Study Protocol

A Phase II randomised cross-over trial of orAl Cannabinoid versus placebo in the Treatment of chemotherapy Induced peripheral neurOpathic paiN (ACTION)

Co-Sponsors	The University of Edinburgh & Lothian Health Board ACCORD Usher Building, The University of Edinburgh 5-7 Little France Road Edinburgh BioQuarter – Gate 3 Edinburgh EH16 4UX
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KEY TRIAL CONTACTS (*Protocol Authors)

Chief Investigator	
Name:	Marie Fallon*
Address:	Edinburgh Cancer Research Centre (IGC), Crewe Road South, Edinburgh, EH4 2XR
Email:	marie.fallon@ed.ac.uk

Lead Co-Sponsor Representative	
Name:	Paul Dearie
Address:	ACCORD, Usher Institute, University of Edinburgh, 5-7 Little France Road, Edinburgh, EH16 4UX
Email:	paul.dearie@ed.ac.uk

Trial Manager	
Name:	Emma Ward
Address:	ECTU, Usher Institute, University of Edinburgh, 5-7 Little France Road, Edinburgh, EH16 4UX
Email:	E.Ward@ed.ac.uk

Trial Statistician	
Name:	Jacqueline Stephen
Address:	ECTU, Usher Institute, University of Edinburgh, 5-7 Little France Road, Edinburgh, EH16 4UX
Email:	Jacqueline.Stephen@ed.ac.uk

PROTOCOL APPROVAL SIGNATURE PAGE

A Phase II randomised crossover trial of orAl Cannabinoid versus placebo in the Treatment of chemotherapy Induced peripheral neurOpathic paiN

ACTION

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

Professor Marie Fallon	Marie Fallon (27-Mar-2026 14:15:27 GMT)	27-Mar-2026	
Chief Investigator	**Signature**	**Date**	
Dr Jacqueline Stephen	J Stephen	30-Mar-2026	
Trial Statistician	**Signature**	**Date**	
Paul Dearie	Paul Dearie (27-Mar-2026 11:58:40 GMT)	27-Mar-2026	
Lead Co-Sponsor Representative	**Signature**	**Date**	

For multi-site trials, the Principal Investigator must sign below to document that the protocol has been read and understood.

Name	Marie Fallon (27-Mar-2026 14:15:27 GMT)	Lothian	27-Mar-2026
Principal Investigator	**Signature**	**Site**	**Date**

DOCUMENT HISTORY

Version Number	Date	Changes
1.0	17 Sep 2025	• New document
2.0	21 Nov 2025	• Updates following REC and MHRA combined review; - Clarification of objectives and outcomes in Section 2 and Section 10 - Additional wording added to Section 4.2 regarding sterilisation and contraception methods - Clarification in Section 11.9 regarding pregnancy of participants or pregnancy of partners of male participants
3.0	19 Mar 2026	• Administrative correction to Sponsor reference and addition of ISRCTN number to page 1 • Section 3.2 additional details of who will collect EORTC CIPN20 outcome assessments added • Section 7 Schedule of Assessments and legend (Table 2) updated • Section 7.4 location of day 98 visit specified • Section 7.5 lab where research samples will be stored updated • Section 7.5 Sampling Table – sample tubes required for research and safety bloods updated • Section 9.3 (Data Information Flow) updated

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LIST OF ABBREVIATIONS

AC	Adenylyl Cyclase
ACC	Anterior Cingulate Cortex
ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AEA	N-arachidonoylethanolamine
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AR	Adverse Reaction
AST	Aspartate Aminotransferase
b.i.d	Twice a day
BMI	Body Mass Index
BOLD	Blood Oxygenation Level Dependent
BP	Blood Pressure
BPI sf	Brief Pain Inventory Short Form
CA	Competent Authority
CBD	Cannabidiol
CBDs	Cannabinoids
CBPM	Cannabis Based Plant Medicines
CBR 1/2	Cannabinoid Receptor 1/2
CBN	Cannabinol
CI	Chief Investigator
CIPN	Chemotherapy Induced Peripheral Neuropathy
CK	Creatine Kinase
CNS	Central Nervous System
CRF	Case Report Form
CRU	Clinical Research Unit

CS	Clinically Significant
CSR	Clinical Study Report
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DMP	Data Management Plan
DSUR	Development Safety Update Report
EOS	End of Study
ECG	Electrocardiogram
eCB	Endocannabinoid
ECS	Endocannabinoid System
eCRF	Electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
EPAS	Edinburgh Palliative and Supportive Care
ET	End of Trial
FAAH	Fatty Acid Amide Hydrolase
FACT-Cog	Functional Assessment of Cancer Therapy–Cognitive Function
FSH	Follicle Stimulating Hormone
GABA	Gamma-Aminobutyric Acid
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	Gamma-Glutamyl Transferase
GMP	Good Manufacturing Practice
HR	Heart Rate
IASP	International Association for the Study of Pain
IB	Investigator Brochure

ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
MAPK	Mitogen-Activated Protein Kinase
MCT	Medium-Chain Triglycerides
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NCS	Not Clinically Significant
NIMP	Non-Investigational Medicinal Product
PDRA	Postdoctoral Research Assistant
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PIS	Patient Information Sheet
PISCF	Patient Information Sheet Consent Form
PPI	Patient and Public Involvement
PSQI	Pittsburgh Sleep Quality Index
QA	Quality Assurance
QoL	Quality of Life
QST	Psychophysical Testing
RBC	Red Blood Cell
REC	Research Ethics Committee
RR	Respiratory Rate
rsfMRI	Resting State fMRI
SAE	Serious Adverse Event

SAR	Serious Adverse Reaction
SOA	Schedule of Assessments
SOC	Systems Organ Class
SD	Standard Deviation
SDV	Source Data Verification
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
THC	Tetrahydrocannabinol
TMF	Trial Master File
TMG	Trial Management Group
TRP	Transient Receptor Potential
TSC	Trial Steering Committee
ULN	Upper Limit of the Normal Range
VAS	Visual Analogue Scale
WOCBP	Women of Childbearing Potential

TRIAL SUMMARY

Trial Title	A Phase II randomised cross-over trial of orAl Cannabinoid versus placebo in the Treatment of chemotherapy Induced peripheral neurOpathic paiN
Study Acronym	ACTION
Clinical Phase	Phase II
Trial Design	Double blind, placebo-controlled, randomised cross-over trial
Trial Participants	Stable chronic chemotherapy-induced peripheral neuropathy
Planned Number of Participants	92
Planned Number of Sites	1
Countries Anticipated to be Involved in Trial	Scotland
Treatment Duration	12 weeks
Follow up Duration	2 (+/- 7 days) weeks post last dose.
Total Planned Trial Duration	30 months
Primary Objective	**Primary clinical objective**: To determine if the oral administration of a CBD solution (MRX1) for 5 weeks provides effective analgesia for CIPN, assessed using the EORTC CIPN20 (sensory subscale) questionnaire, which has been developed explicitly and validated for CIPN. **Primary mechanistic objective:** To determine whether there are pre/post-treatment changes in key pain brain regions, focusing on Anterior Cingulate Cortex (ACC) connectivity in those receiving active treatment during resting state MRI (rsfMRI), and whether these are associated with changes in clinical pain/well-being scores.

Secondary Objectives	**Clinical:** To determine whether 5 weeks of a CBD solution (MRX1) affects: • Side effects • Neuropathy severity • CIPN pain severity using traditional pain assessment • Mood • Cognition • Sleep • Quality of life • Recommended exam for CPIN to allow an objective assessment of neuropathy • Patient Global Impression of Change (PGIC) **Health economic:** • Health economic evaluation to assess potential impact of CBD treatment on health care costs and carer costs • To understand the feasibility of measuring the cost-effectiveness of the IMP and the potential for market viability **Mechanistic** • Whether wider brain changes inferring neuroinflammation accompany 5 weeks of CBD treatment • Relationship of CBD response to patients own endocannabinoid system from baseline to end of study **Exploratory** • To explore period-dependent fluctuations in clinical outcomes • To explore temporal fluctuations in pain, sleep, mood, function and general well-being
Primary Endpoint	**Clinical primary outcome:** EORTC QLQ-CIPN20 sensory scale assessed at the end of each period of the cross-over trial (weeks 5 and 12). **Mechanistic primary outcome:** Changes between baseline and 5 weeks between active and placebo in rsfMRI connectivity of the ACC.

Secondary Endpoint	**Clinical:** • Reported Adverse Events and side effects • Total EORTC CIPN 20 scores and EORTC QLQc30 scores at week 5 and week 12 • BPI SF at week 5 and week 12 • GAD7 and PHQ9 total scores at week 5 and week 12 • FACT-CogV3 total score at week 5 and week 12 • Pittsburgh Sleep Questionnaire at week 5 and week 12 • EORTC QLQc30 at week 5 and week 12 • QST at week 5 and week 12 • Standardised questions within end of week 5 and week 12 **Health economic:** • EQ5D 5L and Health Care Utilisation at week 5, 8 and 12 • Modelled cost per QALY at week 5, 8 and 12 **Mechanistic:** • Wider rsfMRI network architecture beyond the ACC, and white matter microstructural integrity/magnetic resonance spectroscopy at week 5 • eCB levels measures from blood samples (as potential effect modifier) at baseline, 5 8 and 12 • Inflammatory markers measured from blood samples at week 5 and week 12 (as potential effect modifier) **Exploratory:** • Clinical outcomes (EORTC CIPN 20, EORTC QLQc30, PHQ9, GAD7 and BPI SF) incorporating data from baseline, week 5, week 8 and week 12 • Data collected from daily diary during 1-week pre-randomisation, week 5 and week 12.
IMP(s)	MRX-1 Cannabidiol (CBD) oral solution. The formulation is 10% CBD isolate, 0.25% flavouring and 89.75% MCT oil.
IMP Route of Administration	Oral
NIMP(s)	N/A

Lay Summary of Trial	One in 3 people will have cancer in their lifetime. While cancer treatment has improved in the last 15 years, including new and improved chemotherapy treatments and other tumour killing methods, 1 in 4 people will die from cancer. One harmful side effect of these treatments is that they can damage the nerves in the body. This is called Chemotherapy Induced Peripheral Neuropathy (CIPN). CIPN is very common and can affect up to 90% of patients. It causes long-term pain in up to half of patients. This leads to problems carrying out normal day to day activities and affects their quality of life. CIPN is hard to treat with current medicines. In our study, we want to improve pain levels in these patients. This is by looking at a possible treatment for CIPN and seeing how this treatment works. Laboratory work and early studies in patients has shown that substances found in the Cannabis sativa plant called cannabinoids (CBDs) can help with nerve pain like that seen in CIPN. Because of this research, NICE and the International Association for the Study of Pain have asked for research using CBDs. As there hasn't been much research using CBDs in CIPN, our study will test CBD. We also want to include in our study tests which look at what happens in the pain and mood systems in the brain when you take CBD. Our group has experience with clinical trials for cancer patients and also experience of doing special tests to understand more detail of how a medicine works or doesn't work. We also have a special clinic just for CIPN patients, and lots of skill in treating pain. We can measure the different CBDs in the blood before and after treatment and look at the effects on the patient's own natural CBD system. We also have special tools to look at the brain. At the start of our study, patients will answer questions that measure their CIPN symptoms, and also questions about their quality of life, and ask if they are worried and depressed. We will take blood samples to measure the body's natural CBD levels and perform a brain scan in patients using a special machine called an MRI scanner. They will then be split into one of two groups: drug or placebo (dummy drug). Both drug and placebo will look, taste, smell and feel identical in consistency. CBD itself is tasteless. Participants will take drops of identical looking and tasting liquid for a period of 5 weeks of either the CBD (drug) or placebo (a liquid without CBD). A study nurse will both see and speak to the patients by phone during the study, along with the doctor, who will decide if changing the dose of the drug is needed. After 5 weeks, the surveys, blood tests and MRI will be repeated, followed by 2 weeks of 'washout', when participants will not take any study medication. Participants will then receive the treatment that they did not receive in the first 5 weeks for another 5-week period. After this, the surveys and blood tests will be repeated.

	At the end of the study, we will look at the effects of the treatment on pain relief, quality of life, physical function, the brain and mood. We will also look at unwanted side effects, how the blood levels of drug given in the study are linked to the results and also the levels of CBD naturally occurring in the body. This work is important as it will tell us if a larger study is needed to show that CBDs are an effective treatment for CIPN, and how the study should be done. Patient feedback will help to guide the research and to publicise the results.

1 INTRODUCTION

1.1 BACKGROUND

In summary, the cannabis plant contains >144 phytochemicals, known as cannabinoids. Put simply, cannabinoids activate the CB1 and CB2 receptors which are expressed in multiple cell types that play a critical role in the relay/modulation of pain pathways and have shown recent promise for treatment of chronic pain conditions.[1,2] Self-medication with cannabis and cannabinoids is common amongst those with cancer and various symptoms and, in our recent survey of 400 oncology patients, 33% reported use of cannabinoids to manage pain, nausea, sleep, anxiety (unpublished data). Despite widespread reported use by patients, the clinical use of cannabinoids for pain and in particular chemotherapy induced peripheral neuropathy (CIPN) lacks evidence on efficacy and safety.

The Endocannabinoid System (ECS): Cannabinoid receptors (CBRs) 1 and 2 preferentially bind to Gαi/o, influencing the activity of Adenylyl Cyclase (AC), activation of the MAPK pathway and the concentration of intracellular Ca2+. Alternatively, CBRs bound to β-arrestin 2 results in desensitisation, decoupling and/or internalising the receptor.[1] Given that the ECS modulates neuronal and immune cell function, both of which play critical roles in pain, therapeutics targeting this system, such as cannabis-based plant medicines (CBPM) hold potential as novel analgesics in treating various conditions, such as CIPN. The ECS orchestrates a 'retrograde negative feedback mechanism' in the Central Nervous System (CNS). Upon neuronal depolarisation, AEA and 2-AG are synthesised on the postsynaptic terminal in dendritic spines and somatodendritic compartments.[3] They are then released into the neuronal cleft to suppress the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) secretion in GABAergic afferents and the excitatory neurotransmitter glutamate in glutamatergic neurons. Additionally, endocannabinoid (eCB) signalling in non-neuronal tissues regulates several physiological processes, such as spermatogenesis and sebum production and the modulation of the immune system.[4–6] There is strong experimental evidence associating the role of the ECS in the CNS and non-neuronal tissues, and neurogenic and inflammatory pain, including CIPN.[7,8]

Phytocannabinoids: Cannabis is a botanical product derived from the Cannabis sativa plant, a dioicous species of the Cannabaceae and broadly distributed worldwide.[9] The pharmacological activity of phytocannabinoids, also known as plant-based cannabinoids, was observed initially in the 1940s and 1950s with preparations of tetrahydrocannabinol (Δ9 -THC), cannabidiol (CBD) and cannabinol (CBN) extracted from the Cannabis sativa plant, the synthetic cannabinoids Δ6a,10a -THC and its hexyl analogue, synhexyl.[10-12] The discovery of the molecular structure of the main cannabinoid found in the Cannabis sativa plant, Δ9 -THC, was reported in 1971.[13] This led to further research and the identification of the cannabinoid receptor 1 (CBR1), located mainly in the central nervous system (CNS), and the CBR2, principally present in the peripheral system mediating immune functions.[14–16] Consequently, ECS is so named because endogenous cannabinoids were first discovered to activate the same receptors as exogenous cannabinoids.

