Study Protocol for FSD201-010

Trial Title: A Randomized, Double-Blind Placebo Controlled Parallel Group Study of Safety and Efficacy of FSD201 in Patients with Chronic Widespread Musculoskeletal Nociplastic Pain Associated with Idiopathic Mast Cell Activation Syndrome (Disorder)

NCT number: NCT05652907

Document Date: 13Feb2023

Clinical Study Protocol

A Randomized, Double-Blind Placebo Controlled Parallel Group Study of Safety and Efficacy of FSD201 in Patients with Chronic Widespread Musculoskeletal Nociplastic Pain Associated with Idiopathic Mast Cell Activation Syndrome (Disorder)

Protocol FSD201-010

Short Title: Safety and Efficacy of FSD201 for the treatment of chronic pain associated with idiopathic MCAS (MCAD)

Name of Investigational Product:	FSD201
Indication:	Musculoskeletal Nociplastic Pain Associated with Idiopathic Mast Cell Activation Syndrome (Disorder) (MCAS/MCAD)
Study Sponsor:	FSD Pharma 53 Loveton Circle, Suite 104 Sparks, MD 21152, USA
Clinical Trials Management Company/Clinical Trials Specialist:	Sarah Garisto Ozmosis Research Inc. 700 University Avenue Suite 217-2N, Toronto, ON M5G 1Z5 Main Line: 416-634-8300 Fax: 416-634-8333
Document Status:	Final
Country:	USA
Version, Date:	Version 2.3, 13Feb2023

Protocol Approval Signature

Protocol Title:	A Randomized, Double-Blind Placebo Controlled Study of Safety and Efficacy of FSD201 in Patients with Chronic Widespread Musculoskeletal Nociplastic Pain Associated with Idiopathic Mast Cell Activation Syndrome (Disorder) (MCAS/MCAD)
Protocol Number:	FSD201-010
Country:	USA
Version, Date:	Version 2.3, 13Feb2023

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonization (ICH) guidelines for current Good Clinical Practice (GCP), and applicable regulatory requirements.

Sponsor Signatory
Dr Andrzej Chruscinski
Vice President-Clinical and Scientific Affairs, Lucid Psycheceuticals Inc.
(Subsidiary of FSD Pharma, Inc.)

_____
Signature

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Date (DD-MMM-YYYY)

Investigator Signature Page

Protocol Title: A Randomized, Double-Blind Placebo Controlled Parallel Group Study of Safety and Efficacy of FSD201 in Patients with Chronic Widespread Musculoskeletal Nociplastic Pain Associated with Idiopathic Mast Cell Activation Syndrome/ Disorder (MCAS/MCAD)

Protocol Number: FSD201-010

Confidentiality and Current Good Clinical Practice (GCP)/E6(R2)/Compliance Statement

- I, the undersigned, have reviewed this protocol (and any amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and any amendments), GCP, and relevant International Council for Harmonisation guidelines.
- I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by FSD Pharma, Inc. including, but not limited to, the current investigator's brochure.
- Once the protocol has been approved by the research ethics board (REB)/institutional review board (IRB)/independent ethics committee (IEC), I will not modify this protocol without obtaining prior approval of FSD Pharma, Inc. and of the REB/IRB/IEC. I will submit the protocol amendments and/or any informed consent form (ICF) modifications to FSD Pharma, Inc. and the REB/IRB/IEC, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the FSD Pharma, Inc. study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and study records that include all pertinent observations on each of the site's patients will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study regarding the patients' state of health will be regarded as confidential. No patients' names will be disclosed. All patients will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the patient before disclosure of patient information to a third party.
- Information developed in this clinical study may be disclosed by FSD Pharma, Inc. to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

Printed Name	Investigator Signature
Title	Date (DD-MMM-YYYY)
Institution	

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2. Synopsis

STUDY TITLE	A Randomized, Double-Blind Placebo Controlled Parallel Group Study of Safety and Efficacy of FSD201 in Patients with Chronic Widespread Musculoskeletal Nociplastic Pain Associated with Idiopathic Mast Cell Activation Syndrome/ Disorder (MCAS/MCAD)
PROTOCOL NUMBER	FSD201-010
VERSION NUMBER	2.3, 13Feb2023
COUNTRY	USA
NUMBER OF STUDY SITES	Canada 01, USA 02, Total Worldwide: 03
STUDY OBJECTIVES:	**Main Objectives** ● To evaluate the analgesic efficacy of FSD201 compared to placebo in subjects with chronic widespread musculoskeletal nociplastic pain associated with Idiopathic Mast Cell Activation Syndrome/ Disorder (MCAS/MCAD) **Secondary Objectives** ● To evaluate the efficacy of FSD201 as compared to placebo on pain-related function, sleep interference, and global improvement ● To assess safety and tolerability of FSD201 in subjects with chronic widespread musculoskeletal nociplastic pain ● To evaluate the change in serum tryptase, IL-6 and IL-1beta serum biomarker levels
STUDY ENDPOINTS:	**Primary endpoint** Targeted treatment effect of 30% decrease from baseline to Day 28 in the average daily pain intensity score measured by an 11-point numerical pain rating scale (NPRS). Averages will be calculated as follows: Baseline: calculated weekly average from Day -7 to Day -1 Day 28: calculated weekly average from Day 23 to Day 28

	Key Secondary endpoints Key secondary efficacy endpoints will include changes from baseline to Day 56 as measured by: ● Percentage of subjects achieving ≥30% reduction in NPRS score at the end of treatment with FSD201 ● Change in Patient Global Impression of Change (PGIC) after 56 days treatment ● Change or reduction in patient average daily NPRS after 56 days of treatment[1] ● Change in Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance- Short Form (SF) 8a after 56 days treatment ● Change in the PROMIS Pain Interference- SF 8a score after 56 days treatment ● Change in the PROMIS General Life Satisfaction- SF 5a after 56 days treatment ● Change in the PROMIS Fatigue- SF 8a after 56 days treatment ● To determine whether FSD201 treatment reduces serum mast cell tryptase, IL-6 and IL-1beta during treatment Key secondary efficacy endpoints will include changes from baseline to Day 28 and Day 56 as measured by: ● Percentage of subjects achieving ≥30% reduction in NPRS score[1] ● Change or reduction in patient average daily DSIS after 28 and 56 days of treatment[1] ● Change in Patient Global Impression of Change (PGIC) Note: [1]DSIS and NPRS averages will be calculated as follows: Baseline: calculated weekly average from Day -7 to Day -1 Day 28: calculated weekly average from Day 23 to Day 28 Day 56: calculated weekly average from Day 49 to Day 55 for the NPRS and Day 50 to Day 56 for the DSIS **Other Secondary Endpoints** ● Change in pain intensity on the NPRS from baseline to each week of treatment

	● Percentage of subjects achieving ≥50% reduction in NPRS at Day 56[2] ● Change from baseline to Day 56 in PROMIS General Life Satisfaction -SF 5a ● The total amount of rescue medication used Note: [2]DSIS averages will be calculated as follows: Baseline: calculated weekly average from Day -7 to Day -1 Day 56: calculated weekly average from Day 49 to Day 55 **Exploratory endpoints** ● Changes in CRP, IL-2, IL-4, IL-8, IL-10, IL-12 (p70), IL-13, TNF-α and IFN-γ from baseline to Day 14, Day 28 and Day 56; ● Estimation of Plasma levels of PEA as measured at baseline, day 14, Day 28 and Day 56 ● Change or reduction in patient weekly PI-NRS after 28 and 56 days of treatment **Safety endpoints** ● Incidence and severity of treatment-emergent adverse events (TEAEs) throughout the dosing period; ● Incidence and severity of treatment-emergent changes in laboratory values at Day 56; ● Change from baseline in vital signs at each visit.
STUDY POPULATION: **Number of Subjects:** **Number of Groups:** **Age/sex:**	Musculoskeletal Nociplastic Pain Associated with Idiopathic Mast Cell Activation Syndrome (Disorder) (MCAS/MCAD) 60 2 (FSD201, placebo) ≥18 and ≤75, male and female
Selection of Patients	Adults ≥18 years with chronic musculoskeletal nociplastic pain in three or more body regions secondary, more likely to Idiopathic MCAS are selected and randomized to receive either FSD201, 600 mg *b.i.d.* or placebo. 60 study subjects. 1. The subject is ≥ 18 and ≤ 75 years of age at the time of signing ICF;

