed consent form from each trial participant/parent/legal/guardian to allow data sharing to occur.

Personal data will be regarded as strictly confidential. All trial files will be securely stored, and access restricted to staff involved in the study. Research staff at sites will enter data in paper form onto a secure web-based electronic MACRO database, run and maintained by Newcastle University. Data will be entered using participant unique trial numbers. Access to this database will be password protected and limited to staff at research sites or Newcastle University who are involved in the study.

To preserve anonymity, any data leaving the sites will identify participants by their initials, sex, date of birth and a unique trial identification code only.

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the applicable legislation (e.g. General Data Protection Regulations (GDPR).

Essential data will be retained for a period of at least 25 years following close of trial in line with sponsor policy. The CI will be the data custodian.

15.8 Indemnity

The UK sponsor will provide indemnity in the event that UK trial participants suffer negligent harm due to the management of the trial in the UK. For UK sites, this indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS. For the sites outside of the UK, local Sponsors will be expected to seek appropriate insurance to meet the legal and/or regulatory

requirements of each country involved. This will be expected to be in place before any research activity is undertaken at any of the sites.

In the UK, the substantive employers of the protocol authors will provide indemnity in the event that UK trial participants suffer negligent harm due to the design of the trial.

The trial sites will provide indemnity in the event that trial participants suffer negligent harm due to the conduct of the trial at their site. For NHS Organisations in the UK, this indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS. NHS Organisations must ensure that site staff without substantive NHS contracts hold honorary contracts to ensure they can access patients and are covered under the NHS indemnity arrangements. Trial staff without NHS contracts e.g. General Practitioners or Dentists will provide their own professional indemnity.

15.9 Amendments

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not and trial procedures must not be changed without the mutual agreement of the CI, Sponsor and the Trial Management Group. The Trial Steering Committee will be consulted in the event of significant changes to the trial.

Substantial amendments will be submitted to the relevant ethics review organisation and/or competent authority as appropriate. Substantial amendments will not be implemented until this approval is in place. It is the responsibility of the NCTU to submit substantial amendments in the UK. For non-UK sites this responsibility may be delegated by country specific Sponsors to non-UK site staff according to local regulations and policies.

Non-substantial amendments will be submitted to the Health Research Authority (HRA) or equivalent and will not be implemented until authorisation is received.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS R&D Departments in the UK or equivalent, for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will be provided to sites by NCTU .

15.10 Post-Trial Care

Following participation in the trial, participants will return to standard care. Continuation of CBZ treatment after the trial has ended will be at the discretion of the participant's treating clinician. If a patient is withdrawn from the trial, they will return to their standard care.

15.11 Access to the Final Trial Dataset

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 (e.g. growth and bone conformation data, HRQOL outcomes, plasma and serum samples).

16 DISSEMINATION POLICY

Dissemination and communication is central to the MCDS-Therapy project. Throughout the project the trial team will communicate in a number of ways about trial progress. Any information shared about the trial will be approved first by the Sponsor and trial management group. This will ensure no breaches of confidentiality or privacy.

Communications will aim to:

- Raise awareness about MCDS and the MCDS-Therapy project
- Raise awareness about the potential of drug repurposing for rare diseases
- Show how an academic led clinical trial has the potential to deliver a new treatment for an ultra-rare condition
- To show that patients are involved and engaged with the research project

Communications must comply with participant consent and avoid inadvertent or deliberate identification of participants.

The different media for communication and dissemination are detailed below.

16.1 Scientific papers

Publication of research results in peer-reviewed scientific journals is the gold standard for any study. The MCDS-Therapy trial team will aim to publish trial results, whether positive or negative, in this manner. Health economic research, biomarker development results, and any social research carried out will also be published in relevant journals where possible.

16.2 Lectures and posters at national and international academic conferences

Findacure will aim to raise awareness about MCDS-Therapy by speaking about the project, its aims, development and results at national and international rare disease conferences. Key members of the MCDS-Therapy consortium will target academic gatherings in consultation with the wider project management group.