1.2 RATIONALE FOR STUDY

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most frequent side effects of antineoplastic treatment, particularly of lung, breast, prostate, gastrointestinal, and germinal cancers, as well as different forms of leukaemia, lymphoma, and multiple myeloma. Currently, no effective therapies are available for CIPN prevention, and symptomatic treatment is frequently ineffective;[15,16] thus, this is a critical unmet clinical need. Cancer patients have improved survival outcomes, often at the cost of CIPN, so can survive with markedly impaired quality of life. Some patients cannot continue with appropriate chemotherapy because of uncontrolled CIPN, which can

then impact survival. In the UK alone, there are more than 140,000 new cases of CIPN/year and the prevalence runs into almost a million patients in the UK alone. It can be severely disabling in 50% of patients, resulting in pain, poor physical function, and reduced quality of life (QoL).[17,18] The minimal treatment options are reflected in international guidelines which agree that there is a pressing need to find a treatment for CIPN that works and has acceptable side effects, as this is highly clinically relevant. Such treatment may also be suitable for the management of other neuropathic pains. The underlying mechanisms of CIPN are complex, but are thought to involve neuroinflammation.[17] Among possible pharmacological treatments of CIPN, modulation of the eCB system is particularly promising. The possible role of eCB system modulation in providing relief from CIPN symptoms is a hypothesis supported by preclinical evidence but not yet consistently demonstrated in patients.[19] So the strong rationale for investigating cannabis based products for medicinal use (CBPM) and in particular CBD, in CIPN, which will be elaborated on below, can be summarised as relating to a combination of the likely underlying neurobiological mechanisms of CIPN ('pain network' activation, neuroinflammation), the evidence for mechanisms of action of CBPM on these pathways, preclinical and pilot data of the utility of CBPM in CIPN, and the acceptability to the patient population who are very interested in the answer to the role of CBPM for pain. In 2019, NICE reviewed the evidence base for CBD for treating neuropathic pain.[20] "There was no evidence, based on a lack of appropriately designed studies, for using CBD alone (either as a pure product or containing traces of THC)." NICE made a research recommendation for CBD in adults with treatment-resistant neuropathic pain. "The key outstanding question is: for adults with persistent treatment-resistant neuropathic pain, what is the clinical and cost-effectiveness of CB medication?" Additionally, the International Association for the Study of Pain (IASP) task force on cannabis, CBS and cannabis-containing medicines states that: "while there is strong preclinical evidence for the use of CBS in pain relief, this has not been translated into clinical evidence". A comprehensive clinical research agenda with guidance on study inclusion and endpoints has now been published by IASP[21] and has been used to guide the design of our proposed trial. One of the recommendations is that the methodology and endpoints reflect the clinical problem, so we have also drawn on CIPN clinical trial guidelines to address this angle. Using the search terms: CIPN, THC, CBD, and clinical trials, we found 4 trials on ClinicalTrials.gov (search date: 18 August 2024). In addition, we know the Mayo Clinic have now completed a topical CBD study for CIPN (Loprinzi). None of the studies below replicate the study proposed in this protocol.

- CBD for prevention of CIPN Open phase 2 study. NCT04582591
- The kinetics of eCBs in CIPN patients on chemotherapy NCT04376437
- THC:CBD in patients receiving taxane. NCT03782402
- Effects of hemp-CBD capsules on patients receiving neurotoxic chemotherapy to assess severity and duration of CIPN. NCT04398446
- USA Intel: C Loprinzi, Mayo Clinic, Topical CBD (non-randomised, phase 2) cream for CIPN treatment. Not registered. Completed. Oral communication with CI-Negative study and CI undertaking reformulation work.

Our recently completed menthol double-blind placebo controlled RCT in CIPN (ClinicalTrials.gov: NCT04276727) which included functional magnetic resonance imaging (fMRI) is also distinct from this proposed CBD RCT. In it we demonstrated the feasibility of an RCT, including a mechanistic assessment, in CIPN patients. The mechanistic assessments have turned out to be key and have provided a bedside predictor of a clinical response to topical menthol. (In write up for Annals of Oncology), one of the study team involved in the above and the current research protocol (HW) has also successfully completed a fMRI mechanistic study in a gabapentin RCT for chronic pelvic pain (publication in preparation), and complimentary large-scale studies on central effects of increased circulating inflammatory biomarkers.[22] The Modulation of the Endocannabinoid System in CIPN and the Rationale for CBD Formulation in CIPN is as follows. CBD is one of the most abundant cannabinoid

molecules in cannabis out of 568 unique molecules identified thus far. Along with other CBs, terpenes and flavonoids, CBD is thought to promote pain relief via receptors in the body's ECS, which plays a key role in endogenous pain control.[23,24] Delta9 -THC is the main pharmacologically active phytocannabinoid component of the Cannabis sativa plant, and is responsible for the psychoactive effects associated with cannabis use.[25,26] While CBD does not cause this 'high', it has been shown to reduce pain and inflammation.[27] CBD has a low affinity for CBRs[28] and is an inverse agonist of CBRs.[29,30] While the CBRs have both been clearly implicated in antinociception and antineuroinflammation,[31–33] the therapeutic effects of CBD have been attributed to its diverse molecular targets. The key targets are known receptors in CIPN pain relief. CBD is preferred in treating chronic pain because it lacks the rewarding psychoactive effects of THC. Hyperalgesia and allodynia, as seen in CIPN, reflect different environmental stimuli. While predictable painful stimuli can often be avoided, allodynic responses to stimuli in the CIPN patient, like regular touch, and hyperalgesic responses, like exaggerated painful sensation, to the core activities of daily living, cannot.

Most evidence suggests an increase in pro-inflammatory cytokine expression and changes in immune signalling pathways in CIPN. Ultimately, CBD[34, 35, 36] interacts with the endocannabinoid system, as well as other neuromodulator systems to modulate a range of physiological responses including pain perception, inflammation, and mood regulation, potentially offering therapeutic benefits across commonly occurring symptom clusters in CIPN patients but also in other neuropathic pain conditions.

The CIPN clinical trials guidelines group recommends that clinical researchers study interventions and mechanistic pathways mapped out in nonhuman animals.[37] Interest in the possibility of administering CBPM in CIPN patients has followed from preclinical evidence, clinical observations, and a responder analysis in a small pilot study with the cannabinoid agent nabiximols for CIPN.[38] Given the knowledge we have of CIPN, its likely drivers, particularly neuroinflammation, the mechanisms of action of CBD, including its anti-inflammatory activity, and clinical observations, there exists a good rationale for moving forwards with a mechanistic study of CBD in CIPN. From the patient and societal aspect, the knowledge that CBD does not have any analgesic activity in the absence of a pain state, it does not lose its analgesic effect with time in preclinical models, along with the lack of psycho-activity, is very reassuring.[39,40] Unlike other medical conditions, the gold standard measure of chronic pain symptoms is based on patients' subjective reports – which has the added complication of confounding placebo effects, notorious in pain research. This makes the use of quantitative, objective biomarkers critical in studies of potential new interventions for chronic pain conditions like CIPN. Biomarkers & Neuroimaging techniques offer a non-invasive and objective means to assess changes over time in the presence of a particular treatment, disentangling pharmacological from placebo responses.[41-43] We can also examine features at the individual patient level by looking at changes in biomarkers associated with symptom improvement. We propose using objective quantitative blood-based biomarkers and measuring central effects of CBD treatment using MRI, examining changes within an individual. Blood-based biomarkers of inflammation are important, but feasibility restricts to peripheral markers, leaving open the question as to what is happening centrally. However, changes in plasma biomarkers can also be linked to changes in MRI responses, for deeper understanding of responder phenotypes. Hence, to overcome barriers common to neuropathic pain trials, including problems around subjective outcomes, we will examine central effects of CBD in CIPN using MRI. We will also measure plasma cytokines, along with eCB and CBD levels, at baseline and time points through the study, adding further objective biomarkers of treatment response and for mechanistic insight. Functional magnetic resonance imaging (fMRI) maps central functional activity in the brain by indirectly evaluating changes in blood flow and oxygen levels. There are early and consistent findings of functional brain reorganisation in chronic pain patients. Further, pharmacologic investigations of multiple analgesics have shown greater changes in fMRI BOLD responses in pain-related brain regions versus placebo.[44] Hence, a mechanistic

approach to pain RCTs, using fMRI, is increasingly used to quantify central mechanisms of action of novel interventions, un-confounded by subjective reporting and placebo effects. Of additional relevance to this application, multiple studies, including our own, also report measurable associations between markers of peripheral inflammation and changes in brain connectivity detectable on MRI using DTI and MRS[22] indicating the ability to detect changes in neuroinflammation levels as a mode of action of pain relief in the context of the current proposal. Functional brain reorganisation of pain networks is considered to underlie symptoms of chronic pain conditions, including CIPN. Brain areas implicated in human and animal studies of chronic neuropathic pain include regions such as the anterior cingulate cortex (ACC) and changes in wider brain network properties.[44-46] Notably, convergent evidence also suggests that central effects of cannabinoids also exert their effects by acting on these same regions, including the ACC. It is currently unclear whether this includes analgesic effects in patients with CIPN. In terms of molecular neurobiology, the ACC is known to be densely populated with CB1 receptors.[47] Furthermore, in animal models of chronic neuropathic pain, cannabinoid receptors have been demonstrated to have decreased binding capability in the ACC.[48] Additionally, animal models also report increased expression in response to effective CBD treatment in the ACC.[49] Taken together, these studies suggest that the ACC may have a substantial role in cannabinoid analgesia in chronic pain, and is hence the primary focus of the mechanistic imaging component of the study. The ACC is known for its critical involvement in pain processing and emotional regulation, making it a key target for understanding how cannabinoids can modulate pain perception. This region's extensive connections with other brain areas involved in the pain matrix and its potential responsiveness to cannabinoid-induced changes underscore its importance. By focusing on the ACC, the study aims to elucidate the neural pathways engaged by cannabinoids and the consequential effects on pain modulation. This approach would make it possible to gain deeper insights into the neurobiological mechanisms underlying the analgesic effects of cannabinoids, potentially leading to more targeted therapies for chronic pain management. Importantly though, this mechanistic study should be a far more methodologically robust design compared to a standard pain RCT, as it is more likely to give the necessary information to inform a potential phase 3 study.

MRX1 (a CBD solution) has not been subject to clinical studies in humans yet. However, it contains the same active ingredient at the same concentration and route of administration as the marketed product Epidyolex®, which is authorised as a prescription medicine for use in treating selected forms of epilepsy in the UK, Europe and USA. As such, the non-clinical and clinical data gathered for Epidyolex® (in addition to other products containing CBD) is being used to support the safety and efficacy assessment of MRX1. We have been advised by MHRA that due to the aforementioned, they deemed that this study would be Phase 2.

For the past year the CI has had clinical experience of using Epidyolex in the clinic for selected patients with intractable, severe CIPN resulting in a serious impact on well-being and quality of life. Permission to prescribe Epidyolex for CIPN pain had been requested through the Special Request mechanism for non-formulary drugs available in Oncology.

This positive experience has highlighted that for CIPN, a dose of 0.5mg CBD/kg b.i.d., can give effective analgesia. On this basis we chose this low starting dose and have allowed escalation to 50% of the recommended target maintenance dose of Epidyolex in epilepsy.

The keystone of neuropathic pain treatment is either anticonvulsants or antidepressants which are called adjuvant analgesics as they clearly have a primary indication other than pain, ie epilepsy or depression. Local and International guidelines demonstrate that these drugs are commonly prescribed in doses which are usually lower than those used in their primary indication so the approach with Epidyolex suggested dosing as applied to MRX1 is in keeping with current practice with other adjuvant analgesics.

The proposed initial dose of MRX1 is 0.5 mg CBD/kg bw b.i.d (20% of the recommended starting dose of Epidyolex®) escalating to 6.25 mg CBD/kg bw b.i.d (half the recommended target maintenance dose of Epidyolex®) if patients have ongoing pain and no side effects as discussed in section 7.3 of the IB.

2 STUDY OBJECTIVES & ENDPOINTS

Building on preclinical evidence, clinical experience, and knowledge of the challenges in analgesic studies, particularly the placebo response, we will conduct a clinical efficacy and mechanistic phase 2, double-blind, placebo-controlled, randomised cross-over trial of oral Cannabis Based Plant Medicine (CBPM) using a CBD solution (MRX1) in patients with chronic CIPN pain.

2.1 PRIMARY OBJECTIVES AND ENDPOINTS

The two independent objectives are to evaluate the clinical efficacy and mechanism of action of 5 weeks of a CBD solution (MRX1) in patients with chronic CIPN pain. Primary and secondary objectives and corresponding outcome measures are described in Table 2.2.1.