	2. Clinical diagnosis of idiopathic MCAS (in the presence or absence of a generalized hypermobility spectrum disorder (G-HSD) or Ehlers-Danlos Syndrome (EDS)) as per the global consensus diagnostic criteria (consensus-2 criteria (Afrin et al., 2021)); a) Medical history shows a constellation of clinical complaints attributable to pathologically increased mast cell (MC) activity (MC mediator release syndrome) b) Medical history of symptomatic response to inhibitors of MC activation or MC mediator production or action 3. Adults with widespread chronic nociplastic pain (in three or more body regions); 4. Chronic pains of intensity ≥4.0 but ≤9.0 on a Numeric Pain Rating Scale, symptom duration of >6 months 5. Subject signed a Research Ethics Board (REB) or Institutional Review Board (IRB) approved written informed consent and privacy language (Health Insurance Portability and Accountability Act (HIPAA)) and (PIPEDA) authorization before performing any study-related procedures 6. The subject is considered reliable and capable of adhering to the protocol (i.e., able to understand and complete forms and questionnaires, visit schedule, or medication intake according to the judgment of the investigator) 7. Subject agrees to use only acetaminophen (e.g., Tylenol) (up to 1000 mg per dose and not to exceed 3000 mg/day) or diphenhydramine (e.g. Benadryl) (up to 300 mg/day) as rescue medication for chronic widespread musculoskeletal nociplastic pains throughout the trial 8. The subject is willing to maintain current activity and exercise levels throughout the study 9. During the study, the subject agrees not to initiate or change any non-pharmacologic interventions (including chiropractic care, physical therapy, psychotherapy, and massage therapy). Any ongoing non-pharmacologic intervention must be stable for at least 4 weeks before screening and should be continued for the duration of the study 10. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Randomization Visit 11. Female subjects of childbearing potential must use an acceptable method of birth control. Acceptable birth control includes total

	abstinence from heterosexual intercourse, a vasectomized partner, intrauterine device, or double barrier method including condoms sponge, diaphragm, contraceptives (oral, parenteral, or transdermal), or vaginal ring with spermicidal jellies or cream. Subjects considered not of childbearing potential must be surgically sterile (total hysterectomy, bilateral salpingo-oophorectomy, or tubal ligation) or be more than one year post-menopausal, defined as a complete cessation of menstruation for at least one year. Male subjects who are sexually active must use an acceptable method of birth control. Acceptable birth control includes total abstinence from heterosexual intercourse, or use of a double barrier method including condoms sponge, diaphragm, contraceptives (oral, parenteral, or transdermal), or vaginal ring with spermicidal jellies or cream used by partner. Periodic abstinence and withdrawal are not acceptable methods of contraception 12. The subject is in good health as judged by the investigator, based on medical history, physical examination, serum chemistry, hematology, and urine analysis 13. At the screening visit, the body mass index (BMI) is between 18 and 39 kg/m^2 14. The subject is sufficiently fluent in English language to answer the questionnaires in clinic and on the App Randomization Criteria 1. The subject is compliant with daily App entries during the baseline period, as defined by the completion of a minimum of 5 of 7 daily NPRS scores 2. The average daily pain intensity scores on the NPRS are ≥ 4.0 and ≤ 9.0 over the last seven days before the Randomization Visit **Exclusion Criteria:** 1. The subject has pain that cannot be clearly differentiated from or that could interfere with the assessment of chronic musculoskeletal nociplastic pain secondary likely to idiopathic MCAS (e.g., post-herpetic neuralgia, traumatic injury, prior surgery, complex regional pain syndrome) 2. Adults with chronic cancer pain

	3. Adults with inflammatory connective tissue disorder or rheumatological disorder-related pain (e.g., rheumatoid arthritis) 4. Adults with focal musculoskeletal pain 5. Adults with skin diseases (e.g., chronic urticaria, pemphigus, lupus, rosacea etc.) 6. Adults with endocrinological disorders (e.g., acute hypothyroidism, acute adrenal insufficiency etc.) 7. Adults with systemic gastrointestinal conditions (e.g., Inflammatory bowel disease) 8. Significant psychological comorbidities: PHQ-9 score >20; and GAD-7 score >15 (indication of severe anxiety that could interfere with accurate logging of pain ratings) 9. Current or recent (within 12 months of screening) history of a substance use disorder including cannabinoid or alcohol use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (5th edition; DSM-5) 10. Subject has neurologic disorder unrelated to chronic widespread musculoskeletal nociplastic pains (e.g., phantom limb from amputation, vitamin B12 deficiency, chronic inflammatory demyelinating polyneuropathy), circulatory disorder (e.g., peripheral artery disease), a skin condition in the area of neuropathy that could alter sensation (e.g., plantar ulcer), or other painful conditions (e.g., arthritis) that, in the judgment of the investigator, could interfere with reporting of pain due to chronic widespread musculoskeletal nociplastic pains 11. Current severe or uncontrolled major depressive disorder or anxiety disorders. Mild to moderate major depression or anxiety disorders are permitted provided that the investigator assesses the patient as clinically stable and appropriate for entry into the study. Stable doses of the selective serotonin reuptake inhibitors (SSRIs) are allowed for the treatment of depression if the dose is stable for 60 days before Screening Visit 12. Subject has a history of suicide attempt or suicidal behaviour within the last 12 months or has suicidal ideation within the previous 12 months or who is at significant risk to commit suicide, as judged by the Investigator at Screening or during the treatment period

	13. The subject is currently using protocol-specified prohibited medications 14. Positive urine drug screen for illegal or non-prescribed drugs at the Screening Visit or during the treatment period. 15. Pregnant or lactating females or females planning to become pregnant during the study or within 28 days following the last dose of study medication. 16. Male patients planning a partner pregnancy or sperm donation during the study or within three months following the last dose of study medication. 17. Patients with active malignancy or history of malignancy, except for basal cell or squamous cell carcinoma and actinic keratosis. Basal cell carcinoma and small squamous cell carcinoma of the skin which have been excised according to guidelines within the last 5 years or in situ cervical carcinoma that has been fully treated and shows no evidence of recurrence are allowed. 18. Positive human immunodeficiency virus (HIV), hepatitis B or hepatitis C laboratory result. 19. Any clinically significant unstable medical abnormality or acute or chronic disease of the cardiovascular, gastrointestinal, respiratory, hepatic, or renal systems. Subject with aspartate transferase or alanine transferase > 2.5 times the upper limit of normal (ULN) or alkaline phosphatase > 3.0 times ULN. 20. Any clinically significant deviation from normal in physical examination, vital signs, or clinical laboratory tests, as determined by the investigator. 21. Known history of seizure disorder, epilepsy, convulsions, or increased intracranial pressure anytime during the subject's life except for pediatric febrile seizures. 22. Subject has received an investigational therapy of any kind within 28 days or 5 half-lives, whichever is longer, before Screening Visit. 23. Subject has had known hypersensitivity or intolerance to the use of PEA, diphenhydramine (e.g. Benadryl) or acetaminophen (e.g. Tylenol) and/or their associated formulation components 24. The subject is a member of the site staff or relative of a staff member

	26. Individuals with high baseline serum tryptase levels (defined as above the normal range of 2.2 to 13.2 µg/L) suggestive of Primary or Secondary MCAS

INVESTIGATIONAL PRODUCT: **Route of administration:** **Dosage:** **Duration of dosing:**	FSD201 Oral 600 mg BID 56 days
COMPARATOR INVESTIGATIONAL:	Placebo
ANTICIPATED STUDY DURATION:	Study accrual: 8 months Study duration: 10 months

3. Abbreviations and Definitions

ALT	Alanine transaminase
App	Study electronic Application for tracking patient responses
AST	Aspartate transaminase
b.i.d.	Two times a day; *b.i.d.* stands for "bis in die" (in Latin, two times a day)
BUN	Blood Urea Nitrogen
CB2	Cannabinoid Receptor 2
CRP	C- reactive protein
CTA	Clinical Trial Application
CTM	Clinical Trial Management Company
CTS	Clinical Trial Specialist
ECG	Electrocardiogram
eCRF(s)	Electronic Case Report Form(s)
EDS	Ehlers-Danlos Syndrome
EoT	End of Trial
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
G-HSD	Generalized Hypermobility Spectrum Disorder
HIPAA	Health Insurance Portability and Accountability Act (USA)
IB	Investigational Brochure
ICF	Informed Consent Form
IFN-γ	Interferon-γ