16.3 Research staff and clinicians participating in public events

The MCDS-Therapy team will aim to target public events such as Rare Disease Day and Jeans for Genes Day and attend existing public events, such as Newcastle University's Genetics Matters, to encourage engagement with MCDS-Therapy researchers and the general public. The aim throughout these type of events will be to explain the science behind MCDS, and its potential treatment in a clear and interesting manner. Findacure will also look to engage patients to talk at such events about their experiences of living with the condition. Findacure's own annual programme of UK-based events, including a conference on drug repurposing, and a Rare Disease Showcase series, will also provide natural points for interaction between researchers and the wider community.

16.4 Website dissemination

The MCDS-Therapy website (http://www.mcds-therapy.eu) will act as the public home of the trial, and serve to provide information about the project, introductions to the team, explanations of the science, and updates on progress. The news page on the website will host updates and blog posts from the project and members of the consortium. The website will also host an online newsletter and connect to MCDS-Therapy social media accounts. The MCDS-Therapy website will also be employed to distribute recruitment materials such as posters and flyers with the aim of attracting potential participants to contact the research team for more information. The trial online communications policy document details the approach to the website for the project.

16.5 Social media

The MCDS-Therapy trial will use social media responsibly to communicate about the project, with the aim of reaching the scientific community, patients, industry, and policy makers. This type of communication and dissemination is crucial to show the impact of the project and the EU funding and has the potential to improve awareness and understanding about both MCDS and the science behind drug repurposing. Both Twitter and Facebook will be used to provide recruitment updates (i.e. when new sites are open to recruitment or when a site has recruited a patient to the study). Social media will also aid in distributing recruitment materials such as posters and flyers with the aim of attracting potential participants speak to their treating clinician/contact the research team for more information. The trial online communications policy document details the approach to social media for the project.

16.6 Communication with patients, caregivers and the public

Findacure will aim to reach patients, care givers and the public through the MCDS-Therapy website and social media platforms. A patient advisory committee will be formed to run patient focus groups to discuss patient experience of living with MCDS, and opinions of the MCDS-Therapy project.

16.7 Project specific newsletters and leaflets

A mailing list hosted through the MCDS-Therapy website, will provide subscribers with at most a quarterly update on the progress on the MCDS-Therapy project. This will feature information about the project and team as a whole, as well as updates on related research and patient experience pieces.

Initially Findacure will produce leaflets explaining the MCDS-Therapy project, plans for dissemination at Findacure events and conferences attended by the MCDS-Team.

16.8 Rare disease groups

There is currently no active patient group exclusively for patients with MCDS. Findacure will engage with existing groups for achondroplasia around the world, starting with major UK groups to discuss the trial and project. Findacure will use these relationships to increase awareness about the project, grow the MCDS community and promote events.

Findacure actively supports individuals who form new patient associations and charities. If anyone is looking to do this for MCDS, they will provide the necessary support to develop this patient community to support MCDS-Therapy as an independent group.

16.9 Patient conferences

If existing groups run patient conferences, Findacure will seek to attend these meetings to explain the MCDS-Therapy project, progress, and gain patient feedback on the work of MCDS-Therapy.

16.10 Informing patients at end of study

The channels of communication that are developed throughout the study will be used to disseminate the results of the trial to the wider community. Findacure will ensure that study participants are informed about the project results. The trial team will compile an accessible summary of the results that can be shared with all those who enrolled in the trial itself, and provide this information to them directly at the earliest point that still permits appropriate publication and exploitation of the results.