2.1.1 Objectives and Endpoints

Objectives	Endpoint Measure
Primary Objective*	
Clinical: To determine if the oral administration of a CBD solution (MRX1) for 5 weeks provides effective analgesia for CIPN	EORTC CIPN20 sensory scale at end of week 5 and end of week 12
Mechanistic: To determine whether there are pre/post-treatment changes in key pain brain regions, focusing on Anterior Cingulate Cortex (ACC) connectivity in those receiving active treatment during resting state MRI (rsfMRI), and whether these are associated with changes in clinical pain/well-being scores.	rsfMRI connectivity of the ACC at baseline and end of week 5. ACC changes between baseline and 5 weeks in relation to pain (CIPN 20 and BPI sf) and mood (GAD7 and PHQ9) scores.
**The mechanistic analyses are not required to demonstrate clinical benefit and therefore it is not considered a co-primary endpoint.*	
Secondary Objectives	
Clinical	
To determine whether 5 weeks of a CBD solution (MRX1) affects	
Side effects	Reported Adverse Events and side effects
Neuropathy severity	Total EORTC CIPN 20 scores and EORTC QLQc30 scores at week 5 and 12
CIPN pain severity using traditional pain assessment	BPI SF at week 5 and 12
Mood	GAD7 and PHQ9 total scores at week 5 and 12
Cognition	FACT-CogV3 total score at week 5 and 12
Sleep	Pittsburgh Sleep Questionnaire at week 5 and 12
Quality of life	EORTC QLQc30 at week 5 and 12

Recommended exam for CIPN to allow an objective assessment of neuropathy	QST at week 5 and 12
Patient Global Impression of Change (PGIC)	Standardised questions within end of weeks 5 and 12
Health economic	
Health Economics evaluation to assess potential impact of CBD treatment on health care costs and carer costs	EQ5D 5L and Health Care Utilisation at week 5, 8 and 12.
To understand the feasibility of measuring the cost-effectiveness of the IMP and the potential for market viability.	Modelled cost per QALY at week 5, 8 and 12
Mechanistic	
Whether wider brain changes inferring neuroinflammation accompany 5 weeks of CBD treatment;	Wider rsfMRI network architecture beyond the ACC, and white matter microstructural integrity/magnetic resonance spectroscopy at week 5
Relationship of CBD response to patients own endocannabinoid system from baseline to end of study	eCB levels measured from blood samples (as potential effect modifier) at baseline, 5, 8 and 12
Relationship of CBD response to inflammatory markers from baseline to end of study	Inflammatory markers measured from blood samples in Section 7.5 at week 5 and week 12 (as potential effect modifier)
Exploratory	
To explore period-dependent fluctuations in clinical outcomes	Clinical outcomes (EORTC CIPN20, EORTC QLQ-C30, PHQ9, GAD7, and BPI SF) incorporating data from baseline, week 5, 8 and 12
To explore temporal fluctuations in pain, sleep, mood, function and general well-being	Data collected from participant diary during 1-week pre randomisation, week 5 and week 12

By pursuing these secondary objectives, the study not only seeks to validate the efficacy of CBD in treating CIPN but also aims to unravel the complex interactions between CBD, biological systems, and neural mechanisms that underpin its therapeutic effects. This comprehensive approach will greatly enhance the understanding of cannabinoid pharmacology and its potential utility in clinical settings. Crucially it will inform any future Phase 3 study.

3 STUDY DESIGN

3.1 TYPE OF STUDY

A clinical efficacy and mechanistic phase 2 RCT, of MRX1 versus matched placebo oral solution, using a randomised, double-blind, placebo-controlled, cross-over design. Participants will be randomised to one of two treatment sequences (placebo, IMP or IMP, placebo). Participants will receive each of the treatment sequences in a period lasting 5 weeks (10 weeks in total for both), separated by a wash-out period of 2 weeks (no study drug medication), meaning that it takes 12 weeks for each patient to get through the 2 treatment sequences. During each sequence the patient will follow a pre-determined dosing regimen, with the possibility of escalating the dose after clinical assessment each 6-8 days. The assessment is either phone or face to face to coincide with collecting more IMP

from pharmacy. The decision by the clinician to escalate dose, remain on a stable dose, reduce dose or even stop IMP depends on clinical assessment of wanted effects (pain relief) versus unwanted effects (side effects). The decision will be made in conversation with the patient during the consult each week. Participants will not take any study medication during the 2-week washout period. Trial assessments will include structured validated questionnaires to assess CIPN and associated symptom clusters and QoL, as well as 6 blood samples in total for cytokines and endocannabinoid levels along with 2 MRI scans for mechanistic endpoints. We will only do the MRI scans in the first treatment sequence-at baseline and at end of week 5, to minimise what we ask of patients. Should there be any incidental findings from the fMRI, the patient will be discussed and referred to the relevant speciality as appropriate.

The trial will last for 30 months from the project start to the final report. This includes 12 months for set-up, 12 months for recruitment, 4 months to complete study intervention and follow-up for all patients, and 5 months for close-down and reporting.

3.2 JUSTIFICATION OF CROSS-OVER DESIGN AND STRATEGIES TO MAXIMISE RETENTION

The participants recruited will have stable chemotherapy-induced peripheral neuropathy. This will be verified by clinical history and stable EORTC CIPN20 score on 2 separate occasions approximately 2 weeks apart. Analgesic trials often fail and are susceptible to both false negative and false positive results. The placebo response is particularly problematic. This is particularly true at pre confirmatory trial phases. Therefore, we have drawn on the IMMPACT recommendations for proof-of-concept studies of analgesia and extrapolated recommended best practices to this phase 2 study.[37] We have chosen a cross-over design with robust research team training to minimise the placebo response. A cross-over design is suitable for a CIPN study, as each participant may have different neuropathy features, just as with any neuropathic pain study, but the response to active and placebo treatments will be compared directly within that participant hence eliminating the between-subject variability that is present in a parallel-group study. In this study, other criteria for a cross-over trial are also fulfilled: we are proposing a treatment which will only temporarily decrease or eliminate symptoms and know from previous work and our clinical experience that CBD effects will stop immediately or within days of stopping treatment. In addition, to earlier CIPN cohort work and the recently completed MINT trial (NCT04276727, currently in analysis), we do not expect a "Period effect" within the timescale of the trial. The potential carryover effects will be prevented by using a wash-out period of 2 weeks. From existing pharmacokinetic knowledge, this is sufficient for pain to return to baseline.

An Epidyolex phase 1 study: supports choice of 2 weeks.[50]

At the lower dose of 750mg IMP twice daily in the multiple dosing part of the study, after dosing for 7 days and steady state demonstrated, T1/2 was 56.4 hours, so 2 weeks is approx. 6 half-lives. This is a high dose example, but there aren't many multiple dosing studies published, and we would expect it to be more than 6 half- lives with the lower doses used in this study.

The above multiple dose was fasted, there was also a food effect arm. Though exposure increased significantly with food, no effect was found on half-life.

One problem in cross-over trials is that participant expectations for the second period after the cross-over may be influenced by how they believe they have responded to the treatment in the first period,[51,52] and, in turn, their reported pain levels in the second period may be influenced by their expectations based on the first period.[53] At the start of the study, participants will know that they will receive two treatments during the 12-week study period, one the active CBD and the other a placebo which looks, smells and tastes the same. They will know that neither they nor ourselves know the order of these treatments.[54] We will train both research team and patients carefully in both methods of assessing pain and with staff communicating with the patient, to minimise placebo effect. This strategy of training participants on how to report pain and training staff in how to

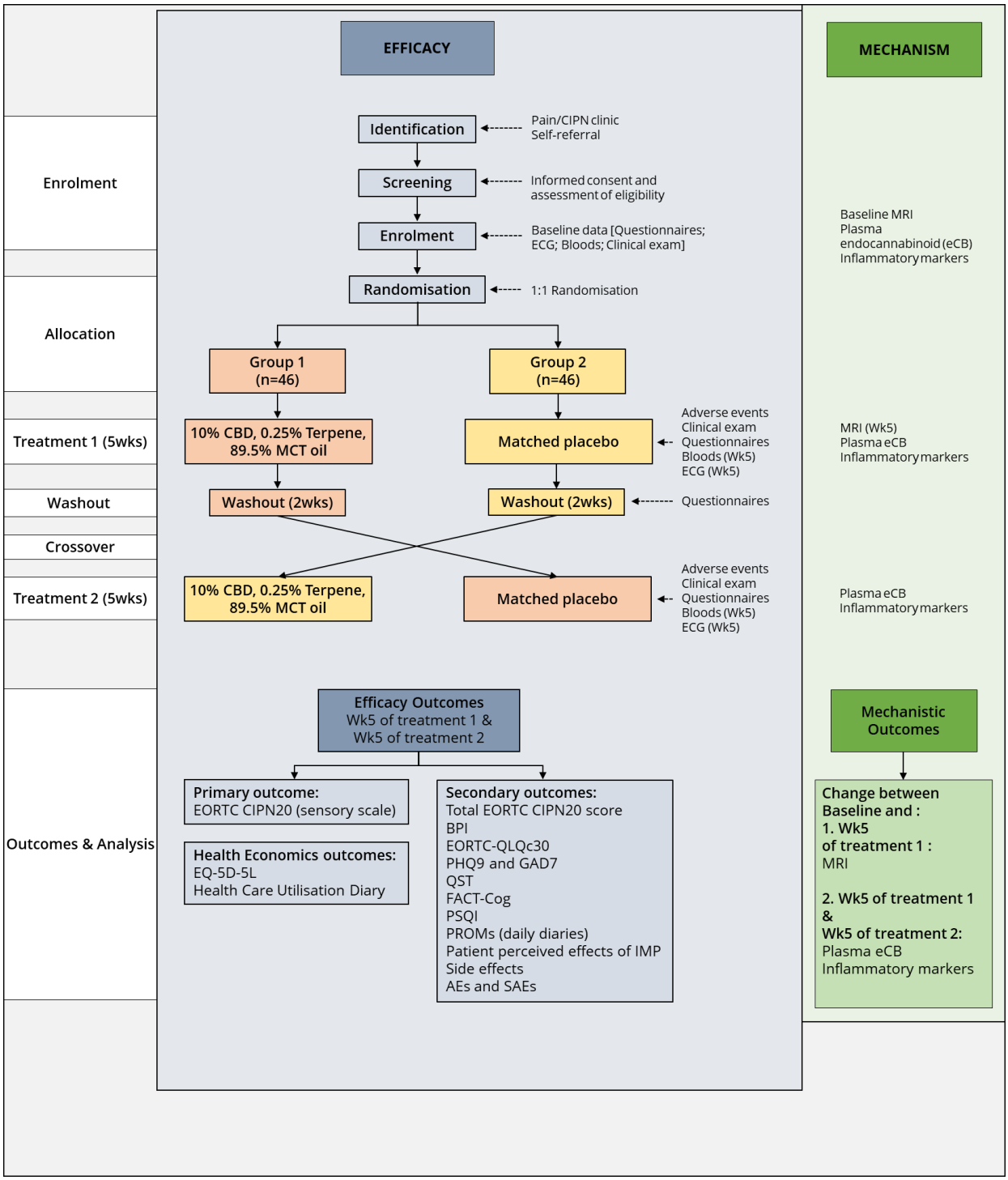
communicate with patients during a study and do assessments are consistent with the IMMPACT recommendation to blind patients and investigators to as much methodological information as possible about the clinical trials in which they participate[55]. Neuropathic pain studies are particularly susceptible to large placebo responses. The strategies outlined above may allow the participant to be more objective about pain reports than in a parallel group study where there is often the hope that allocation has been to the active arm. A meta-analysis of neuropathic pain trials found that cross-over trials had the further advantage of significantly lower placebo group response rates than parallel-group trials and this was associated with a statistically significant treatment benefit.[56]

Furthermore, the cross-over design can enhance the statistical power of the study by effectively increasing the sample size, as each participant serves as their own control. This design not only improves the efficiency of the study by requiring fewer participants to achieve the same statistical power but also reduces variability between treatment conditions. It allows for the direct comparison of treatment effects within the same individual, thus controlling for inter-participant variability that might otherwise obscure genuine treatment effects. This aspect is particularly advantageous in studying conditions like neuropathic pain, where subjective experiences of pain can vary widely between individuals due to genetic, psychological, and environmental factors. Implementing a cross-over design, therefore, helps to mitigate these variables, providing a clearer picture of the treatment's efficacy and enhancing the overall robustness of the study findings.

To minimise study outcome bias, we will have team members who communicate with patients during the study and discuss and agree on IMP titration, assess and report adverse effects and be available for the study patients. In addition, where possible, separate team members, who have no role in the day-to-day assessment and communication with the study patients, will perform the EORTC CIPN20 outcome assessments at weeks 5 and 12. Appropriate training of research staff will be provided.

Retention in the study should be facilitated by an easy to access and responsive research team. We know from previous embedded qualitative work in RCTs conducted by our team, that these features were highly valued and encouraged continuing participation (Middlemas).

3.3 STUDY FLOW DIAGRAM



4 STUDY POPULATION

Patients who have received neurotoxic chemotherapy and as a result have chemotherapy induced peripheral neuropathy. This has to have been present for at least 3 months duration and has to have been stable in severity for at least the last 6 weeks.

4.1 NUMBER OF PARTICIPANTS

The aim is to randomise 92 participants with stable CIPN over a period of 12 months. To achieve this, we will replace failed screening with new patients until 92 are enrolled. Participants will be enrolled in the trial for 14weeks. We have assumed MRI completion in 76 participants based on our previous analgesic RCTs with MRI as an assessment.

4.2 INCLUSION CRITERIA

1. 18 years or over
2. At least 3 months post neurotoxic chemotherapy
3. Stable CIPN over at least 6 weeks
4. EORTC CIPN20 sensory scale > 10
5. 0-10 VAS (Visual Analogue Scale) PAIN ≥ 3
6. Willing and able to give written consent
7. Willing not to take additional cannabinoids during the trial period
8. Willing to use effective contraception throughout the trial (A woman is considered of childbearing potential (WOCBP), i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. See below for accepted effective contraception[1].
9. Willing to continue effective contraception for 30 days after completion of trial for woman participants and for 90 days for male participants
10. No contraindications to MRI scan

[1]Methods considered to be effective contraceptives:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner (provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success)
- Sexual abstinence, defined as refraining from heterosexual intercourse during the entire trial period and for 90 days post study completion. The reliability of sexual abstinence will be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception

- Male subjects, if heterosexually active with a female partner of childbearing potential, must agree to use barrier contraception (male condom).

4.3 EXCLUSION CRITERIA

1. Patients who have had any changes to analgesia in last 30 days

2. Patients who have had any intervention which may result in a change to CIPN during the course of the study[2]

3. Patients currently taking any of the following medication; opioids, erythromycin, clarithromycin, fluconazole, itraconazole, sulfamethoxazole, clopidogrel, rifampicin, warfarin, selected antiepileptic agents (including phenytoin, carbamazepine, sodium valproate) clobazam, stiripentol, Everolimus[3]

4. Patients currently taking any antidepressants and anticonvulsants if used as adjuvant analgesics

5. Routine use of cannabis products for medicinal or recreational purposes (at any time in the last 4 weeks) or of any illicit drug precludes inclusion in the study (CBD at Baseline)[4]

6. Patients with severe pain due to CIPN on VAS;>8/10

7. Female patients who are not post-menopausal and not using highly effective contraception (as detailed at end of this section)

8. Male patients who are not using highly effective contraception with female partner (as detailed at the end of this section)

9. Patients who are pregnant or breastfeeding

10. Chronic alcohol use

11. Any liver disease with abnormal bilirubin, AST or ALT: History of severe liver disease (Alanine transaminase (ALT) and/or aspartate aminotransferase (AST) more than 3-times the upper limit of normal (ULN)) and bilirubin greater than 2 times the ULN OR moderate to severe hepatic impairment (Child–Pugh class B or C).

12. Current or recent (≤12 months) substance use disorder or misuse of prescription medicines; positive drugs of abuse (DoA) screen when performed at investigator's discretion.