IL-1beta	Interleukin 1 Beta
IL-6	Interleukin 6
IMP	Investigational Medicinal Product (a medicinal product that is being tested or used as a reference, including as a placebo)
IND	Investigational New Drug Application
IRB/IEC	Institutional review board/ Independent Ethics committee
MAD	Multiple Ascending Dose
MC	Mast Cell
MCAD	Mast Cell Activation Disorder
MCAS	Mast Cell Activation Syndrome
MedDRA	Medical Dictionary for Regulatory Activities - is a medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products (updated twice a year)
MMRM	Mixed Model for Repeated Measure
NPRS	11-point Numerical Pain Rating Scale (24-hour recall)
NSAID	Nonsteroidal anti-inflammatory drug
PEA	Palmitoylethanolamide
PFT	Pulmonary Function Test
PGIC	Patient Global Impression of Change
PI	Principal Investigator
PI-NRS	Pain Intensity Numerical Rating Scale (7-day recall)
PIPEDA	Personal Information Protection and Electronic Documents Act (Canada)
PK	Pharmacokinetic
PROMIS	Patient-Reported Outcomes Measurement Information System
RTSM	Randomization and Trial Supply Management
SAD	Single Ascending Dose
SM	Systemic mastocytosis
SpO_2(%)	Oxygen Saturation
TEAE(s)	Treatment-Emergent Adverse Event(s)
um-PEA	Ultramicronized Palmitoylethanolamide
VEGF	Vascular Endothelial Growth Factor

4. Background Information

4.1. Introduction

Chronic pain affects one in five adults in North America and contributes to higher healthcare costs and lost productivity in the region. In addition, chronic pain has been linked to impaired mobility, activity of daily living challenges, opioid dependence, anxiety, depression, poor perceived health and reduced quality of life. Chronic pain is a pathological response associated with the prolonged disease state—one in four Canadians aged 15 or older (estimated 7.63 million) live with chronic pain. In Canada, chronic pain has significant impacts on physical and mental health, family and community life, society, and the economy, with the total direct and indirect cost of $38.3 to $40.4 billion in 2019 (Campbell et al., 2020) and in and in the USA, an estimated 50 million Americans, or just over 20 percent, have some form of chronic pain (Zelaya et al., 2020).

Mast cells are cellular regulators of physiologic and pathologic pain responses and facilitate neuroimmune cross-talk for pain modulation. Systemic activation of mast cells in Mast Cell Activation Syndrome (MCAS) results in the release of neuroinflammatory mediators, causing widespread pain in multiple body sites. Criteria for the diagnosis of MCAS have been recently published (Afrin et al., 2021). In this document, consensus-2 criteria for MCAS include one major and 6 minor criteria. For the diagnosis of MCAS, patients must have the major criterion (Constellation of clinical complaints attributable to pathologically increased MC activity) and at least one of the minor criteria. MCAS is an immunological condition in which mast cells excessively release chemical mediators (tryptase, histamine along with others), resulting in a wider range of pain and chronic symptoms, including anaphylaxis or near-anaphylaxis episodes (Valent et al., 2012). Hence, tryptase levels are associated with mast cell activation and serve as a marker of mast cell activity. Pro-inflammatory and pro-nociceptive cytokines like TNF-α, IL-6, IL1beta and VEGF are also involved with the activation of mast cells (Sev'er, et al., 2009). MCAS, being complex and heterogeneous in clinical presentation is classified into three major types: Primary MCAS, Secondary MCAS, and Idiopathic MCAS (Akin et al., 2010, Afrin et al., 2021). Chronic widespread musculoskeletal nociplastic pain, arising from neurogenic inflammation, is likely associated with 'idiopathic MCAS.' Nociplastic pain is an idiopathic pain that is mechanistically different from nociceptive pain, which is caused by ongoing inflammation and tissue damage (Fitzcharles et al., 2021). Nociplastic pain is defined as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" (Kosek et al., 2021).

Two types of outcome assessments will be used as measures of patient's health status: 1) Clinical Outcome Assessment (COA) are those that depend on someone's judgment, such as the patient, a clinician, or a caregiver, and 2) Biomarker assessments in which a defined characteristic is measured as an indicator of normal biological processes, pathogenic processes, or responses to an

exposure or intervention, including therapeutic intervention. Biomarkers are designed to have measurement properties that are minimally subject to human influence. Biomarkers can in principle be used to measure treatment effects when they can be demonstrated to predict some meaningful clinical outcome but do not measure that clinical outcome directly. Biomarkers can, however, be useful in the development of therapeutics as measures of important attributes of the biological effect of the treatment, such as target engagement, which can be useful for development purposes even when falling short of being able to substitute for a COA as an outcome measure. In studies of pain treatments, the primary outcome assessment is almost always a COA because the goal of treatment is clinical benefit. A 30% decrease in pain as assessed by COA has previously been reported to represent a clinically significant value (Younger et al., 2009). Because the use of biomarkers has increased the success of therapeutic development across a range of indications, there is a growing interest in the use of biomarkers in clinical trials of pain, particularly early trials. (Katz, 2021).

In most patients with cutaneous mastocytosis (defined by the absence of dense compact mast cell (MC) infiltrates in tryptase-stained bone marrow sections), normal or near-normal serum tryptase levels (median 10 ng/ml, range 2-23 ng/ml) were measured. By contrast, in the vast majority of patients with systemic mastocytosis (SM), elevated serum tryptase levels (median 67 ng/ml) were found. In addition, there was a significant correlation between the grade of infiltration of the BM by neoplastic mastic cells and tryptase levels in patients with SM ($r = 0.8$). Moreover, tryptase levels differed significantly among the groups of patients with different types of SM. In summary, serum tryptase is a reliable biomarker that can be used to estimate the burden of MC in patients with mastocytosis and to distinguish between categories of disease (Sperr et al., 2002). An additional publication (Akin, 2014) utilizes as elevated baseline tryptase level as a criterion to classify primary disorders of mast cell activation. Another study highlights the long-term effects of IL-6 on human mast cells, which are associated with expression of SOCS3 through methylation of SOCS3 promoter and suppression of the spontaneous production of soluble sIL-6R. Interestingly, the inverse relationship between serum levels of sIL-6R and IL-6 observed in mastocytosis has been reported for colorectal cancer, neuroblastoma, and juvenile arthritis. Therefore, suppression of` sIL-6 production by IL-6 may occur in other types of cells as well as mast cells and may thus reduce formation of the trans-activating IL-6/sIL-6R pro-inflammatory complexes. These findings have relevance in mast cell driven diseases associated with elevated levels of IL-6 including mastocytosis where treatment directed at lowering IL-6 levels could have a therapeutic benefit (Desai et al., 2016).

Human cytokine interleukin-37 (IL-37), a unique IL-1Beta family member, has strong protective and anti-inflammatory properties, influencing cellular metabolism. The effect of IL-37 on inflammation in mastocytosis are well studied and suggest that the hematopoietic expression of IL-37 can reduce the inflammatory state in this disease. IL-37 limits excessive inflammation, which suggests that IL-1 Beta may be beneficial to the metabolic and inflammatory process and is

a candidate as a potential new therapeutic agent (Conti et al., 2019). These studies above explain the rationale behind the importance of biomarkers in this study of FSD 201.

Palmitoylethanolamide (PEA) is an endogenous lipid that blocks histamine release and mast cell degranulation. Preliminary reports have provided evidence that PEA downregulates hyperactive mast cells in a dose-dependent manner (Mazzari et al., 1996; Rankin and Fowler, 2020). PEA's modulation of mast cell responses can serve as a novel target for treating and managing debilitating pain conditions (Passavanti et al., 2019). Many clinical trials assessing the safety and efficacy of ultramicronized PEA (um-PEA) on chronic pain have been published in the last decade. Overall, um-PEA at doses up to 2700 mg/day administered to patients with various chronic pain syndromes, such as burning mouth syndrome, migraine with aura, fibromyalgia, low back pain, or chronic pelvic pain, induced a significant decrease in pain intensity, compared to control groups (Paterniti et al., 2013; Schifilliti et al., 2014; Marcucci et al., 2016; Paladini et al., 2016; Germini et al., 2017; Passavanti et al., 2017; Ottaviani et al., 2019; Stochino Loi et al., 2019; Papetti et al., 2020). Several studies showed that the quality of life and psychological well-being of patients were also improved. Um-PEA also showed efficacy in slowing the decline in pulmonary function in patients with amyotrophic lateral sclerosis (ALS). In addition, clinical studies have demonstrated that um-PEA is generally very well tolerated. Overall, more than 3500 patients have received either ultramicronized or micronized PEA in clinical studies, and no adverse events were reported in most studies at doses as high as 2700 mg/day. Only a few cases of diarrhea and pre-existing chronic venous insufficiency were reported in one trial. Another trial reported one case of drowsiness and another of palpitations (Paladini et al., 2016).