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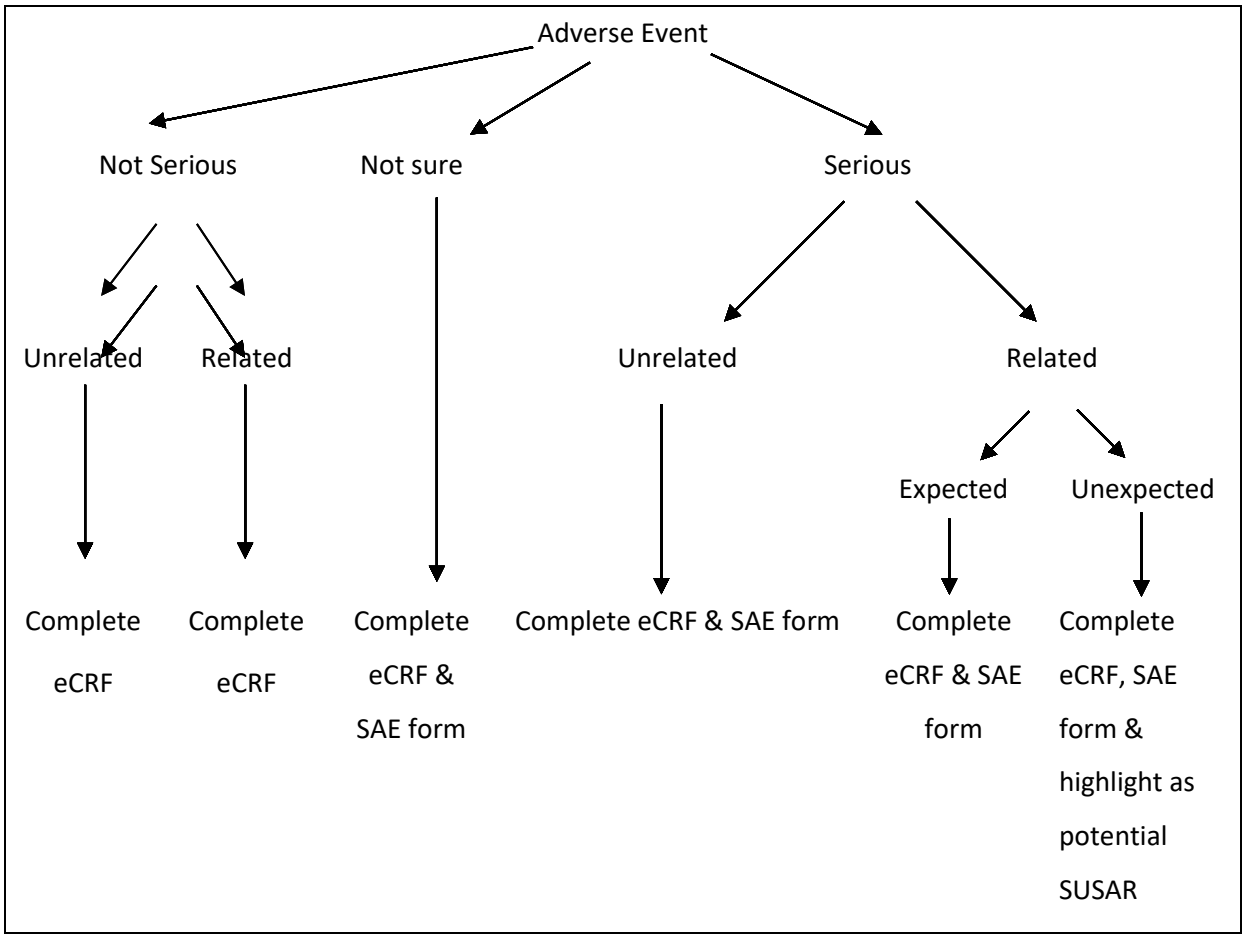
18 APPENDICES