13. Patients with hypersensitivity to any of constituents of IMP in the IB

14. Any hospital admission for mental ill health in last 5 years

15. Suicidal thoughts or severe depression within the past year

16. Any live vaccines within 14 days before study entry

[2]Any treatment, oncological or non-oncological, which could change CIPN during the course of the study (including changes to hormone treatment in the 30 days prior to recruitment, patients who start neurotoxic chemotherapy during the study, patients who start any drug which can cause CIPN during the study). These are the most likely scenarios in our patient group which we are therefore giving as examples but this is not an exhaustive list.

[3] All concomitant medication will be reviewed as part of the screening process. Relevant Cannabidiol–Psychoactive Drug Interactions, as listed in Appendix 1, will be considered.

[4]Urine samples will be collected at baseline and week 8 (pre-dose) and analysed via a dipstick at time of collection. We can detect any THC taken in the previous 35-40 days with the dipstick which means in practical terms we will capture any illicit THC use. This is to measure any cannabis/cannabinoid use out with the IMP. If the test results are positive for THC the participant will be withdrawn.

4.4 CO-ENROLMENT

Co-enrolment will only be considered if patients are in observational studies or other non-interventional non-CTIMP studies (not related to pain), with formal documentation and authorization from the Sponsor as per ACCORD POL008. This will be assessed and decided on by a case-to-case approach. If a patient is co-enrolled in two studies, the individual study managers will be responsible for managing relevant study data. Records for both studies will be forwarded to GPs. Each individual study PI will need to coordinate this. Co-enrolment will only be permitted if this does not pose any significant additional burden upon participants, their families or research staff.

4.5 JUSTIFICATION FOR INCLUSION OF VULNERABLE POPULATIONS

Not applicable to this trial.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

We have 1000 patients yearly receiving neurotoxic chemotherapy in Lothian (20% West Lothian, St John's Hospital). Therefore, at least 500 patients will meet the criteria for chronic CIPN. In addition to this, there will be a pool of patients treated in previous years who continue to have chronic CIPN. This will add at least 300 patients. Minimum total pool in 12 months is 800 patients.

Oncology colleagues will refer patients to our Pain and CIPN clinics in the Edinburgh Cancer Centre and St John's Hospital, West Lothian. This clinical care is established irrespective of clinical research, so also forms part of the direct clinical care team. The usual care teams will be either our own CIPN clinics team or the oncology teams. If appropriate, patients will be approached by the usual care team about the study and given a Patient Information Sheet (PIS). Interested potentially eligible patients will then attend our research clinics held at the Edinburgh Cancer Centre where further discussion, consent and formal assessment of eligibility for the trial can take place. As this is a mechanistic study and funded as such, all patients will be asked to have MRI as part of the study. We will start recruitment to this mechanistic study including those participants who are willing and do not have a contraindication to MRI until 76 participants have been recruited. Thereafter as we will have our desired MRI sample size, we will recruit to the study without doing any further MRI scans until the target of 92 participants is reached. The no contraindication to MRI inclusion criteria will remain to ensure the same participant population is recruited throughout.

Approved study posters may be displayed to both staff and patients with information about the study and how to get in contact with the local site research team.

5.2 CONSENTING PARTICIPANTS

Potential participants identified at the Pain and CIPN clinics in the Edinburgh Cancer Centre and St John's Hospital, West Lothian, will be invited by a member of their usual care team to attend the research clinic held at the Edinburgh Cancer Centre. Consent will be taken by the Principal Investigator (PI) (or member of the research team delegated by the PI on the delegation log) and will ensure that written informed consent is obtained from each participant prior to entry into the study

and completing any study specific procedures. Patients will be given verbal and written information and sufficient time (minimum of 24 hours) to review the information and to ask questions and have them answered before providing written informed consent.

After recruitment of 76 participants, the research team will manually score through the relevant consent box for MRI and write 'not applicable' alongside before the participants' screening and consent visit. The research team will explain to the patient why MRI does not apply.

As a clinical trial of an investigational medicine product (CTIMP), the process of obtaining consent for inclusion in the trial will follow the process set out in the relevant sections of Good Clinical Practice (GCP) compliance. The PI (or delegate) taking informed consent will be GCP trained, suitably qualified and experienced. The research team will have specific training in how to describe the study to patients with the aim of minimising bias towards the IMP and also in clarity in relation to cross-over and the wash out period.

5.3 SCREENING FOR ELIGIBILITY

Participant eligibility will be verified by a clinical trial physician after written informed consent has been obtained. Screening logs will be kept for all patients screened, recording which eligibility criteria have not been met and any other reasons for not going into the study.

Pre-randomisation assessments of EORTC CIPN20, VAS, pregnancy status (where applicable) and CBD will be documented to confirm eligibility. As stated above, patients who fail to be randomised will be replaced in the study, until 92 patients are recruited.

Confirmation of eligibility will be recorded within the participants' medical records and in the Case Report Form (CRF).

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

All ineligible and non-recruited participants who are considered for entry into the study will be recorded on the screening log and the reason given for being ineligible and/or not recruited e.g. patient decision, clinician decision, inclusion and/or exclusion criteria prohibited entry.

Ineligible patients, and those who decline to participate will be offered best available care within the Pain and CIPN clinic.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

After assessment for eligibility and written informed consent, a member of the research team will perform the randomisation using a web-based randomisation service managed by the Edinburgh Clinical Trials Unit (ECTU). Participants will be randomised 1:1 to one of two treatment sequences (placebo, IMP or IMP, placebo) using random permuted blocks. The trial Pharmacy team will be blinded and will be notified of the randomisation sequence via an email generated by the web-based randomisation service or sent by the research team. Pharmacy, on receipt of a signed prescription by an appropriate clinician on the delegation log, will dispense the IMP or placebo to the local research nurse. In line with local pharmacy policy, proof of identify will be required from the research team member every time they collect IMP from pharmacy.

For patients who also having an MRI scan, the Postdoctoral Research Assistant (PDRA) overseeing the MRI scans will meet patients at the baseline visit and explain the scanning procedure in detail. The MRI scan will be completed after randomisation on the same day as the Day 1 visit, so that IMP

can be collected on the same day. Randomisation, after a phone call to obtain an EORTC-CIPN20 sensory pain score, will take place within 8-10 days of the consent and baseline visit.

5.5.2 Treatment Allocation

The IMP/placebo will be provided to participants by a member of the research team following randomisation. Another face-to-face assessment will occur at week 3 and at the end of week 5 where a repeat MRI scan is completed. Participants will not take any study medication during the 2-week wash-out period. Following this wash-out period of 2 weeks, the participant moves into period 2 of the study and is provided with the corresponding IMP/placebo during a face-to-face assessment at start of week 8. A face-to-face assessment will occur at week 10 when the participant will be provided with their final 2-week supply of IMP/placebo.

Individual dose titration can occur every 6-8 (usually every 7) days until and including the start of week 5, if there is uncontrolled pain but no side effects to the IMP/placebo. If at any time pain increases or side effects occur, IMP/placebo dose can be titrated back to last acceptable dose and participant will be informed to contact the study team immediately in these situations.

All participants will receive written information about dosing of the IMP as risk management, but it is during the weekly face to face or phone call that an assessment is made together with the patient of the appropriateness of escalating dose or even reducing, staying the same or stopping dosing.

The oral solution has a fixed concentration and participants will be given written information about the number of mls to be taken at baseline and that this should not be increased until after the weekly phone call with the research team. To avoid confusion, all communication, written and verbal with participants will refer to dose in mls (see titration schedule in Section 6.4).

At the baseline assessment the research team will demonstrate the use of the syringe provided using a placebo oral solution and how to measure the dose prescribed each week.

The treatment will be provided in bottles containing 100mg/ml of IMP or matched placebo. The bottle is supplied fitted with syringe adapter and supplied with 5 ml and 1ml graduated amber dosing syringes.

5.5.3 Emergency Unblinding Procedures

The Research Team will remain blinded to treatment allocation at all times, apart from the case of agreed unblinding for patient safety and care purposes.

The blinding code will only be broken in emergency situations for reasons of patient safety, where knowledge of the treatment administered is necessary for the treatment of a serious adverse event or when required by local regulatory authorities. If a participant's randomisation code is broken, they will cease treatment with the study drug but will continue to be followed up.

The Investigator will document the reason for breaking the blind in the participant's medical records and in the Investigator Site File. The main usual caring clinician will be notified of the need to unblind directly by the CI or designate along with any subsequent action/s. If possible, participants, investigators, nurses and other attending clinicians will remain blind to the trial drug allocation for the duration of the treatment phase and will not have access to the trial number-treatment allocation code for the duration of the interventional phase of the trial.

A member of the research team will have the ability to unblind via the database. Unblinding (emergency or otherwise) can be carried out by using dedicated contact details. The above procedure will be used to unblind by the Sponsor for the submission of a SUSAR report to the

regulatory agencies. The Trial Team will update records to indicate the Sponsor has requested the unblinding due to a SUSAR.

Participants will be given an emergency contact card to carry while participating in the trial which will contain a number for the local research team who will be available during office hours. An alert will also be on any medical records with details of the trial and the research teams contact details.

5.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case record form if possible. The participant will have the option of withdrawal from:

(i) study medication with continued study procedures and collection of clinical and safety data;

(ii) all aspects of the trial but continued use of data collected up to that point. To safeguard rights, the minimum personally-identifiable information possible will be collected.

(iii) all aspects of the trial including data collected up to that point where it is possible to delete this data e.g. this data will not be used in the final data analysis. To safeguard rights, the minimum personally identifiable information possible will be retained e.g. consent form.

Randomised patients who wish to be withdrawn from the study before they have undertaken any study related procedures will be withdrawn from the study and another participant will be recruited to replace them. There will be no other replacements for participant withdrawals. Data on the original participant will be kept on the CRF/database if the participant agrees to this.

5.7 TREATMENT DISCONTINUATION – STOPPING CRITERIA

Study drug will be discontinued for an individual participant if any of the following occur in the participant:

- Pregnancy;
- SAE considered related (possibly, probably or definitely) to study drug
- AE of CTCAE Grade ≥3 and considered related (possibly, probably or definitely) to study drug
- Anticipated side effect which is severe
- Any suicidal ideation (see details of assessment and actions below)**
- AST or ALT ≥3 x ULN in the presence of bilirubin ≥ 2 x ULN (participant outcomes will be followed up until levels are back to a non-clinically significant level);
- Prolongation of QTc: >450 ms (male), >470ms (female)
- Patient request to stop
- Patient needs a medication which is contra indicated with MRX1
- Significant weight changes-increase or decrease by 5% of body weight which can only be explained by IMP e.g., not due to significant increase in mobility

Participants who stop treatment for any of the above-mentioned reasons will continue to be followed up until the end of the current treatment period, unless they specifically ask, or is recommended by the investigator based on participant clinical status, to be withdrawn from all aspects of the trial. If clinically appropriate they will be asked if they might be willing to complete questionnaires as planned. If the opinion of the PI is that this is too burdensome, a compromise of completing the endpoint questionnaires alone might be appropriate. Another member of our wider

research team would facilitate collection of these data in these patients to minimise bias in the regular ACTION research team.

** We are using the PHQ-9 at regular timepoints in the study. It gets scored into 5 groups (https://www.mdcalc.com/calc/1725/phq9-patient-health-questionnaire9) :
0-4: no issue
5-9: mild, watch and wait and repeat at next planned time point
10-14: moderate depression - trial nurse to check in, ensure existing action plan (counselling, follow-up, and/or pharmacotherapy) and if not PI refer to GP
15-19 moderate to severe: PI / delegated clinician review and inform GP as should be considered for pharmacotherapy
20+ severe depression: PI / delegated clinician review and inform GP every phone call or email that day.
Within the PHQ-9 there is a specific question about suicidal ideation - A score of 2 or more should be an in person clinical review that day and score of 1 should be phone call that day and in person review if assessed as necessary.

No specific threshold of the overall score should trigger stopping medication but worsening scores in the moderate-severe range with suicidal idea should prompt an urgent review and will likely result in stopping medication (as discussed with Professor Andrew McIntosh, Professor of Psychiatry, University of Edinburgh, with particular interest in symptom science).

This process will be documented in advance in the Safety Management Plan. Additional internal or external experts may be consulted by the Sponsor, as necessary.

6 INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

6.1.1 Study Drug Identification

The IMP (MRX1 oral solution) is an oral solution containing 100 mg/ml of cannabidiol (CBD) as an active pharmaceutical ingredient (API) dissolved in medium chain triglycerides (MCT) with a proprietary flavouring. It is classified as a Schedule 2 controlled drug, in line with the Misuse of Drugs Regulations. For the purposes of cannabis-based IMP prescribing there is no requirement to be on the specialist register as there is for prescribing cannabis-based medicines.

It is presented in a 30 ml amber glass bottle, fitted with a push in bottle adaptor and sealed with a tamper-evident, child-resistant cap. The bottle is supplied with a 5ml and 1ml graduated dosing syringe.

The formulation is 10% CBD isolate, 0.25% flavouring and 89.75% Medium-Chain Triglycerides (MCT) oil (see Table 1).

The proposed initial dose of MRX1 is 0.5 mg CBD/kg bw administered twice daily (b.i.d) for 7 days (20% of the recommended starting dose of Epidyolex®) escalating to 6.25 mg CBD/kg bw b.i.d (half the recommended target maintenance dose of Epidyolex®) if patients have ongoing pain and no side effects. This is the estimated therapeutic dose.

Titration will be based on individual responses to IMP. The dose will be increased every 7 (6-8) days as per study regimen, if there is ongoing pain and no side effects (detailed in section 6.2).

Downward titration is permitted if either, pain increases (paradoxical effect due to Bell shaped dose response curve) or side effects emerge, after an increase in dose.

Table 1 - Qualitative and quantitative composition of MRX1

Component	Reference to standards	Function	Quantity		
			mg/mL	%w/w	per bottle
Cannabidiol	B.P. / Ph. Eur. (3151)	Active ingredient	100.0	10.48	3.000 g
MRX1 flavouring	In-house	Flavouring	2.500	0.2620	86.90 µl
Medium-chain Triglycerides	B.P. / Ph. Eur. (0868)	Solvent	851.7	89.26	26.96 ml
		TOTAL	**954.2**	**100.0**	**30.00 ml**

6.1.2 Study Drug Manufacturer

The trial drug is manufactured (under contract with MRX Medical Limited who are the supplier of the trial drug) by:
SGS Quay Pharma,
QUAY House, 28 Parkway,
Deeside Industrial Park,
Deeside,
CH5 2NS,
UK

6.1.3 Marketing Authorisation Holder

Development and GMP manufacture and QP release:
SGS Quay Pharma,
QUAY House, 28 Parkway,
Deeside Industrial Park,
Deeside,
CH5 2NS,
UK

6.1.4 Labelling and Packaging

SGS Quay Pharmaceutical Limited will be responsible for the packaging and labelling of the trial drug. Each bottle will contain 30mls of IMP.
Medication labels will be in English and comply with the legal requirements of Annex 13 of the European Union's Good Manufacturing Practice (GMP) and subsequent UK amendments. They will include storage conditions for the drug, but no information about the participant.