4.2. FSD201

FSD Pharma Inc. is developing FSD201, an agent that primarily targets medical conditions where inflammation and pain are the major concerns and offers promising hope for the treatment of such conditions. PEA is an endogenous biologically active lipid belonging to the class of *N*-acylethanolamines (NAEs) and exerts anti-inflammatory, analgesic, and neuroprotective properties for the maintenance of homeostasis. PEA is synthesized in the body in response to external stressors and tissue injury. The pleiotropic effects of PEA involve several mechanisms, including activation of the peroxisome proliferator-activated receptor α (PPARα), the downregulation of mast cell activation of type 1 vanilloid transient receptors (TRPV1) channel, and prevention of NFkB nuclear translocation among others. PEA also inhibits the release of synthesised mast cell mediators, including histamine and TNF-α.

4.3. Safety and Pharmacokinetic (PK) data from FSD201 Phase I SAD/MAD Study in Healthy Individuals

To evaluate the safety and tolerability of FSD201, a single-center, Phase 1, randomized, double-blind, placebo-controlled, sequential SAD/MAD study with a food-effect arm was conducted.

48 healthy male or female adult light smokers or non-smoker subjects were included in this study. The **primary objective** of the study was to evaluate the safety and tolerability of FSD201 following oral administration of single ascending doses (SAD) ranging from 600 mg to 2400 mg and multiple ascending doses (MAD) ranging from 600 mg to 1200 mg administered twice a day (*b.i.d.*) for seven consecutive days, in healthy subjects. The study's **secondary objectives** were to characterize the pharmacokinetic (PK) profile of FSD201 following single and multiple oral doses in healthy subjects and evaluate the effect of food on the absorption of FSD201. The study schematic is shown in Figure 1.

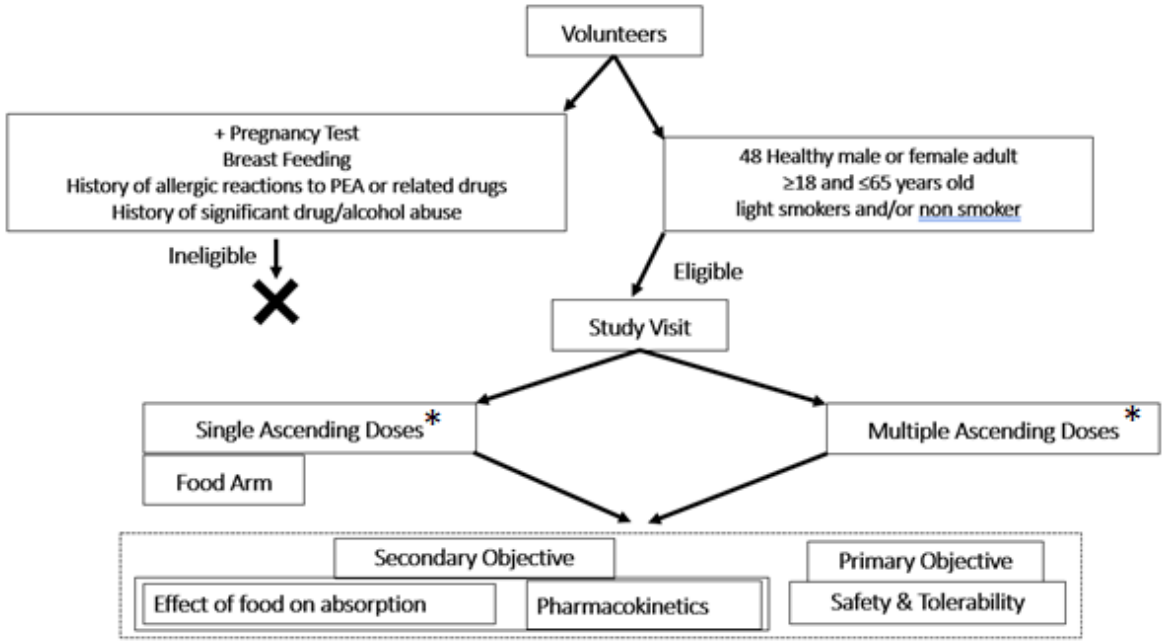

Figure 1 Study Schematic of FSD201 Phase I Clinical Trial.

Absorption of FSD201 increased in a less than dose-proportional manner over the dose range of 600 to 2400 mg following oral administration of single doses of FSD201 in healthy subjects. Administration of FSD201 under fed conditions resulted in a significant increase in PEA absorption rate – for a dose of 1200 mg of FSD201 in a fed state (Figure 4), it was seen that the

peak plasma concentration was seen to be about 250 ng/mL in about 2 hours as compared to 50 ng/mL in about 45 minutes in fasting state. However, it did not appear to affect the time to reach the peak of concentration of PEA in the high-fat diet, as shown in Figure 4. Peak plasma levels and total exposure during a dosing interval increased in a dose-proportional manner across the dose range 600 to 1200 mg following repeated oral doses. However, the $C_{min\ ss}$ appeared to increase less than in a dose-proportional manner, as shown in Figure 2.

There appears to be no significant accumulation of FSD201 following repeated doses with 600 and 1200 mg. Following multiple dosing, steady-state was achieved within seven days at the 600 mg dose level and within four days at the 1200 mg *b.i.d.* dose level, as shown in Figure 3.

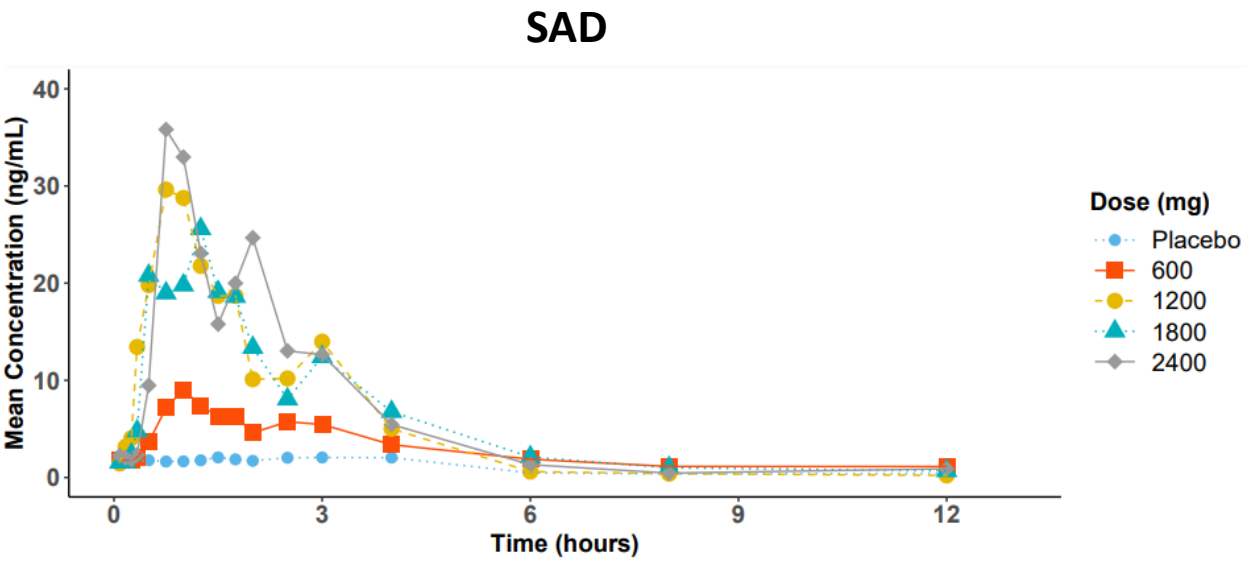

Figure 2 Mean Plasma Pharmacokinetic Concentrations for FSD201 in the SAD Study (Part A)