18.1 Appendix 1 – UK Safety Reporting Diagram



Contact details for reporting SAEs and SUSARs

Please send SAE form(s) via secure email to nctu.mcds-therapy.sae@nhs.net

Or via secure transfer methods as instructed at the site SIV

18.2 Appendix 2 – UK Amendment History

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
Substantial Amendment 1	V2.0 26/07/2019	MHRA: 01/10/2019 REC: 26/09/2019	Trial Manager	Protocol sections updated (see cover letter for full detail): Safety Review and Primary Outcomes, Exploratory Biomarkers, Eligibility, Stage 2 treatment reduction option, Bone Markers, Safety Visit, Study Schedule, PPI, Website, Patient groups. Other documents updated: PIS Legal Guardian Stage 1 and 2, PIS 12-15 years, GP letter. Other changes: PI[a] change at Newcastle upon Tyne Hospitals NHS Foundation Trust Addition of NHS Fife as a PIC site New documents: Protocol Synopsis, PIS 16+ Stage 1 and 2, MCDS Medication Diary dosing instructions 16+, MCDS Medication Diary Baseline and Stable Dose, PIS Stage 2 7-11 and 12-15 years, Recruitment Flyer
Substantial Amendment 2	V2.0 26/07/2019	MHRA: 13/11/2019 REC: N/A	Trial Manager	RSI for study updated to the following: Tegretol 100 mg 5ml Liquid updated 11 April 2019, date of revision of text 27 March 2019 Tegretol 100mg Tablets updated 12 April 2019, date of revision of text 27 March 2019 Tegretol 200mg Tablets updated 12 April 2019, date of revision of text 27 March 2019 Tegretol 400mg Tablets updated 12 April 2019, date of revision of text 27 March 2019

Substantial Amendment 3	V3.0 21/02/2020	REC: 19/03/2020 HRA: 16/04/2020 MHRA: 26/03/2020	Trial Manager	This amendment includes updates to the CT Application Form, protocol (archiving, typographical errors, minor clarifications, and x-ray timeframes), updates to the PIS /Consent forms and amended patient diaries. See cover letter for further details.
Substantial Amendment 4	V4.0 27/08/2020	REC: 01/10/2020 HRA: 02/10/2020 MHRA: 01/10/2020	Trial Manager	Amendment to restart study, updating protocol and participant information in line with new visit timelines. Also, to incorporate minor formatting issues from SA03 in place of a non-substantial amendment.
Substantial Amendment 5	V5.0 28/10/2020	REC: 01/03/2021 HRA: 09/03/2021 MHRA: 08/03/2021	Trial Manager	SA5 is a COVID-19 related update to the protocol. Please see the cover letter which accompanies this amendment for full details of all changes.

Substantial Amendment 6	V6.0 30/06/2021	REC: 04/08/2021 HRA: 02/09/2021 MHRA: 23/08/2021	Trial Manager	This amendment includes updates to Stage 2 timelines and various changes in stage 2 sponsorship responsibilities. Please see the cover letter which accompanies this amendment for full details of all changes.
Substantial Amendment 7	V7.0 21/10/2021	REC: 04/01/2022 HRA: 27/01/2022 MHRA: 25/01/2022	Trial Manager	The protocol has been updated with changes to key trial staff as well as to the contents table and footers. V5 was added to the 'previous versions' as this was erroneously missed from the last update. Various Participant Information Sheets have also been updated - please see the cover letter which accompanies this amendmendment for full details of all changes.
Substantial Amendment 8	V7.0 21/10/2021	REC: 06/05/2022 HRA: 09/05/2022 MHRA: N/A	Trial Manager	Stage 2 12-15 Participant Information Sheet has been updated - please see the cover letter which accompanies this amendmendment for full details of all changes.