6.1.5 Storage

The bottles will be transported to the Western General Hospital from SGS Quay Pharma, Deeside. The trial drug will be stored in sealed bottles at room temperature (permitted range 15-25°C) in the pharmacy within the Western General Hospital, within a specific IMP storage area compliant with regulatory requirements for storage of schedule 2 controlled drugs. Storage temperature will be monitored. It will be dispensed to a member of the research team and an accountability log maintained. If the research team member is bringing the trial drug to the patient in RIE, to be given

after the scan, he/she will follow NHSL policy. In the rare event that the IMP is not collected by the participant at their scan visit, the IMP will be returned, following NHSL policy, to the clinical trials pharmacy from which it was dispensed and stored accordingly.

Storage temperatures will be recorded by monitoring on a min-max thermometer or a continuous temperature monitoring device. In the event of an excursion above 25°C or below 15°C then the stock will be quarantined as soon as an excursion is identified until it can be established whether it is fit for use by the Co-Sponsor according to GS010. The Trial Manager should be notified about any excursions.

6.1.6 Regulatory Release to Site

The regulatory green light checklist will be signed off by the Sponsor or Trial Management team, once required approvals are in place.

6.1.7 Destruction of Trial Drug

Opened bottles of the trial drug will be destroyed at the end of the trial or before with permission of the Sponsor, after reconciliation with the database and accountability logs by a member of the pharmacy team. In addition to this, unused bottles of the trial drug must be destroyed by a member of the pharmacy's controlled drugs team. Evidence of destruction will be kept in the pharmacy site file.

6.1.8 Summary of Product Characteristics (SPC) Booklet or Investigators Brochure

The MRX1 Investigator's Brochure (IB) will be used to assess relatedness of any side-effects to the treatment.

6.2 PLACEBO

The formulation is 0.25% flavouring and 99.75% MCT oil. CBD is tasteless so the placebo looks, tastes and smells exactly as the active IMP.

6.2.1 Labelling and Packaging

As for active study drug, the placebo will be packaged and labelled according to CTA approval by;

SGS Quay Pharma,
QUAY House, 28 Parkway,
Deeside Industrial Park,
Deeside,
CH5 2NS,
UK

Medication labels will be in the local language and comply with the legal requirements of Annex 13 of the European Union's Good Manufacturing Practice (GMP). They will include storage conditions for the drug, but no information about the patient.

6.2.2 Storage

As for active study drug.

6.3 DOSING REGIMEN

The starting dose will be oral solution 0.5 mg/kg b.i.d, administered morning and evening and taken with food.

The dose will be increased as described below if there is ongoing pain and tolerable or no side effects (e.g., drowsiness or nausea, diarrhoea).
A maximum dose of 6.25 mg/kg b.i.d will be allowed.
Trial drug will be dispensed at start of week 1, week 3, week 8 and week 10.
The placebo will have identical dose regime.
The IMP has an in-use period of only 7 days after first opening.
If any IMP is taken after the 7 days, this will be noted but not reported as a non-compliance or safety event. There is a low risk of microbial contamination as the product is non-aqueous and not supportive of microbial proliferation. The risk to the participant is low if they do take the IMP after 7 days. A reminder will be placed on the bottle, on participant diary and on the drug escalation instructions to mitigate against this happening.

6.4 DOSE CHANGES

Dose Escalation
For the first five weeks there will be the option for dose-escalation every 6-8 days if the participant has ongoing pain and no side effects as described in section 11.4.3 below. This process will be repeated after the 2-week washout for the second 5-week study period after cross-over.
This regimen is evidenced from the Epidyolex (Licenced CBD) regimen, with a slightly more conservative starting dose (0.5 vs 0.6 mg/kg/b.i.d in Epidyolex SPC).
10mg of the IMP is equivalent to 0.1ml.
To minimise risk of participant confusion, all written and verbal communication with the participant will be in mls per dose.

Week	Dose (mg/kg b.i.d)
1	0.5
2	1.5
3	3
4	4.5
5	6.25

Participants will be allowed to titrate up to a maximum of 6.25mg/kg b.i.d. Participants will not self-escalate using this regimen, but will do this with the support of the trial nurse and/or doctors on the delegation log as required. Dose changes will be discussed, decided upon and recorded in the CRF, along with clear reasons for these changes. Appropriate quantities of medication will be dispensed by the trial pharmacy on receipt of a completed pre-agreed prescription template by the CI or designee.
Titration will be based on individual responses to IMP. The dose will be increased every 6-8 days as per regimen, if there is ongoing pain and no side effects.
A maximum dose of 6.25mg CBD/kg b.i.d ie, twice daily will be allowed via four potential dose escalations.
Downward titration is permitted if either pain increases or side effects emerge after an increase in dose.
Prior to any dose escalation the CI or designee will contact the participant to discuss their general well-being, any potential side effects to IMP, level of pain (assessed by EORTC CIPN20 sensory score and VAS score) and make a clinical decision re-escalating dose as per titration regimen. If minor side effects noted which are acceptable to the participant, in the presence of ongoing pain, the dose can be changed. If moderate side effects noted the dose will be reduced to the previous titrated dose. If severe side effects are noted, IMP will be stopped and reassessed in 24 hours and as often as clinically

indicated and 1 day prior to next CTU attendance. All decisions will be carried out in consultation with the participant.
Dose decreases and periods longer than 8 days on a given dose level are allowed and clearly documented in the CRF.
If a participant experiences exacerbation or worsening of CIPN (deterioration in CIPN 20 score by more than 15%), which could potentially occur due to the biphasic response to CBD, this will be managed by downwards dose titration of CBD, and will be reported as AE or SAE as categorised.
If the participant suffers from side effects from the study drug but there is improvement in pain they may opt to, in discussion with the study team, either continue on the current dose, or reduce to the previous dose of IMP. This will be documented in the CRF along with clear reasons for actions.
The following expected mild or moderate side effects will be documented in the CRF:

- Drowsiness
- Fatigue
- Diarrhoea
- Sleep disturbance
- Increased appetite
- Decreased appetite

6.5 PARTICIPANT COMPLIANCE

Compliance is always a critical concern in clinical trials. By maintaining frequent contact with patients, at least once weekly, we aim to foster open and honest communication. It is essential for us to accurately know the intake of the IMP during the trial. We assure participants that their overall care will remain unaffected, even if their compliance with the medication regimen is less than perfect. We emphasize the importance of honesty in reporting medication intake over strict adherence to the regimen. This approach helps us maintain trust and encourages accurate data collection, which is essential for the success of the trial.
Compliance to the drug regimen will be monitored by two different methods to determine the preferred approach for future trials. These methods are:

- Self-reported; participants will be asked if they have taken the trial drug or if they have missed any doses. Any missed doses will be documented in the CRF and if a participant misses 3 or more consecutive doses or 6 doses overall, this will be recorded as a deviation.
- Participants will be asked to return unused trial drug to the research team at each visit. The pharmacy team will measure the remaining CBD oral solution and document the measurement in the CRF. Pharmacy will then dispose of the remaining solution, and record this on the destruction log, following Sponsor approval. The volume of remaining solution will be reported to the research team for input into the CRF. Failure to return IMP at more than one visit will be recorded as a deviation. In the event of a dispute in results, this method will be used to assess compliance.

If a participant fails to comply with the IMP regimen for non-medical reasons and their compliance falls below 75%, the situation will be evaluated. The first time this occurs, the possibility of withdrawing from the study will be discussed with the participant. Should non-compliance happen again, the participant will be withdrawn from treatment but still followed up for data collection. If poor compliance is caused by side effects, it will be addressed according to the established side effects management plan and the pre-agreed criteria for withdrawal. All of above scenarios will be documented in CRF

6.6 OVERDOSE

An overdose is defined as administering any amount of the study drug that exceeds the intended dose. Considering the carefully planned doses of the study drug, an overdose is deemed unlikely. However, there is a possibility of self-medicating mistakes by participants. To minimize this risk, we will do regular monitoring during clinic visits and through phone calls from the Principal Investigator or their delegate. Since MRX1 has no specific antidote, general supportive care will be administered as necessary based on medical assessments. In the event of an overdose, the Investigator will:

- Assess the patient as soon as possible after the overdose is detected or reported;
- Closely monitor the participant for any AE/SAE and laboratory abnormalities for minimum of 8 days until systemic concentrations of MRX1 are expected to or can no longer be detected;
- Document the details of the overdose in the source notes and eCRF.
- Report the overdose as a protocol deviation.

An overdose or incorrect administration of study drug does not automatically qualify as an AE, but may result in an AE. Any AEs that occur due to an overdose or incorrect use of the study drug must be recorded in the AE section of the eCRF. If such an associated AE meets the seriousness criteria, the event should be reported as an SAE.

6.7 OTHER MEDICATIONS

6.7.1 Non-Investigational Medicinal Products

Not applicable.

6.7.2 Permitted Medications

All concomitant medication will be recorded and the participant should inform the study team (during office hours) or through the emergency contact number (outside of office hours but also a member of the study team) of any new prescribed medication or over the counter medication which the participant wishes to take.

6.7.3 Prohibited Medications

Any medication or therapy that is exclusionary for eligibility at Screening, remains prohibited during the study, including:

- Non-approved concomitant medications). including any prescription and non-prescription medicines, supplements, marijuana, or vaccines within 14 days of Day -4 to-1 and throughout the study. This includes potent enzyme inducers of CYP3A4 or CYP2C1918 (US FDA, 2023), as listed in the Exclusion Criteria (Section 4.3
- Any investigational drug within 30 days or <5 half-lives, whichever is longer, prior to first dose of study drug and throughout the study.
- Any treatment, oncological or non-oncological, which could change CIPN during the course of the study (including changes to hormone treatment in the 30 days prior to recruitment, patients who start neurotoxic chemotherapy during the study, patients who start any drug which can cause CIPN during the study). These are the most likely scenarios in our patient group which we are therefore giving as examples but this is not an exhaustive list.

Note: Paracetamol (up to 4g/day) or ibuprofen (up to 1.2g/day) use is permitted but will be documented. Hormonal contraceptives are also permitted.

If prohibited therapy is required for the treatment of an AE, study drug should be discontinued and an End of Trial visit performed. Any use of concomitant medication must be recorded in the source documents and the eCRF, including the name of medication, daily dosage, route of administration, duration of use, and reason for use.

We will make it easy for participants to discuss (24-hour contact available) potential use of any new concomitant medication with the Investigator, as soon as possible, unless of course this is for an urgent clinical indication.

7 STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

Safety assessments will be completed as per the Schedule of Assessments in Table 2.
A symptom-directed physical examination includes detailed physical examination of CIPN, as covered by QST. Symptom-directed physical exam and questionnaire may also be conducted at the discretion of the Investigator at any time if considered necessary for safety.
The following QST measures will be assessed at the painful site and at a control site:
Mechanical detection threshold for touch (brush),
Mechanical detection threshold (Von Frey detection),
Von Frey pain threshold,
Mechanical pain sensitivity threshold (pin prick),
Pain summation to 5 repetitive pinprick stimuli using a neurotips needle (wind up),
Thermal detection thresholds for the perception of cold (roller cold temperature 25 degrees) and warmth (roller warm temperature 40 degrees).
All parameters will be reported as “no difference”, “increased” or “decreased” referring to the comparison between the test site and the control site.

Mental state question:
In addition to the planned mood screening with the PHQ9, the study team will have training to ask in a consistent and acceptable way if the participant has experienced any suicidal ideation since last assessment on the previous week. If the answer is yes, a pre-determined protocol (NHS Lothian) will be followed and CI informed. The CI or delegated clinician will assess the participant within the same day (within 24 hours) and a clinical decision will be made and the IMP stopped if required as per stopping criteria.

12-Lead ECG:
The Investigator will interpret the ECG tracings using the following categories: normal, abnormal NCS or abnormal CS. If abnormalities are noted on the ECG, these will be recorded in the eCRF. The ECG tracing will be checked by a trial clinician prior to first dose.
During the study, the CRU’s normal ranges for ECG parameter values will be used. Abnormal results will be indicated as CS or NCS by the Investigator.

Clinical Laboratory Tests:
Safety Tests
Blood and urine will be collected for standard clinical laboratory safety tests which will be analysed at the Oncology CRU’s local laboratory (Western General Hospital) or the local laboratory at St John’s Hospital. Screening samples will be collected in a fasted state. All other samples may be collected in a non-fasted state.

Biochemistry
Biochemistry testing will include the following and will be checked by a trial clinician prior to first dose:

- Electrolytes: sodium, potassium, chloride, calcium, anion gap, bicarbonate;

- Liver function tests: AST, ALT, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total, indirect and direct bilirubin;
- Renal function: urea, creatinine, phosphorus, uric acid;
- Metabolism: glucose, albumin, total protein, globulin, cholesterol, triglycerides;
- Potential muscle toxicity: creatine kinase;
- Inflammation: C-reactive protein and neutrophil:lymphocyte ratio;
- Calculation of estimated glomerular filtration rate (eGFR [CKD-EPI]).

Haematology

Haematology testing will include the following and will be checked by a trial clinician prior to first dose:

- Red blood cell (RBC) count;
- Red cell distribution width;
- Haematocrit;
- Haemoglobin;
- Mean cell haemoglobin;
- Mean corpuscular haemoglobin concentration;
- Mean cell volume;
- White blood cell count with differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes);
- Platelets;
- Mean platelet volume.

Coagulation

Coagulation testing will include:

- International normalised ratio (INR);
- Prothrombin time;
- Activated partial thromboplastin time (APTT).

Urinalysis
Qualitative: a dipstick test will be performed on a freshly voided urine sample including tests for proteins, glucose, blood (erythrocytes), leucocytes, ketone bodies, nitrate, bilirubin, urobilinogen, and pH.
Quantitative: any urine dipstick result of more than trace value (except pH) will trigger a quantitative analysis for all of the following parameters: protein, protein/creatinine ratio, glucose, red blood cells, white blood cells, and organism.
If available, the quantitative result will override dipstick results for decision making, e.g. for eligibility or clinical assessment.

Pregnancy and FSH Testing

Pregnancy testing required for all women of childbearing potential (WOCBP) or where there is doubt of post-menopausal status. A urine sample will be collected from all pre-menopausal women at Day 1 and week 14 for pregnancy dipstick testing. If the result is ambiguous or positive, a blood sample should be obtained to confirm the result.

Drug Screening
Urine will be collected for cannabinoid screening at baseline and week 8 (pre-dose) using a dipstick test.