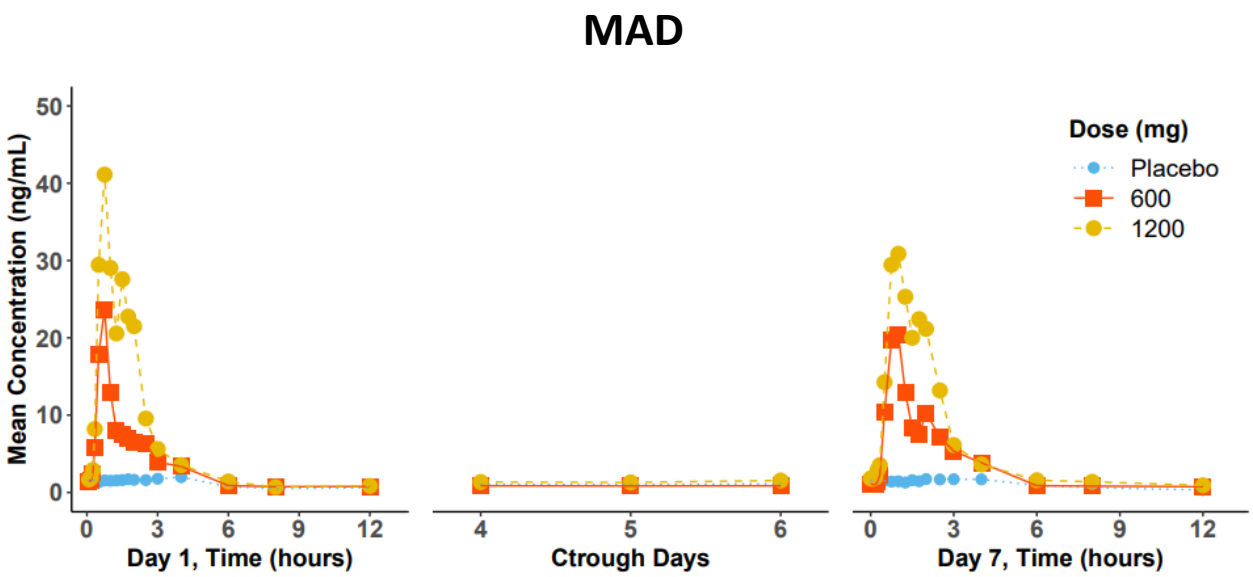

Figure 3 Mean Plasma Pharmacokinetic Concentrations for FSD201 in the MAD Study (Part B, Day 1 through Day 7)

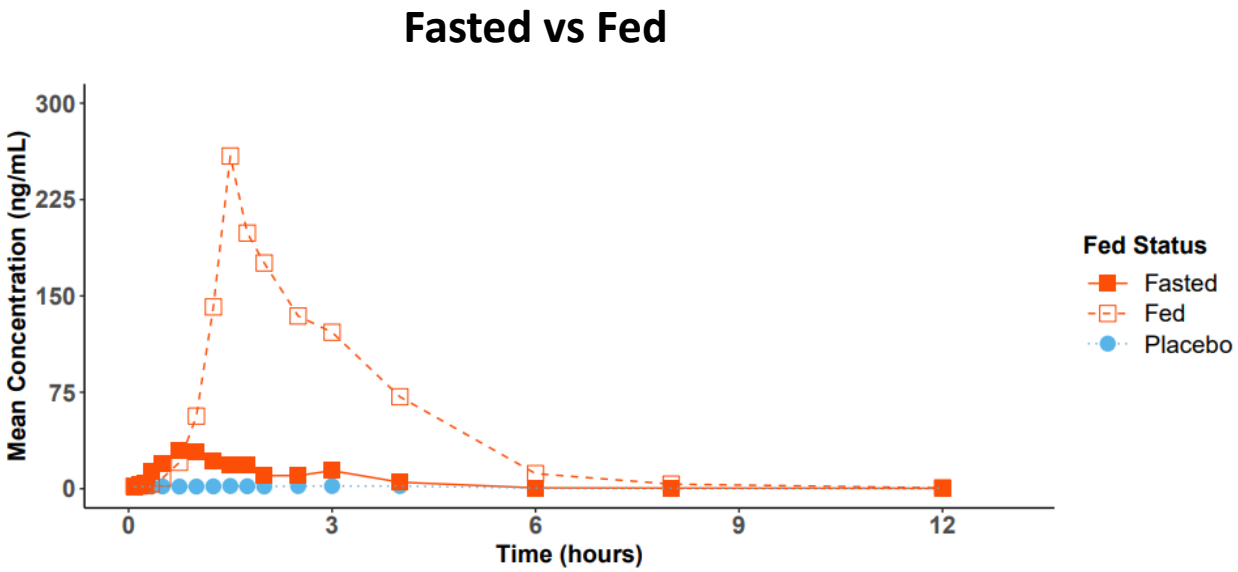

Figure 4 Arithmetic Mean Plasma Concentration vs Time Profiles of FSD-201 for single dose of 1200 mg in fed and fasted individuals

Overall, FSD201 following an oral administration of a single dose, ranging from 600 mg to 2400 mg, and multiple doses ranging from 600 mg to 1200 mg *b.i.d.*, were safe and well-tolerated in normal healthy subjects. No serious adverse events (SAEs) were reported for these studies. The safety results seen in this Phase I trial were consistent with published information. There were no Treatment-Emergent Adverse Events (TEAEs) related to clinical laboratory results, ECGs, and physical examination in both the SAD and MAD recipients. No clinically relevant differences were observed between the treatment groups with respect to mean values and changes from baseline for clinical laboratory results, vital signs, and ECG results.

In the SAD study, one vital sign abnormality (hypotension) was experienced by one subject in Cohort 2 [1200 mg], observed during the scheduled measurements, considered a TEAE. This TEAE was considered mild and represented a transient lowering of systolic blood pressure of less than 10 mmHg. Overall, no safety issues were observed for clinical laboratory, vital signs, ECGs, or physical examination results.

4.4. Study Governance

This study is a prospective, randomized, double-blind, placebo-controlled sponsor-initiated trial. The study's design is set to accept individuals who meet the criteria for chronic widespread musculoskeletal nociplastic pain (arising from neurogenic inflammation) secondary to likely "Idiopathic MCAS." The study will be conducted at three centres: one in Canada and two in the USA. The study will be conducted under an IND (US FDA) and CTA (Health Canada). Participants will be randomized on Day 0 in a ratio of 2:1 to receive 600 mg FSD201 or placebo orally twice daily for 56 days.

4.5. Description of the study population

Adults (≥18 years and ≤ 75 years.) with chronic widespread musculoskeletal nociplastic pain (in three or more body regions) likely related to 'idiopathic MCAS' are selected and randomized to receive either FSD201 600 mg *b.i.d.* or placebo.

5. Study Objectives

5.1. Main Objectives

- To evaluate the analgesic efficacy of FSD201 compared to placebo in subjects with chronic widespread musculoskeletal nociplastic pain;

5.2. Secondary Objectives

- To evaluate the efficacy of FSD201 as compared to placebo on pain-related function, sleep interference, and global improvement;

- To assess safety and tolerability of FSD201 in subjects with chronic widespread musculoskeletal nociplastic pain;
- To evaluate the change in serum tryptase, IL-6 and IL-1beta serum biomarker levels.

5.3. Study Endpoints

5.3.1. Primary endpoint

Targeted treatment effect of 30% decrease from baseline to Day 28 in the average daily pain intensity score measured by an 11-point numerical pain rating scale (NPRS). Averages will be calculated as follows:
Baseline: calculated weekly average from Day -7 to Day -1
Day 28: calculated weekly average from Day 22 to Day 28

5.3.2. Key Secondary endpoints

Key secondary efficacy endpoints will include changes from baseline to Day 56 as measured by:

- Percentage of subjects achieving ≥30% reduction in NPRS score at the end of treatment with FSD201[1]
- Change in Patient Global Impression of Change (PGIC) after 56 days treatment
- Change or reduction in patient average daily NPRS after 56 days of treatment[1];
- Change in Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance- Short Form (SF) 8a after 56 days treatment
- Change in the PROMIS Pain Interference- SF 8a score after 56 days treatment
- Change in the PROMIS General Life Satisfaction- SF 5a after 56 days treatment
- Change in the PROMIS Fatigue- SF 8a after 56 days treatment
- To determine whether FSD201 treatment reduces serum mast cell tryptase, IL-6 and IL-1beta during treatment.

Key secondary efficacy endpoints will include changes from baseline to Day 28 and Day 56 as measured by:

- Percentage of subjects achieving ≥30% reduction in NPRS score[1]
- Change in Daily Sleep Interference Scale (DSIS) after 28 and 56 days of treatment[1]
- Change in Patient Global Impression of Change (PGIC).

Note:
[1]DSIS and NPRS averages will be calculated as follows:
Baseline: calculated weekly average from Day -7 to Day -1
Day 28: calculated weekly average from Day 22 to Day 28
Day 56: calculated weekly average from Day 49 to Day 55 for the NPRS and Day 50 to Day 56 for the DSIS

5.3.3. Other Secondary Endpoints

- Change in pain intensity on the NPRS from baseline to each week of treatment
- Percentage of subjects achieving ≥50% reduction in NPRS at Day 56[2]
- The total amount of rescue medication used.