Substantial Amendment 9	V8.0 21/10/2022	REC: 27/10/2022 HRA: 01/12/2022 MHRA: 29/11/2022	Trial Manager	The purpose of this amendment is to: 1. To extend the Stage 1 only Treatment period by an additional optional 12 months. Participants who wish to continue on the study IMP would therefore receive up to 36 months of treatment with the IMP. The Stage 2 schedule of events remains unchanged. The protocol has been updated to reflect these changes. New participant information documents, informed consent forms, GP letter and patient drug diaries have been created to as part of this amendment 2.To update the study SmPC and RSI to Tegretol® 100mg/5ml Liquid, Tegretol 100mg tablets, Tegretol 200mg tablets and Tegretol 400mg tablets, all dated 10 Jun 2022. In this update, hyperammonaemia has been added in the list of adverse drug reactions with unknown frequency within section '4.8 Undesirable Effects' and as such this adverse drug reaction will be added to the study RSI. The updated RSI will not be implemented until the start of the next DSUR reporting period (14 Nov 2022). As the trial safety blood test would flag excess ammonia before 3. The end date of the study has been changed to 31 May 2023.
Minor Amendment 2	V9.0 16/10/2023	REC: TBC HRA: TBC MHRA: TBC	Trial Manager	The purpose of this amendment is to bring the Last Patient Last Visit (LPLV) date forward to 31st January 2024 as the latest trial visit date possible. The vast majority of participants will not be affected by this amendment as their final visits have either already taken place or they will take place, according to their existing visit schedules, weeks to months before the 31st January 2024. This minor change will ensure that sufficient time is available for the final data cleaning, data download and statistical analysis to enable the final trial report to be completed by 31st May 2024.

18.3 Appendix 3 – Tanner stage assessment

	Breast	Pubic Hair	Genitals	Pubic Hair
Stage 1	Small nipples. No breast. 	No pubic hair. 	No signs of puberty. Scrotum, testes, and penis as in childhood. 	No pubic hair. 
Stage 2	Breast and nipples have just started to grow. The areola has become larger. Breast tissue bud feels firm behind the nipple. 	Initial growth of long pubic hairs. These are straight, without curls, and of light color. 	Initial growth of scrotum and testes. The skin on the scrotum has become redder, thinner, and more wrinkled. The penis may have grown a little in length. 	Few hairs around the root of the penis. The hairs are straight, without curls, an of light color. 
Stage 3	Breast and nipples have grown additionally. The areola has become darker. The breast tissue bud is larger. 	The pubic hair is more widespread. The hair is darker, and curls may have appeared. 	The penis has now grown in length. Scrotum and testes have grown. The skin of the scrotum has become darker and more wrinkled. 	Hairs are darker and curlier and still sparse, mostly located at the penis root. 
Stage 4	Nipples and areolas are elevated and form an edge towards the breast. The breast has also grown a little larger. 	More dense hair growth with curls and dark hair. Still not entirely as an adult woman. 	The penis has grown in both length and width. The head of the penis has become larger. The scrotum and testes have grown. 	More dense, curly, and dark hair. The hair growth is reaching the inner thighs. 
Stage 5	Fully developed breast. Nipples are protruding, and the edge between areola and breast has disappeared. 	Adult hair growth. Dense, curly hair extending towards the inner thighs. 	Penis and scrotum as an adult. 	Pubic hair extends upwards to the umbilicus. It is dense and curly. 

18.4 Appendix 4 – CTCAE grading relevant to MCDS-Therapy IMP DLTs

MedDRA Code	MedDRA SOC	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Definition	
10002272	Blood and lymphatic system disorders	**Anaemia**	Haemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a reduction in the amount of haemoglobin in 100 ml of blood. Signs and symptoms of anaemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.	
1019491	Blood and lymphatic system disorders	**Haemolysis**	Laboratory evidence of haemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 g decrease in haemoglobin	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction.	
10001551	Investigations	**Alanine aminotransferase increased**	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.	Also consider Hepatobiliary disorders: Hepatic failure

10001675	Investigations	**Alkaline phosphatase increased ***	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-	A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.	
10005364	Investigations	**Blood bilirubin increased**	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.	Also consider Hepatobiliary disorders: Hepatic failure
10011368	Investigations	**Creatinine increased**	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-	A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen.	Also consider Renal and urinary disorders: Acute kidney injury
10064848	Renal and urinary disorders	**Chronic kidney disease**	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death	A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure.	

* For the purposes of this trial, increased alkaline phosphatase refers to liver impairment (liver ALP).