In the event that repeat assessments are required for confirmation of eligibility, the results of the re-test must be made available prior to dosing.
These analyses will be performed at Western General Hospital laboratory. It is critical that the results from these safety blood tests (see stop criteria) are reviewed by the Investigator before any dosing occurs on Day 1.

7.2 STUDY ASSESSMENTS

The study Schedule of Assessments is presented in Table 2. All study assessments and procedures are as described below.

Results of routine medical tests may be provided to the participant or discussed with the participant, or if the Investigator determines they are abnormal and requires medical follow-up. The abnormal results will then be followed up as appropriate by whichever clinician in NHS Lothian has specialist knowledge in that area of abnormality, but the responsibility for this follow up lies with the PI.

Pre-screening and Consent:
A member of the study team will complete pre-screening using the patient's medical records. A screening log will be kept. If the patient is potentially eligible, their name and date of birth will be collected for the purposes of making an appointment. Identifiable data will not be recorded on the eCRF until after written informed consent has been obtained.

Screening and Baseline:
When the participant attends the study appointment, the study team will consent the participant and complete safety and screening assessments. If ineligible, or unwilling to participate, this will be documented in the screening log. A baseline assessment consisting of a physical examination and questionnaires will be completed by the clinical research team (as detailed in Table 2 Schedule of Assessments).
A thorough review of significant medical history, demographics, and relevant prior and current medications/treatments used within 30 days prior to Screening will be recorded.

All Screening evaluations must be completed and reviewed by the Investigator to confirm eligibility before Day 1. This review must be clearly documented.

The eligibility form and pre-randomisation information will be completed on the eCRF.

For the first 76 patients who are receiving MRI scans, the Postdoctoral Research Assistant (PDRA) overseeing the MRI scans will meet patients at the baseline visit and explain the scanning procedure in detail. The MRI scan will be completed prior to receiving the study drug. Randomisation after a phone call to patient will have happened at some point in the 48 hours before the scan.

The participant will be asked to complete the study questionnaires as detailed in Table 3: Questionnaire Use.

Questionnaires will be completed with the participant at each visit and responses will be entered onto the eCRF by a delegated member of the research team.

A participant diary, which can be completed either on paper or electronically, will also be provided to record daily pain scores, sleep, mood, and physical functioning for 7 days following the screening visit. If a paper version of this diary is used, the study team will review the document for completeness and enter this into the CRF.

Randomisation and provision of IMP/placebo – Day 1 (CRU Attendance):

Randomisation into period 1 of the study, after a phone call to obtain a EORTC CIPN20 pain score, will take place within 8-10 days of the baseline visit.
The IMP/placebo will be given to participants by a member of the study team.
Participants will undergo a review of any new medical history or prior medications, and assessment as per Table 2 Schedule of Assessments.
Results of all assessments performed on screening, including safety laboratory tests, must be available and reviewed by the Investigator for final confirmation of eligibility before dosing.
Eligibility or safety concerns should be discussed with the PI or designee at any point.

Phone Contact:
The nurse will phone the participant at least once a week to assess pain and side-effects, complete the appropriate questionnaires, and confirm the IMP/placebo dose. Individual dose titration will be discussed during these calls, if relevant. At the weekly contact the patient will be reminded that each bottle can only be used for one week once opened.
PI or designee will call patient 24 hours before attendances at CRU or weekly phone assessment for titration to check on well-being, side effects and appropriateness of further dose titration either increasing, decreasing, remaining the same or taking a break. A script will be prepared for pharmacy depending on the outcome of this call. The IMP/placebo can then be available for participant arriving to Oncology CTU.
At the start of week 5 and the start of week 12, the PI or designee will phone the participant to discuss and capture required data to inform dose titration for those weeks.

CRU Attendance:
A CRU visit will occur at start of week 3 and at the end of week 5 where face-to-face assessments (as detailed in Table 2 Schedule of Assessments), questionnaires (as detailed in Table 3 Questionnaire Use), the IMP is collected by the participant (week 3 only) and opened IMP bottles are returned, and a repeat MRI scan is completed (end of week 5 only).
At each face-to-face assessment, the participant's weight will be measured and recorded. If a participant has lost or gained more than 5% of their body weight at screening (automatically calculated in the eCRF), this will be reviewed by the study team. If there is a clear explanation for this level of weight loss, such as a marked improvement in physical activity (see Section 5.7), then we would not withdraw the participant but would review general well-being and follow-up weights. If the significant weight change can only be described by the IMP, the participant will be withdrawn from the IMP and be followed up clinically.

Following a wash-out period of 2 weeks, the participant moves into period 2 of the study and is provided with the corresponding IMP/placebo. The assessments (except MRI) are the same as those during period 1, with the same individual titration of IMP.
CRU visits will then occur the start of week 8 and week 10, at the end of week 12 and week 14.
A participant diary, which can be completed either on paper or electronically, will also be provided to record daily pain scores, sleep, mood, and physical functioning for 7 days during Weeks 5 and 12. If a paper version of this diary is used, the study team will review the document for completeness and enter this into the CRF.

At the end of week 5 and the end of week 12, participants will be asked a standardised question regarding their impression of change (PGIC). PGIC is a 7-point scale depicting a patient's rating of

overall improvement. Participants rate their change from start of each study period as “very much improved,” “much improved,” “minimally improved,” “no change,” “minimally worse,” “much worse,” or “very much worse.”

All participants will be reviewed 2 weeks post- stopping study IMP, in the CIPN clinic (see: Study Flow Diagram [Figure 1] and Table 2).
End of IMP Visit:

Participants may be discharged from the CRU after all end of week 12 assessments have been completed.

End of study follow up: Participants will attend a scheduled follow up appointment at the PIs CIPN outpatient clinic: 2 weeks after end of study and/or as clinically indicated by a call to the research team. This will allow collection of any side effects data and an assessment of CIPN and general well-being. EORTC CIPN 20, BPI SF, Urine Pregnancy test, safety blood samples (FBC, U&Es, LFT, thyroid function test) and questions regarding suicidal thoughts (validated PHQ questionnaire) will be collected. Post-study participants will continue to have access to ongoing, optimal clinical care without any fixed end date.

Unscheduled Visits and Assessments:

In the event of the requirement for an unscheduled visit or assessment, the following may apply;

- Review of clinical history and careful reassessment of drug history
- Vital signs assessment performed, along with appropriate general physical examination and disease specific examination
- 12-lead ECG assessment may be repeated, at the discretion of Investigator
- Repeat clinical laboratory tests may be taken for safety reasons or for technical issues with the samples.

Unscheduled visits or assessments may also be performed to assess, verify, and/or follow-up on any abnormalities or safety concerns at any time, at the discretion of the Investigator. Information from these unscheduled visits or assessments will be documented in the source documents and eCRF.

Table 2: Schedule of Assessments

	Study Period 1								Study Period 2						End of Study	
Time window	Screening /Baseline Day -10 to Day -1	Random -isation +/- 1 day	Day 1 (Wk 1) +/- 1 day	Day 8 (Wk 2) +/- 1 day	Day 15 (Wk 3) +/- 1 day	Day 22 (Wk 4) +/- 1 day	Day 29 (Wk 5) +/- 1 day	Day 35 (Wk 5) - 2 days	Day 43 (Wk 7) +/- 1 day	Day 50 (Wk 8) +/- 1 day	Day 57 (Wk 9) +/- 1 day	Day 64 (Wk 10) +/- 1 day	Day 71 (Wk 11) +/- 1 day	Day 78 (Wk 12) +/- 1 day	Day 84 (Wk 12) -1 day	Day 98[n] (Wk 14) + /- 2 days
CRU attendance	x		x		x			x		x		x			x	x[n]
Phone contact[a]		x		x		x	x		x		x		x	x		
Screening for eligibility	x															
Informed Consent	x															
Confirmation of eligibility		x														
Physical Examination[b]	x															
QST	x							x		x					x	
Baseline Assessments (Medical History, Demographics, Height[c]))	x															
Weight, BMI	x		x		x			x		x		x			x	
Clinical Blood Samples[d]	x							x							x	x
Clinical urine samples	x									x						

Pregnancy Testing[e]	x		x pre-dose													x
Urine THC test	x									x						
MRI[f]			x					x								
Vital Signs[g]	x				x			x		x		x			x	
Concomitant Medications[h]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
IMP Titration (repeat EORTC CIPN20 and VAS)[i]				x	x	x	x				x	x	x	x		
Ongoing eligibility check[j]			x pre-dose	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse Events[k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood Samples (eCB,CB, CK)[l]	x (pre-dose)				x			x		x		x			x	
12 lead ECG	x							x		x					x	
Randomisation		x														
IMP issue[m]			x		x					x		x				
Patient diary completion	x							x							x	
IMP return					x			x				x			x	

Note: In all cases, actual assessment times will be recorded in the eCRF. When scheduled at the same time point, the order of assessments will be: ECG, vital signs, laboratory assessments including safety blood and urine collection, then CBD blood collection

a) Phone calls will take place at least weekly but if the participant would prefer a face-to-face visit this will be arranged.
b) Full physical examination performed at Screening. Symptom-directed physical examination and questionnaire performed at all other time points as indicated. On Days 1 through 77+/-1, symptom-directed physical examination and questionnaire will be assessed pre-dose titration.
c) Height required at Screening only. Height and weight will be recorded in centimetres (cm) and kilograms (kg).
d) Clinical laboratory tests include haematological tests, biochemical analyses including liver function tests (LFTs), coagulation profiles and urinalysis (as detailed in Section 7.5). Safety Blood samples include FBC, U&Es, LFT, thyroid function test.
e) For women of child bearing potential. Pregnancy test will be repeated pre-dose in participants when required to re-confirm eligibility and result reviewed prior to first dose of IMP.
f) Participants taking part in the MRI scan only. MRI scan at Week 5 to be completed at Day 35 (-2 days)
g) Assessment may be repeated once per schedule time point, at the discretion of Investigator, to obtain a clinically reliable result.
h) Including check for use of analgesic, antidepressant, anticonvulsants, opioid medication
i) Participants will be administered study drug orally twice daily (b.i.d) at 12-hourly (±1 hour) intervals, commencing on the morning (AM) of Day 1 through to the morning (AM) of Day 84+/-1. On the morning (AM) of Day 84 +/-1, participants will receive their final dose of study drug (Section 5.1.1).
j) Ongoing eligibility will be assessed by monitoring for any potential IMP-related side effects. This will be facilitated by both assessments at CRU visits but also by a phone call from PI or designee at least once weekly and always up to 24 hours before day of proposed dose titration.
k) Adverse events will be reported from the time of consent/screening until the End of Study visit at Week 14. Events that occur before consent will be recorded as part of the participant's medical history.
l) Cannabinoid screen (eCB and CB) at Screening/Baseline visit and at the following time points: Days 15, 35, 50, 64, 84 (allowing for +/- 1 days at follow-ups, but patient should take last dose of IMP on the morning of day 35 and day 84 visits)
m) Participants will be administered study drug orally twice daily (b.i.d) at 12-hourly (±1 hour) intervals, commencing on the morning (AM) of Day 1 through to the morning (AM) of Day 84+/-1. On the morning (AM) of Day 84 +/-1, participants will receive their final dose of study drug and return the unused IMP on this day of assessment visit (Section 5.1.1)
n) This follow up visit will occur in the CIPN clinic.

Table 3: Questionnaire Use

Questionnaire	Screening/Baseline	Randomisation	Day 15 Week 3	Day 29 Start of Week 5	Day 35 End of Week 5	Day 43 Week 7	Day 50 Start of Week 8	Day 64 Week 10	Day 78 Start of Week 12	Day 84 End of Week 12	Day 98 Week 14
EORTC CIPN20	X	X	X	X	X		X	X	X	X	X
EORTC QLQ-C30	X				X		X			X	
Health Care Utilisation Diary	X				X		X			X	
PSQI	X				X					X	
PHQ9	X		X	X	X	X	X	X	X	X	X
GAD 7	X		X	X	X	X	X	X	X	X	X
BPI sf	X	X	X		X		X	X		X	X
VAS 0-10	X	X	X	X				X	X		
EQ-5D-5L	X				X		X			X	
FACT-Cog baseline and follow-up	X				X					X	
PGIC					X					X	

7.3 COMPLIANCE ASSESSMENTS

Participants will return all IMP and bottles will be weighed to detect remaining IMP.
Participants will give 6 blood samples during the study which will give information about safety, endocannabinoid and cytokine levels.
Face-to-face and phone IMP review will help to assess compliance and also non-compliance.
If a participant does not complete an assessment this will be recorded as a deviation with the exception of non-completion of the diary which will be recorded in the eCRF only.
If a participant does not complete their participant diary for 7 days or more, or for 3 consecutive days, this will be recorded as a deviation and withdrawal of the participant will be considered by the Investigator.

7.4 LONG TERM FOLLOW UP ASSESSMENTS

Ongoing clinical assessments will happen at the PI's CIPN clinic at day 98 as per Schedule of Assessments but also as indicated by the participant's clinical problems.

7.5 STORAGE AND ANALYSIS OF SAMPLES

All samples for ongoing cytokines and endo cannabinoid analysis will be stored at the Institute for Genetics and Cancer laboratory (University of Edinburgh) for analysis at the end of the trial. The analysis of these samples will be performed at King's College, London, in Kim Wolff's lab. Samples will be retained for 12 months post-analysis. Permission from the study team will be obtained prior to sample destruction.

Professor Kim Wolff, MBE
Professor of Analytical, Forensic and Addiction Science
Head of the Drug Control Centre (DCC)
Director of King's Forensics
Principal Fellow of the Higher Education Academy (PFHEA)
King's College London

It is only the urine screening of cannabinoids and safety bloods which are critical to the trial conduct, other samples are for use at final analysis to understand mechanisms of action of CBD.
Consent will be sought for storage until time of analysis.