Note:
[2]DSIS averages will be calculated as follows:
Baseline: calculated weekly average from Day -7 to Day -1
Day 56: calculated weekly average from Day 49 to Day 55

5.3.4. Exploratory endpoints

- Changes in CRP, IL-2, IL-4, IL-8, IL-10, IL-12 (p70), IL-13, TNF-α and IFN-γ from baseline to Day 14, Day 28 and Day 56.
- FSD201 plasma exposure will be performed by analyzing plasma samples.
- Change or reduction in patient weekly PI-NRS after 28 and 56 days of treatment.

5.3.5. Safety endpoints

- Incidence and severity of treatment-emergent adverse events (TEAEs) throughout the dosing period
- Incidence and severity of treatment-emergent changes in laboratory values at Day 56
- Change from baseline in vital signs at each in-patient visit.

6. Study Design

6.1. Description of Study Design

This study is a randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of FSD201 in adult subjects with musculoskeletal nociplastic pain associated with MCAS.

The study design consists of up to 17 days screening period, a 56-day treatment period, and a 7-day follow-up period. Each subject will participate in the trial for up to 80 days.

6.2. Patient Recruitment

Subjects will be recruited by physician databases.

All subjects will provide written informed consent for the study at the beginning of the Screening Visit, prior to performance of any of the study procedures and collection of study data.

The subject's eligibility for randomization will be determined at Visit 2 according to the inclusion and exclusion criteria set forth in Section 10.1.

A unique identification number will be given to study subjects to keep their information anonymous. Subject numbers will be assigned in sequential order (i.e., the first subject's identification number will be 001, etc.). This number will be used in all CRFs.

Demographic Data and Medical History

The subject's demographic information and medical history will be recorded at the Screening Visit and documented on the appropriate CRF. This will include:

- Demographic information: sex, age, race and ethnicity
- Medical history for the past 10 years prior to screening and other relevant history will be collected, including other types of pain (e.g., arthritis); surgeries; diabetes; cancer; cardiovascular events; and gastrointestinal problems
- Data on MCAS will be captured separately, in detail, including date of onset, and attempted treatments

After providing written informed consent, potential study subjects will be screened for study eligibility during the maximum 17 days screening and baseline period. During this time, subjects will complete daily entries to collect daily pain and sleep disturbance scores, and document rescue medication use (acetaminophen or diphenhydramine). Entries will be collected by means of a Study electronic Application (App) developed for this trial. The app can be installed on the patient's own device (assisted by the study coordinator), or the patient will be provided with a device (phone or tablet) to record these entries daily.

The values recorded on the last seven days before the randomization/Visit 2 will be used to determine the baseline scores. Subjects who completed entries in the App on at least 5 out of 7 days before randomization /Visit 2 and have an average pain intensity between 4.0 and 9.0 that meets the study-specified threshold and who continue to meet all other study eligibility criteria will be enrolled in the study.

Patients who meet the eligibility criteria will be randomized on Visit 2 in a ratio of 2:1 to receive 600 mg FSD201 or a placebo orally twice daily for 56 days. Subjects will take their first dose of the investigational either FSD201 or placebo in the clinic. An assessment for allergy or hypersensitivity reaction will be conducted immediately after the first dose; signs and symptoms to be evaluated include flushing, skin rash, urticaria, fever, dyspnea, bronchospasm, edema, angioedema, hypotension, and anaphylaxis.

Subjects will continue completing daily App entries throughout the 56 day treatment period including their 11-point pain scale over the last 24 hours, their sleep disturbance score, their rescue medication and their Investigational Compliance.

Subjects will return to the site at Day 14, Day 28 and Day 56/ Early termination visit. A phone call will be made to each subject seven (7) days after the last intake of the investigational product.

Subjects will be monitored for adverse events (AEs) from the date of first dose until the last follow-up visit (AEs noted between signing of Informed Consent Form (ICF) and first dose should be recorded as Medical History). Any SAEs occurring within 7 days after the last investigational medicinal product (IMP) intake will be collected. Efficacy and safety will be assessed as outlined in the schedule of events (Table 1).

6.3. Overall Program Design and Plan

A timeline of study activities is shown in Figure 5.

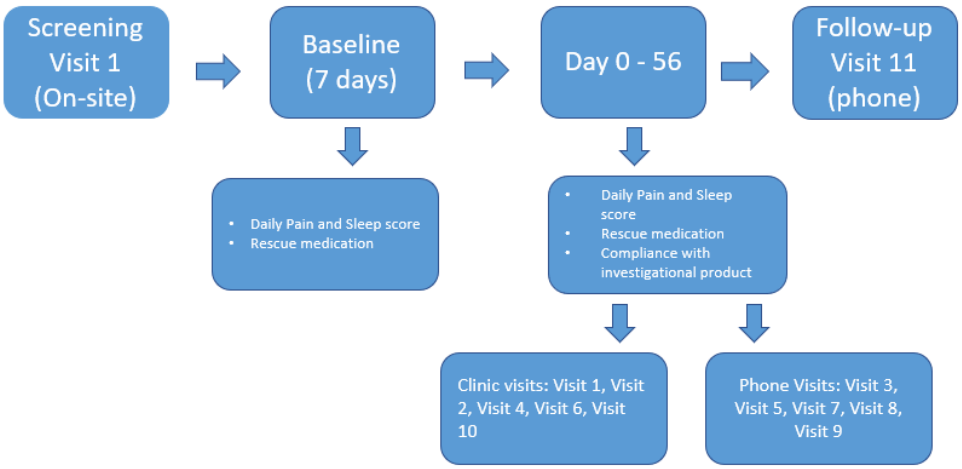

Figure 5 Schematic of Clinical Activities from Visit 1 (Screening) until Visit 11 (Follow-up)

6.4. Study Procedures and Evaluations

Visit Number	1		2	3	4	5	6	7	8	9	10	11	ET
Study Day	Day -17 to Day -8	Day -7 to Day -1	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Day 63	N/A
Type of Visit	On Site	N/A	On Site	Phone	On Site	Phone	On Site	Phone	Phone	Phone	On Site	Phone	On Site
Written informed consent	X												
Demographic data	X												
Medical and medication history	X		X										
MCAS/MCAD History	X												
Physical examination (1)	X		X		X		X				X		X
Body Mass Index (BMI)	X												
Weight and Vital signs [BP, pulse, RR] (2)	X		X		X		X				X		X
Safety Laboratory Testing (3)	X		X		X		X				X		X
HIV, Hepatitis testing	X												
Pregnancy test (4)	X		X		X		X				X		X
Urine drug screen	X		X		X		X				X		X
Blood test (biomarkers) (5)	X		X		X		X				X		X
FSD201 Plasma exposure			X		X		X				X		X
Review of Inclusion / Exclusion criteria	X		X		X		X				X		X
Sleep Disturbance SF (PROMIS)			X		X		X				X		X
Pain Interference (PROMIS)			X		X		X				X		X
General Life Satisfaction (PROMIS)			X		X		X				X		X
Fatigue (PROMIS)			X		X		X				X		X
Anxiety (PROMIS)			X		X		X				X		X
Pain Intensity Numerical Rating Scale (PI-NRS)	X		X		X		X				X		X
Pain Catastrophizing Scale (PCS)			X		X		X				X		X
Health Questionnaire (PHQ-9)	X												
Anxiety Disorder (GAD–7)	X												
Patient Global Impression of Change (PGIC)											X		X
Randomization			X										
Allergy Assessment			X										
Adverse event recording			X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X
Connect to patient App/provide device	X												
11-point NPRS	X	X	X	X	X	X	X	X	X	X	X		X
DSIS Sleep scale	X	X	X	X	X	X	X	X	X	X	X		X
Rescue medication intake recording	X	X	X	X	X	X	X	X	X	X	X		X
Review of patient results in App			X		X		X				X		X
Investigational product dispensing			X		X		X						
Investigational product return and accountability					X		X				X		X
(1) A detailed physical examination to be performed at Visit 1 and a focused exam to be performed at all other visits													
(2) Vital signs measurements [T, HR, BP, SO2, RR]													
(3) Safety Laboratory Testing (Hematoloty, Biochemistry, Urine analysis)													
(4) Serum pregnancy will be performed at Visit 1 screening; Urine pregnancy to be performed at all other visits													
(5) Biomarkers: At Visit 1, only Serum Tryptase performed; all biomarkers performed at other visits													
(6) To be performed within 14 (±2) days of discontinuation or withdrawal													

Table 1 Schedule of Events

A schedule of events is shown in Table 1. Visits 3-11 may occur ±2 days from the days listed in the table, except for Visit 4, which may occur from Day 12 to Day 15.

7. Description of Procedures

7.1. Subject Enrollment Procedures

Subjects will be recruited by various methods, including advertising, physician referral, brochures posted in health-care facilities, and subject databases.

Prior to screening a patient, each institution must have submitted all necessary regulatory documentation to Ozmosis Research Inc. Access to the electronic case report forms (eCRFs) will only be granted once this has been received. All sites should contact Ozmosis Research Inc. at the information provided on the cover page to verify study availability.

All subjects will provide written informed consent for the study at the beginning of the Screening Visit, prior to performance of any of the study procedures and collection of study data. Subjects will be assigned a unique subject number when the signing the informed consent.

A subject's eligibility for randomization will be determined at Visit 2 according to the inclusion and exclusion criteria set forth in Section 10.1. Failure to meet specific inclusion or exclusion criteria will be reviewed on a case-by-case basis, and enrollment waivers will be completed as necessary. The sponsor must agree to any waivers prior to patient being randomized.

Upon enrollment into the study, an RTSM system will be used to assign patient to a treatment arm, according to the randomized treatment list. The system will assign a wallet number to the patient based upon treatment arm. Patients will be assigned the first wallet at Visit 2, a second wallet at Visit 4, and 2 additional wallets at Visit 6 (all in the same treatment arm)

Protocol treatment should begin within 17 working day of patient registration.

Note: it is the responsibility of the investigator in charge to satisfy themselves that the patient is indeed eligible before requesting registration.

7.1.1. Demographic Data and Medical History

The subject's demographic information and medical history will be recorded at the Screening Visit and documented on the appropriate CRF. This will include:

- Demographic information: sex, age, race and ethnicity
- Medical history for the past 10 years prior to screening and other relevant history will be collected, including other types of pain (e.g., arthritis); surgeries; diabetes; cancer; cardiovascular events; and gastrointestinal problems
- History of chronic widespread musculoskeletal nociplastic pain

7.1.2. Prior Medications

Prior and Concomitant Medications: Medications taken for the past 3 months preceding screening will be recorded at the Screening Visit (Visit 1). Prior medications include analgesics of all types, anti-inflammatory drugs, antidepressants, and anticonvulsants. Patient will be allowed to continue their current pain medication regimen as long as they are not taking a prohibited medication listed in Section 8.2.2. In addition, they should not start any other analgesics while in the study.

7.1.3. Treatment Assignment/Randomization and Blinding

At the Screening Visit (Visit 1), subjects who meet all entry criteria, including minimum pain score will be trained on completing the App entries and will enter the Baseline Period if the results of the laboratory tests confirm their eligibility. During this period, subjects will capture their 0-10 NPRS scores daily using the App. At Visit 2, App entries will be reviewed and those subjects who have an average daily pain intensity score ≥ 4.0 and ≤ 9.0 on the 0-10 NRS over the 1-week Baseline Period will be randomized to either FSD201 or placebo treatment in a double-blind manner; subjects will be required to have completed at least 5 of the daily diaries during the Baseline Period.

Randomization

Eligible patients who consent to participate in the trial will be randomized through the RTSM using a randomization list in a 2:1 manner with FSD201 or placebo.

Blinding

The investigators, site staff, monitor and sponsor will be blinded to the study assignment.

Unblinding

The study investigators, statistical team, and sponsor will be blinded to the trial randomization code. The Principal Investigator may decide to unblind a subject's treatment code in the case of a medical emergency or in the event of a serious medical condition, for which the knowledge of the treatment is essential for the clinical management of the subject's condition. The investigator should promptly document and explain to the Sponsor any premature unblinding (e.g. accidental unblinding, unblinding due to a serious adverse event, etc.) of the study participant. Women who become pregnant during the study period and male subjects whose partner becomes pregnant will be withdrawn from the study and unblinded due to unknown risks to the fetus. A subject's treatment may also be unblinded in the event of a suspected unexpected serious adverse event (SUSAR) in order to determine reportability of the event to regulatory authorities. Whenever possible, the Sponsor will be notified prior to breaking the blind.

When study participant unblinding is required, the investigator will use the RTSM system to determine treatment arm. Only the PI will have this function available. Unblinding will be documented in the Investigator site file (ISF) and the CRF. Unblinding the treatment assignment for the study will occur after database lock when all trial subjects have completed their end-of-treatment or study discontinuation visit.

Treatment

Investigational product (FSD201 or placebo) will be dispensed at Visit 2 (one wallet containing 15 days treatment), Visit 4 (one wallet containing 15 days treatment), and Visit 6 (2 wallets for a total of 28 days treatment). Outside of the visits, subjects are to orally self-administer the investigational product *b.i.d.* at home during the Treatment Period. The last dose of investigational product is to be taken in the morning of Visit 10. The investigational product is to be taken with a glass of water, within 30 minutes of a meal/food.

Subjects who forget to take their dose at the usual required time should take it immediately upon noting that it was missed. If a dose is missed altogether, the subject should record this in the daily dose compliance tracker (App) and continue with the normal scheduled dose on the following dose.

Adherence to Treatment: Following App review the Investigator or Investigator's designee will determine adherence to treatment. Subjects will be asked to bring their medication at Visit 4 and Visit 6 for an investigational product count. Subjects who missed >20% of the doses will be considered non-compliant. Non-compliant subjects will be counselled to adhere to the medication regimen and will be used for a sub-analysis study.

Safety Measures

General Physical Examination: A general physical assessment of the major body systems will be performed at the Screening Visit (Visit 1). An abbreviated physical exam focusing on the previously identified abnormalities or any patient reported symptoms will be performed at Visit 2, Visit 4, Visit 6, Visit 10 and the Early Termination Visit(if applicable).

Pregnancy Test (if applicable): At the Screening Visit, a serum pregnancy test will be performed. At Visit 2, Visit 4, Visit 6, Visit 10, and Early Termination a urine pregnancy test will be conducted at the clinic.

Vital Signs: Sitting blood pressure, heart rate, body temperature, oxygen saturation using Pulse oximetry and breathing rate will be measured at each visit after the subject has been sitting quietly for at least 5 minutes. Data will be recorded in the appropriate CRF.

Clinical Laboratory (Non fasting): Clinical laboratory testing will be performed at the Screening Visit (to determine and confirm eligibility) Visit 2, Visit 4, Visit 6, Visit 10 (End of Treatment) and in the event of Early Termination as shown in Table 2. Blood (~15 mL) and urine samples will be collected. The clinical laboratory analyses will include:

- Biochemistry: LFTs (serum ALT, AST, alkaline phosphatase, γ-glutamyl transpeptidase (GGT), albumin, bilirubin), CK, Cr (eGFR), blood urea nitrogen (BUN), HbA1c, lipid assessment, sodium, potassium, chloride, bicarbonate, and glucose

- Viral testing: HBV (antibody and antigen), HCV (antibody), HIV (antibody)
- Hematology: CBC with differential, PT/ INR, PTT
- Urinalysis: total urinalysis (chemical), drug test, Albumin/Cr ratio, urine pregnancy test including a microscopic examination
- Biomarkers: CRP, tryptase, cytokine panel (IL-1 beta, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 (p70), IL-13, TNF-α and IFN-γ) (only serum tryptase performed at Visit 1, all biomarkers performed at subsequent visits)

	Visit 1	Visit 2	Visit 4	Visit 6	Visit 10	Early Termination
	Screening	**Day 0**	**Day 14**	**Day 28**	**Day 56**	
Hematology						
CBC with differential	X	X	X	X	X	X
PT/ INR	X	X	X	X	X	X
PTT	X	X	X	X	X	X
Biochemistry						
HCV and HBV testing	X					
HIV testing	X					
Sodium	X	X	X	X	X	X
Potassium	X	X	X	X	X	X
Chloride	X	X	X	X	X	X
Bicarbonate	X	X	X	X	X	X
LFT (ALT, AST, GGT, ALP, albumin, bilirubin)	X	X	X	X	X	X
CK	X	X	X	X	X	X
Albumin/ Creatinine ratio	X	X	X	X	X	X
Creatinine (eGFR)	X	X	X	X	X	X
Blood urea nitrogen (BUN)	X	X	X	X	X	X
Glucose	X	X	X	X	X	X
HbA1C	X	X	X	X	X	X
Lipid assessment	X	X	X	X	X	X
beta-HCG (serum pregnancy)	X					
Biomarkers						
CRP		X	X	X	X	X
Serum Tryptase	X	X	X	X	X	X
Cytokine Panel*		X	X	X	X	X
FSD201 Exposure						
FSD201 Plasma Level		X	X	X	X	X
Urine Analysis						
Drug Test	X	X	X	X	X	X
Urine Pregnancy Test		X	X	X	X	X
Urinanalysis (chemical)	X	X	X	X	X	X

Table 2 Lab Requirements

* IL-1 beta, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 (p70), IL-13, TNF-α -and IFN gamma.