Sample	Analysis	Location of Lab	Endpoint	Documentation
Research Bloods: 1 x 9ml plasma tube	Plasma endocannabinoids Cytokines: G-CSF IL-16 IL-1beta IP-10 TNF-alpha IL-1beta IL-6	Professor Kim Wolff, MBE Professor of Analytical, Forensic and Addiction Science Head of the Drug Control Centre (DCC) Director of King's Forensics	Primary: Mechanistic-endogenous levels of CBD Relationship of cytokines to response and to central neuroinflammation	Database with storage details

		Principal Fellow of the Higher Education Academy (PFHEA) King's College London		
Clinical Bloods • 2.6ml EDTA tube (haematology) • 4.9 ml Serum tube (biochemistry) • 2.7ml Plasma tube (glucose) • 2.9ml Plasma tube (coagg)	Safety Tests Blood and urine will be collected for standard clinical laboratory safety tests which will be analysed at the Oncology CRU's local laboratory (Western General Hospital). Screening samples will be collected in a fasted state if possible. All other samples may be collected in a non-fasted state. Biochemistry Biochemistry testing will include: • Electrolytes: sodium, potassium, chloride, calcium, anion gap, bicarbonate; • Liver function tests: AST, ALT, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total, indirect and direct bilirubin; • Renal function: urea, creatinine, phosphorus, uric acid; • Metabolism: glucose, albumin, total protein, globulin, cholesterol, triglycerides; • Potential muscle toxicity: creatine kinase; • Inflammation: C-reactive protein and neutrophil:lymphocyte ratio;	NHSL Laboratory Medicine, Western General Hospital	Safety endpoints	CRF

	• Calculation of estimated glomerular filtration rate (eGFR [CKD-EPI]). Haematology Haematology testing will include: • Red blood cell (RBC) count; • Red cell distribution width; • Haematocrit; • Haemoglobin; • Mean cell haemoglobin; • Mean corpuscular haemoglobin concentration; • Mean cell volume; • White blood cell count with differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes); • Platelets; • Mean platelet volume. Coagulation Coagulation testing will include: • International normalised ratio (INR); • Prothrombin time; • Activated partial thromboplastin time (APTT). If available, the quantitative result will override dipstick results for decision making, e.g. for eligibility or clinical assessment. Pregnancy A urine sample will be collected from all WOCBP at screening and week 14 for pregnancy dipstick testing. If the result is ambiguous or			

	positive, a blood sample should be obtained to confirm the result.			

8 DATA COLLECTION

Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the Sponsor-appointed monitors, auditors, Quality Assurance representatives, REC representatives, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the Sponsor immediately that this request has been made.

Study monitors appointed by the Sponsor will conduct ongoing, regular visits to the study sites to verify the eCRF data is accurate and complete according to source documents, the safety and rights of participants are being protected, and that the study is being appropriately conducted according to the protocol, other study agreements, ICH GCP and local regulatory requirements. Monitoring visits may be conducted remotely if required on some occasions. Details will be provided in a Monitoring Plan. See also Section 9.4.

After monitoring, the eCRF data will be validated by Sponsor-designated data management using a series of programmed checks and listing reviews according to relevant internal standard operating procedures. Queries will be either automatically or manually generated and added to the eCRF to be resolved promptly by authorised site personnel. After all data discrepancies are resolved, medical coding completed, serious adverse events (if any) reconciled with the CRF, and external data integrated, the database will be locked and provided to the Statistician for analysis.

Data will be retained as required by ICH GCP and local ethics requirements.

8.1 SOURCE DATA DOCUMENTATION

The source data will be a combination of oncology records, pain/CIPN clinic records and the case report form. All of these records are accessed as part of the normal background understanding of eligibility of participation but also as part of background assessment when referred to the Pain/CIPN clinic.

Source data captured directly in the eCRF will be detailed in a source data plan. Source data worksheets will be created and used to aid data entry into the eCRF.

8.2 CASE REPORT FORMS

Electronic case report forms are to be used with personal data, but the eCRF will provide data protection by design and default, including encryption of data while it is being stored (at rest) and encryption while it is being entered or transferred into the eCRF. This will be developed with ECTU and approval of the Sponsor.

8.3 TRIAL DATABASE

All consented participants will be allocated a unique trial participant number. A bespoke database hosted on the servers of University of Edinburgh will be used to record the data, entered by a member of the research team.

The data from the database will be used for analysis of the trial and will be archived for a minimum of 25 years. The archived database will be stored on the servers of University of Edinburgh requiring user authentication for access.

If participants opt to complete diaries online, they will receive a link to the database where they can register using their trial participant number, and input their answers directly on to database. Email addresses will be stored, however these will require archiving at the end of the study. If participants opt to complete paper diaries, a member of the research team will input the answers onto the database. Paper copies will be stored by the research team in a locked cabinet in a locked room with limited access.

To enable 24-hour unblinding, participant names and dates of birth will be entered onto the database and stored securely for the duration of the trial. Any data not required for analysis (e.g. participant names) will be removed from the database at the end of the trial.

8.4 STUDY DOCUMENT TRANSLATIONS

Not applicable. Family members should not be asked to translate documents if English is not their first language.

9 DATA MANAGEMENT

9.1 DATA MANAGEMENT PLAN

All aspects of data collection, data processing (entry/uploading, cleaning, and query management), and the production of the final dataset ready for analysis and/or archiving will be detailed in a separate Data Management Plan (DMP).

9.2 PERSONAL DATA

The following personal data will be collected as part of the research during the course of the trial: Name, community health index (CHI) number, email address, mobile telephone number, address, ethnic and demographic identity of a participant, diagnosis, neurotoxic treatment of a participant. These data are required for safe conduct of the study and will be stored in an NHS Lothian locked area within a secure room used only by the clinical research team. These are not shared with anyone outside of the clinical research team who are in direct contact with the patient.

CHI number, mobile telephone number and address will be stored at site only and not on the study database. Name, email address, date of birth, ethnic and demographic identity, diagnosis, and neurotoxic treatment of a participant will be held securely on the trial database. Any data not required for analysis will be removed from the database at the end of the trial.

All data will be collected, processed and stored in line with the General Data Protection Regulation (GDPR). Local paper files containing personal data will be physically stored by each site's research team in a locked office with limited access. Electronic personal data will be stored on The University of Edinburgh's secure servers that require user authentication. Computers and database access will be password-protected. Personal data will be stored for a minimum of one year following the end of the trial.

The data will meet the 'data protection by design and default' principles of the UK GDPR legislation at every stage of the Data Information Flow.

De-identified data will be shared with approved researchers and research projects post data analysis via the Edinburgh Clinical Trials Unit Data Sharing Committee.

9.3 DATA INFORMATION FLOW

Only personal data will be clinical source data required for the safe and meaningful conduct of the study, including chemotherapy received, diagnosis, other treatments. This will then be stored on a database and anonymised.

The consent form and the ID log will be where identifiable data is collected and this will be stored in the ISF with limited access. The consent form and ID log will contain the participants' names. Contact details (email address) and participant names and dates of birth will be held securely on the trial database to contact the participant about diary completion and to enable emergency unblinding. Contact details (telephone number) will be stored on site only to contact the participant about pain scores. All other data collected will be anonymised. Any blood results that are collected will be transcribed to the eCRF with the source remaining within the medical notes.

Dr Mulvey, based at the University of Leeds, is a co-investigator on the grant and holds an Honorary Fellow status at the University of Edinburgh. He will act as co-supervisor for a University of Edinburgh PhD student alongside the CI Professor Fallon (primary supervisor). Dr Mulvey will be responsible for overseeing the analysis of QST data to be performed at the end of the trial. Dr Mulvey will not be transferred any trial data directly and will only have access to anonymised outputs generated from the PhD students analyses.

9.4 DATA STORAGE

Personal data will be physically stored by the research team at the Edinburgh Palliative and Supportive Care group (EPAS) offices, which require code access and within a room and locked filing cabinet which require further code access, only known to the EPAS team.

Trial data will be stored on an CTU database hosted on The University of Edinburgh secure server, requiring user authentication for access. The database will be validated, ensuring integrity and security of the data to be collected. This will include email address (with consent) to send out the diaries.

9.5 DATA RETENTION

Data will be retained for 25 years post study completion. Personal data will be stored for 1 year post trial.

9.6 DISPOSAL OF DATA

We will employ the contemporary guidance by the UoE Research Data Service regarding deletion of data once the retention period is over.

9.7 EXTERNAL TRANSFER OF DATA

Personal identifiable data collected or generated by the study will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s). Pseudonymised data may be

shared outside the UK with the specific organisations who have allowed use of their questionnaires as part of the study.

9.8 DATA CONTROLLER

A data controller is an organisation that determines the purposes for which, and the manner in which, any personal data are processed.
The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site, or collaborating institution in the local country where the study is being conducted).

9.9 DATA BREACHES

Any data breaches will be reported to the University of Edinburgh (dpo@ed.ac.uk) and NHS Lothian (Loth.DPO@nhs.scot). Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

10 STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

10.1.1 Clinical primary outcome

Participants will be randomised to one of two treatment sequences (placebo, IMP or IMP, placebo). 39 participants per sequence (total sample size 78) in a 2x2 cross-over design would give 90% power to detect a mean difference of 2.5 in the EORTC QLQ-CIPN20 sensory scale. We have assumed the standard deviation (SD) of within-participant differences to be 6.66,[57, 58] analysis by two group t-test (Cross-over ANOVA, nQuery v8.0) and 5% 2-sided significance level. We increased the planned sample size to 92, to allow for up to 10% dropout (only 4% in our recent trial in a similar patient population; NCT04276727; in analysis) and any deviations from the assumed primary outcome variance.
The minimum clinically important difference is justified as follows. On the absolute scale, using the distribution-based approach and considering, based on clinical guidelines, values from 33% to 50% of the SD values recorded in longitudinal assessments, the minimum clinically important difference on the EORTC QLQ-CIPN20 sensory scale would be between 2.5 and 5.9[58]. Feedback from our PPI representatives has confirmed that the lower end of this range, 2.5, should be considered a minimum clinically important difference.

10.1.2 Mechanistic MRI primary outcome

Change in connectivity in interoceptive brain regions will be assessed between baseline and week 5 in a parallel group comparison during the first cross-over trial period. The total study number, will have 92 participants to allow for drop-outs to have a minimum of 39 participants in each arm. The mechanistic outcomes require a smaller sample : 34 participants per MRI group will give 81% power to detect a standardised mean difference of 0.5, assuming 0.7 correlation between baseline and 5 weeks, 2-sided 5% significance level and using analysis of covariance[59]. We increased the planned sample size to 38 per group to allow for occasional scans not providing analysable data due to technical difficulties or excessive participant motion.

10.2 PROPOSED ANALYSES

A detailed statistical analysis plan (SAP) will be finalised prior to database lock and unblinding of the statistician to randomised treatment allocations. The SAP will include full details of the methods for handling missing data, alongside the estimand, as defined in the addendum to the ICH E9 guidance on statistical principles for clinical trials.[60]

The primary analyses will be conducted on an intention-to-treat basis, with all randomised patients being analysed in the treatment sequence to which they were allocated, regardless of the subsequent treatment they received. All results will be presented as point estimates and 95% confidence intervals with associated p-values. Results will be reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidance for cross-over clinical trials[61] and relevant content of the 2025 revision of the overarching CONSORT guidance[62].

10.2.1 Clinical Outcomes

The primary clinical outcome, EORTC CIPN20 sensory scale collected at the end of week 5 and end of week 12, will be analysed using a normal linear mixed model, with fixed effects for treatment sequence (placebo, IMP or IMP, placebo), period (1, weeks 1-5 or 2, weeks 8-12) and treatment (placebo or IMP) and a random effect for participants nested within sequence. The treatment effect will be reported as a mean difference (IMP minus placebo) and 95% confidence interval. Secondary outcomes (collected at the end of week 5 and end of week 12) will be analysed with a similar approach using generalized linear mixed models appropriate to the distribution of the outcome.

10.2.2 Health Economics Outcomes

We aim to understand the feasibility of measuring cost-effectiveness of the IMP and the potential for market viability. Basic early decision modelling will be undertaken to enable a headroom analysis for the indication of CIPN and indicative cost-effectiveness of CBD. We will assess the sensitivity of the EQ-5D to sufficiently measure the impact of the IMP on QALYs. Limited data will be collected on concomitant medications and health service use which may be modified using the CBD. Mechanisms of health service pathway impact will be established through stakeholder consultation and observed data; and incorporated into the model. Sensitivity analysis will facilitate understanding of the drivers of uncertainty in the evidence for cost-effectiveness.

10.2.3 Mechanistic Outcomes

The 'ENIGMA HALFpipe' pipeline will be used to carry out pre-processing and functional connectivity analysis of MRI data[63]. This is a standardised software, designed to enable reproducible MRI analysis and is available through our long-standing collaboration with the International ENIGMA consortium[63]. Functional connectivity of the ACC will be determined using a seed-based analysis of resting state blood oxygenation level-dependent (BOLD) data, examining temporal correlations in time series between the seed (ACC) and the rest of the brain. Change in connectivity of the ACC (between baseline and 5 weeks) will be analysed using group (IMP/placebo) by time (pre/post) interaction effects using flexible factorial models. Further analysis of dynamic network properties will be performed using publicly available tools.

11 PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Where we state side effects, we refer to the more commonly occurring adverse reactions which we will actively screen for each week at the patient assessment.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Investigators Brochure (IB).

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after informed consent until 4 weeks after last dose of IMP will be recorded in the Case Report Form (CRF) or AE log. In the case of an AE, the Investigator will initiate the appropriate treatment according to their medical judgment. If dose reduction is required due to side effects, this will be captured in the CRF and not as an AE. Expected potential side effects will be listed in CRF. See Section 11.6 below for list of expected side effects (what is known in literature and from the Epidyolex studies, derived from section 7.9.1 of the IB). These expected side effects would not be reported as AEs if they are of mild severity.
There is a side effect of potential suicidal ideation. This will be asked at each contact (weekly) from consent and if noted, the nurses will ensure safeguarding processes are followed as per NHS Lothian guidance.

11.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at 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.

^Any hospitalisation that was planned prior to enrolment will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria. Hospitalisation for an exacerbation of their cancer or cancer treatment related problems will not be reported as a SAE as this is a known reason for hospitalisation for this population group.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be related to the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SPC) booklet or Investigators Brochure.

11.2 IDENTIFYING AES AND SAES

Participants will be asked about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents,

used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments e.g. laboratories.

There will be a list of expected potential AEs as a result of the patient group which would be exempt from formal reporting. These relate to the underlying cancer illness, either progression or complication as a direct result of the cancer and also related to clinical problems as a result of CIPN (see section 11.6).

11.3 RECORDING AES AND SAES

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the research team who is delegated to record and report AEs/SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF/AE log and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

11.3.1 Pre-existing Medical Conditions

Pre-existing medical conditions other than CIPN and cancer (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

11.3.2 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the patient's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

11.4 ASSESSMENT OF AES AND SAES

Each AE must be assessed for seriousness, causality, severity and ARs must be assessed for expectedness by the Principal Investigator or another suitably qualified physician in the research team who has been delegated this role.

For randomised double-blind studies, AEs will be assessed as though the participant is taking active IMP. SUSARs will be unblinded by ACCORD before they are reported to REC and CA (by ACCORD).

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

11.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 11.1.

11.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

11.4.3 Assessment of Expectedness

If the event is an AR the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the Investigator Brochure sections 6 and 7.6-7.9.

There is no expected event for placebo.

A 2022 systematic review described the following: A total of 454 participants used CBD in the trials. The most common AEs of CBD were mild or moderate and included gastrointestinal symptoms (59.5%), somnolence (16.7%), loss of appetite (16.5%), and hypertransaminasemia (ALT/AST) (12.8%). Serious adverse effects include mainly hypertransaminasemia with serum levels elevations greater than three times the upper limit of the normal (6.4%), seizures (1.3%), and rash (1.1%). All SAEs reported in the studies were observed on CBD as an add-on therapy to anticonvulsant medications, including clobazam and valproate. The conclusion was: recent RCTs involving oral CBD administration for at least a week suggest that CBD has a good safety and tolerability profile, confirming previous data. However, it can potentially interact with other drugs and its use should be monitored, especially at the beginning of treatment[64].

The event may be classed as either:

- **Expected**: the AR is consistent with the toxicity of the IMP listed in the IB section 6.
- **Unexpected**: the AR is not consistent with the toxicity in the IB section 6.

Fatal and life-threatening SARs should usually be considered unexpected. Fatal SARs can only be expected for IMPs with an MA in the EU, when it is clearly stated in the list of ARs of the SPC (Section 4.8) that the IMP causes fatal SARs.

11.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE/SAR/SUSAR and record this on the CRF/AE log or SAE form according to one of the following categories:

- **Mild**: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
- **Moderate**: an event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

11.5 RECORDING OF AES

All adverse events for each participant will be recorded on the AE log and will be assigned the appropriate MedDRA Systems Organ Class (SOC) code by a member of the trial management team.

11.6 REPORTING OF SAES/SARS/SUSARS

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to ACCORD Research Governance **within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 11.4.2, Assessment of Causality and 11.4.3, Assessment of Expectedness.

The SAE form will be transmitted via email to safety@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.
All reports sent to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).
ACCORD will onward report SAEs to MRX as follows:

Once the site has completed its assessment of: (a) the seriousness; (b) the causality; (c) the expectedness; and (d) the severity of an SAE or SUSAR, the Sponsor will report to the Company details of the SAE or SUSAR and the outcome of its assessment within fifteen (15) days. Any follow-up reports shall be sent directly to the Company by email. The Sponsor shall ensure that the initial report to Company and any follow up reports do not contain any personal data in the meaning of Data Protection Law.
The Sponsor will provide the Company with a copy of the annual safety report, within one (1) month of submission to the competent authority(ies)/REC(s).
Company contacts:nick.clarkson@mrxmedical.com and jack.morgan@anandadevelopments.com.

Pre-defined clinically relevant complications recorded as outcomes in the case report form (listed below) will not be additionally reported as adverse events.

Events that will not be recorded as Adverse Events

- Hospitalisation, or other SAE criteria, for an exacerbation of their cancer, cancer related problems or cancer treatment related problems, such as sepsis, will not be reported as a SAE as this is a known reason for hospitalisation for this population group. Exception is any suspicion that hospitalisation is linked to the IMP
- Cancer or cancer treatment related events (following clinical assessment) e.g., anaemia with the exception of the events listed below if moderate or severe
- Cancer related serious complications, an example of which is spinal cord compression (could not be related to the IMP). These will not be reported as SAEs.

Participants will be asked weekly about the common side effects highlighted below as they will contribute to titration decisions.

Expected Side Effects to be captured in the CRF, which will be reported as AEs if moderate or severe, but not mild;

- Drowsiness
- Fatigue
- Diarrhoea
- Sleep disturbance
- Increased appetite
- Decreased appetite

If any of the above-mentioned side effects are assessed to be SAEs, these will be reported to ACCORD.

11.7 REGULATORY REPORTING REQUIREMENTS

ACCORD is responsible for pharmacovigilance reporting on behalf of the Co-Sponsors (The University of Edinburgh and NHS Lothian).

ACCORD has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction. Unblinding of the sponsor for reporting purposes can be carried out via the trial database.

ACCORD (or delegate) will inform Investigators at participating site of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update Report. This annual report lists all SARs and SUSARs reported during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

DSUR onward reporting requirements: ACCORD will onward report DSURs to MRX within one month: nick.clarkson@mrxmedical.com and jack.morgan@anandadevelopments.com.

11.8 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of SAE form.

11.9 PREGNANCY

In animal studies (primates) some abnormalities in foetal development were noted with CBD. All females of child bearing potential will be required to use a form of agreed effective contraception and male subjects, if heterosexually active with a female partner of childbearing potential, must agree to use barrier contraception (male condom).

Although pregnancy is not considered an AE or SAE; as a matter of safety, the Investigator will be required to record any female participant's pregnancy (up to 30 days after the study) or any pregnancy of a female partner of a male participant (up to 90 days after the study), who became pregnant while participating in the study. The Investigator will need to record the information on a Pregnancy Notification Form, which will not record any personal identifiable information and submit this to the ACCORD office within 14 days of being made aware of the pregnancy. The study team would ask the participant's (or participant's partner's) GP to let their pregnancy care team know that they were in this study. The study team would also ask their GP regarding the outcome of the pregnancy.

All pregnant female participants and pregnant partners of male participants will be followed up until the outcome of the pregnancy by the Obstetrics team as part of standard care.

12 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), A Trial Manager and coordinating nurse.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

12.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details are detailed in CR015 DMC & TSC Charters. We will seek approval from NIHR for external appointees.

12.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The DMC will provide recommendations about stopping, modifying or continuing the trial to the Trial Steering Committee (TSC) following each DMC meeting reviewing unblinded safety data. There is no formal stopping rule or formal schedule of interim analyses.

The terms of reference of the Data Monitoring Committee, including stopping guidance, and the names and contact details are detailed in CR0015 DMC & TSC Charters.

The DMC Charter will be signed by the appropriate individuals prior to the trial commencing.

12.4 INSPECTION OF RECORDS

Investigators and institutions (NHS Lothian) involved in the study will permit trial related monitoring and audits on behalf of the Co-Sponsors, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the Co-Sponsors direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

12.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the Co-Sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

12.6 STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary.

13 GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all necessary approvals will be obtained and any conditions of approvals will be met.

13.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

13.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

13.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the Co-Sponsors.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

13.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

13.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

13.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.
- ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local Investigator Site files (ISFs). Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

13.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

13.3.6 Data Protection Training

Research staff are responsible for completing mandatory data protection training in accordance with local policy.

13.3.7 Information Security Training

All University of Edinburgh employed researchers, students and study staff will complete the Information Security Essentials modules and will have read the minimum and required reading setting out ground rules to be complied with.

NHS Lothian employed researchers and study staff will comply with NHS Lothian mandatory Information Governance IT Security training. .

Non-NHS Lothian staff that have access to NHS Lothian systems will familiarise themselves and abide by all NHS Lothian IT policies, as well as employer policies

13.3.8 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the Co-Sponsors or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.3.9 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including where applicable the UK General Data Protection Regulation legislation with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

14 STUDY CONDUCT RESPONSIBILITIES

14.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Proposed amendments will be submitted to the Co-Sponsors for classification and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to implementation.

14.2 PROTOCOL NON-COMPLIANCE

14.2.1 Definitions

- **Deviation** - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subjects rights, safety, or well-being, or study outcomes.
- **Violation** - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

14.2.2 Protocol Waivers

Prospective protocol deviations, i.e., protocol waivers, will not be approved by the Co-Sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

14.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the Co-Sponsors every 3 months. Each protocol violation will be reported to the Co-Sponsors within 3 days of becoming aware of the violation.

The time window for study visits and phone calls is detailed in Table 2. If study visits or phone calls take place out with this time window, it will be recorded on the database but not reported as a deviation/violation.

Deviation logs/violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

14.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the MHRA. This is defined as an urgent safety measure and the investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).

The Investigator will then notify the MHRA (clintrialhelpline@mhra.gsi.gov.uk) (or other Regulatory Authority where relevant), the REC and ACCORD, in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

14.4 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the Co-Sponsors (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the Co-Sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether

the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

14.5 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 25 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will be destroyed with permission from the Co-Sponsors.

14.6 END OF STUDY

The end of study is defined as the last participant's final visit.

The Investigators and/or the trial steering committee and/or the Co-Sponsors have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, Regulatory Authority, R&D Office(s) and Co-Sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the Co-Sponsors via email to resgov@accord.scot.

In accordance with ACCORD SOP CR011, a Research Study Report will be provided to the Co-Sponsors (QA@accord.scot) and REC within 1 year of the end of the study. [Note for paediatric trials this timeline is 6 months].

Within one year of the end of trial, the Investigator will publish summary results on the publicly accessible database that the trial was registered with, on behalf of the Co-Sponsors.

The Investigator will submit a short confirmatory e-mail to the MHRA (CT.Submission@mhra.gsi.gov.uk) once the result-related information has been uploaded to the public registry. The subject line of the email notification must state: 'End of trial: result-related information: IRAS ID XXXXXXX'. The Co-Sponsor(s) will be copied in this e-mail (QA@accord.scot). It should be noted that you will not get an acknowledgment e-mail or letter from the MHRA.

14.7 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

The trial drug is not licensed at this point and currently would not be available post study.
Participants will be offered follow-up in the CIPN clinics and have access to best available care.

14.8 INSURANCE AND INDEMNITY

The Co-Sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the Co-Sponsors' responsibilities:

- The Protocol has been authored by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The Co-Sponsors require individual sites participating in the study to

arrange for their own insurance or indemnity in respect of these liabilities. Sites which are part of the United Kingdom's National Health Service have the benefit of NHS Indemnity.

- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

15 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the Co-Sponsors although the study team will be responsible for retaining data, publishing findings and submitting necessary reports derived from the data. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

15.2 PUBLICATION

The study report will be submitted to the Co-Sponsors and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the study report. The Chief Investigator will provide the study report to ACCORD, for review, prior to finalization, where applicable. The study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the publicly accessible database that the trial was registered with, on behalf of the Co-Sponsors, within 1 year of the end of the study. Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion) and to participants via the study website. This will be accompanied by activity on social media to raise awareness amongst the general public. These activities will be informed by the PPI panel.

Opportunities to engage with the public will be further optimised by working alongside organisations such as CRUK, IASP, Macmillan, Maggie's Centre and other local patient support groups to inform patients, make the research more accessible and share study findings.

15.3 DATA SHARING

Anyone interested in secondary analysis of the de-identified trial data should contact the Chief Investigator in the first instance. After the end of the trial, a core group involving the chief investigator, co-investigators, and ECTU data sharing representative(s) will provide oversight of the data requests. A contract detailing appropriate access to study results will be in place between the University of Edinburgh and MRX MEDICAL LIMITED Company Number 13352302,Ibex House, 61 Baker Street, Weybridge, England, KT13 8AH

Biomarker blood samples will be banked in the Oncology Research Facility for analysis at a later date. A contract will be in place in relation to these anonymised samples and sharing of results generated with the University of Edinburgh.

15.4 PEER REVIEW

The grant application has been peer reviewed via the NIHR EME committee and externally appointed reviewers. Future publications will be peer reviewed according to the requirements of the specific publication. The trial protocol has been reviewed by the grant holders, Edinburgh Clinical Trials Unit and the PPI panel.

NIHR/EME will expect regular formal updates.

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17 Appendices

17.1 APPENDIX 1: CANNABIDIOL–PSYCHOACTIVE DRUG INTERACTIONS

Name of drug	Class of drug	Mechanism of interaction	Clinical suggestions when co-administered with CBD
Carbamazepine	Anti-epileptic drug	Will decrease the level or effect of cannabidiol by affecting hepatic/intestinal enzyme CYP3A4 metabolism.	Consider an increase in cannabidiol dosage (based on clinical response and tolerability) when co-administered.
Lamotrigine	Anti-epileptic drug	CBD will increase the level or effect of lamotrigine by inhibiting UGT2B7 activity.	Consider reducing the dose when concomitantly using UGT2B7 substrates such as morphine, losartan, diclofenac, tamoxifen, and ibuprofen.
Oxcarbazepine	Anti-epileptic drug	Will decrease the level or effect of CBD by affecting hepatic/intestinal enzyme CYP3A4 metabolism.	Consider an increase in CBD dosage (based on clinical response and tolerability) when co-administered with a strong CYP3A4 inducer.
Phenobarbital	Anti-epileptic drug	Will decrease the level or effect of CBD by affecting hepatic/intestinal enzyme CYP3A4 metabolism or CYP2C19 metabolism. CBD discreetly potentiates the anticonvulsant effect of phenobarbital.	Consider an increase in CBD dosage (based on clinical response and tolerability) when co-administered with a strong CYP3A4 inducer. Consider reducing the dose of sensitive CYP2C19 substrates, as clinically appropriate, when co-administered.
Phenytoin	Anti-epileptic drug	Will decrease the level or effect of CBD by affecting hepatic/intestinal enzyme CYP3A4/CYP2C19 metabolism. CBD may potentiate the anticonvulsant effects of phenytoin.	Consider an increase in CBD dosage (based on clinical response and tolerability) when co-administered with a strong CYP3A4 inducer. Consider reducing the dose of sensitive CYP2C19 substrates, as clinically appropriate, when co-administered.
Chlordiazepoxide Clonazepam Ethosuximide	Benzodiazepine	CBD reduces the anticonvulsant effects of these drugs	Consider an increase in the dose of these drugs when co-administered.
Clobazam or Diazepam	Benzodiazepine	CBD will increase the level or effect of clobazam or diazepam by affecting hepatic enzyme CYP2C19 metabolism. CBD	Consider reducing the dose of sensitive CYP2C19 substrates, as clinically appropriate, when co-administered.

Name of drug	Class of drug	Mechanism of interaction	Clinical suggestions when co-administered with CBD
		increases clobazam plasma concentrations.	
Lorazepam	Benzodiazepine	CBD will increase the level or effect of lorazepam by decreasing its metabolism and potentially inhibit UGT2B7 activity.	Consider reducing the dose when concomitantly using UGT2B7 substrates.
Morphine	Opioid	CBD will increase the level or effect of morphine.	CBD may potentially inhibit UGT2B7 activity. Consider reducing the dose when concomitantly using UGT2B7 substrates.
Desipramine	Tricyclic anti-depressant	Desipramine will increase the level or effect of CBD by affecting hepatic/intestinal enzyme CYP3A4 metabolism.	Consider reducing the CBD dose when co-administered with a moderate CYP3A4 inhibitor.
Imipramine	Tricyclic anti-depressant	CBD will increase the level or effect of imipramine by affecting hepatic enzyme CYP2C19 metabolism.	Consider reducing the dose of sensitive CYP2C19 substrates, as clinically appropriate, when co-administered.
Trimipramine	Tricyclic anti-depressant	CBD will increase the level or effect of trimipramine by affecting hepatic enzyme CYP2C19 metabolism.	Consider reducing the dose of sensitive CYP2C19 substrates, as clinically appropriate, when co-administered.

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