A central lab will be used for analysis in this study. Data will be recorded in the appropriate CRF. Laboratory data may be repeated at the discretion of the Investigator.

Adverse Events (AE): At Visit 2, subjects will be instructed to call the study center in the event of any AEs that may require medical attention, regardless of possible relatedness to the study medication. At each visit and during the telephone calls, the study staff will prompt the subject to report all AEs that have occurred since the last visit. See Section 12 for more details on how AEs are defined, reported, and managed.

7.1.4. Pain Assessments

Numerical Pain Rating Scale (NPRS): This self-administered questionnaire will be conducted using the Study electronic App. This 11-point scale (from 0-10) will ask the patient to assess their pain level over the past 24 hours. This scale will be assessed once each day during screening, baseline and treatment.

Pain Intensity Numerical Rating Scale (PI-NRS): This self-administered questionnaire will be conducted in the clinic. This 11-point scale (from 0-10) will ask the patient to assess their pain level over the past 7 days. This scale will be assessed at visit 1, 2, 4, 6 and 10, or early termination if applicable.

Pain Interference – Short Form 8a (PROMIS): This form is a self-administered questionnaire where subjects will be asked to **measure the effect of pain on their** social, cognitive, emotional, physical, and recreational activities at visit 2, 4, 6 and 10, or early termination if applicable.

Pain Catastrophizing Scale (PCS): Subjects will be asked about their feelings while experiencing or thinking about pain – they don't necessarily have to be in pain while completing this questionnaire. This will be performed at visit 2, 4, 6 and 10, or early termination if applicable.

7.1.5. Sleep Scores

Sleep Disturbance – Short Form 8a (PROMIS): This form is a self-administered questionnaire where subjects will be asked to rate the attributes of their sleep over the past week. A total score is obtained by adding the results of each question (8 in total) to get a score out of 40. This will be assessed in clinic at Visits 2, 4, 6 and 10.

Daily Sleep Interference Scale (DSIS): This self-administered questionnaire is used to quantify sleep interference due to pain. This scale should be completed by patients once a day (upon awakening) to accurately capture variability in sleep interference due to pain. This questionnaire will be conducted using the Study electronic App. This scale will be assessed once each day during screening, baseline and treatment.

7.1.6. Questionnaires

Patient Global Impression of Change (PGIC): This self-administered questionnaire assesses the global status of the subject by asking the subject if s/he feels that his/her condition has improved, has not changed, or has worsened since the beginning of the study. The PGIC questionnaire will be administered at Visit 10 (End of Treatment) and in the event of Early Termination.

Fatigue – Short Form 8a (PROMIS): A self administered questionnaire that assesses the consequences of pain on a person's ability to enjoy their life. It will be administered at visit 2, 4, 6 and 10, or early termination if applicable.

General Life Satisfaction – Short Form 5a (PROMIS): A self-administered questionnaire that assesses the overall life satisfaction of the subject. This questionnaire will be administered at visit 2, 4, 6 and 10, or early termination if applicable.

Anxiety - Short Form 8a (PROMIS): A self-administered questionnaire that assesses the subjects overall change in mood symptoms (depression, anxiety, and anger) since the beginning of the study. This questionnaire will be administered at visit 2, 4, 6 and 10, or early termination if applicable.

Generalized Anxiety Disorder (GAD–7): A self-administrated test to assess generalized anxiety disorder. The normative data enable users to discern whether an individual's anxiety score is normal, or mildly, moderately, or severely elevated. This questionnaire will be administered at Visit 1 (screening) to exclude patients with scores score >15.

Patient's Health Questionnaire (PHQ-9): A self administered questionnaire that diagnoses and measures severity of depression in a subject. This questionnaire will be administered at Visit 1 (screening) to exclude patients with scores score >20.

7.1.7. Withdrawal/Discontinuation Procedures

A subject may be discontinued from the study at the discretion of the Investigator for medical reasons, or if the subject wishes to withdraw. **Subjects who do not meet the additional criteria for entering the Treatment Period at Visit 2 will be discontinued from the study and considered screen fails**. Women who become pregnant during the study and males whose partners become pregnant during the study will immediately be discontinued from the study. Refer to Section 12.8 for Pregnancy report criteria. Subjects may, at the Investigator's discretion, also be discontinued at any time due to non-adherence to treatment regimen (e.g., <80% of the doses taken, failed urine drug test) and missed visits. If a subject does not return for a scheduled visit, every effort will be made to contact the subject, and document the subject outcome, if possible.

Based on previous studies of PEA and the FSD201 Phase 1 trial, the most likely AEs would be related to gastrointestinal intolerance and/or diarrhea. Based on this, laboratory changes consistent with severe diarrhea including a decrease in kidney function (eGFR < 60 mL/min/1.73m^2) or hyperkalemia/hypokalemia (serum potassium < 3.0 mmol/L or serum potassium > 5.5mmol/L) will cause the patient to be discontinued from treatment. In addition, patients who experience a single SAE probably related to the study drug will also be discontinued (whether or not this SAE is related to gastrointestinal intolerance/diarrhea). Individual stopping criteria are summarized in Table 3.

Stopping Criteria	Value for Stopping
Kidney Function (eGFR)	<60 mL/min/1.73m^2
Potassium	<3.0 mmol/L or >5.5mmol/L
Development of an SAE probably related to the study drug	1 SAE

Table 3 Individual Stopping Criteria

All subjects who withdraw or are discontinued by the Investigator (for any reason) will have an Early Termination Visit performed within 14 (±2) days of discontinuation or withdrawal. If subjects have ongoing AEs at the time of discontinuation, the site should follow up with the patient until all AEs are resolved or closed.

The study will be stopped if there are four individuals with SAEs probably related to the study drug in the FSD201 treatment group. This represents 10% of the expected 40 patients in the FSD treatment group.

8. Treatment Plan

8.1. Product, Dose and Mode of Administration Dose

FSD201 is provided as a 600 mg tablet. Participants will be provided with a wallet containing 3 blister cards (sufficient for 15 days of dosing). Subjects should take one (1) tablet twice daily after food approximately 12 hours apart. The subjects will receive a total of 4 wallets over the course of the study, dispensed at Visits 2, 4 and 6.

8.1.1. Investigational Therapy

All randomized subjects will receive the study drug from Day 0 to Day 56 (Visit 2 to Visit 10). Subjects will take one tablet in the morning and one tablet in the evening (i.e., approximately every 12 hours, approximately at the same time every day, and at least 8 hours apart) according to their randomized treatment arm assignment as described below:

Arm A: FSD201 600 mg tablet *b.i.d.* for oral administration after food.
Arm B: One placebo tablet (i.e., matching 600 mg FSD201 tablets) *b.i.d.* for oral administration after food.

The first dose of the study drug will be taken at the site.

8.2. Description of Compound, Packaging, Labeling, Storage

FSD201: Each white-colored oval Oral tablet formulation contains 600 mg of FSD201 drug substance (ultramicronized *N*-(2-hydroxyethyl)hexadecanamide). The excipients used in tablet formulation include Microcrystalline Cellulose, Croscarmellose Sodium, Povidone, Magnesium Stearate, Silicon Dioxide and Polysorbate 80 (vegetal origin).

Placebo: Oral tablet formulation containing Microcrystalline cellulose, Dicalcium Phosphate, Croscarmellose Sodium, Magnesium Stearate and Silicon Dioxide. The placebo tablet will be identical in appearance to the study drug.

Primary and Secondary Packaging: Tablets are provided in blister cards of 10 tablets per card, 3 cards per wallet, sufficient for 15 days of dosing.

Labelling: The blister cards will not be labelled individually. The wallet of three blister cards will be labelled according to applicable regulations.

Storage: The blister cards should be stored in the wallet bearing the study label. The investigational product should be stored at room temperature (15-25°C) out of reach of children.

8.2.1. Rescue Medication

Acetaminophen (maximum daily dose 3,000 mg) or diphenhydramine (maximum daily dose 300 mg) is allowed, starting at the screening visit.

8.2.2. Concomitant and Prohibited Medication

Medications taken for pain associated with chronic widespread musculoskeletal nociplastic pains (arising from neurogenic inflammation) secondary or likely "idiopathic MCAS" during the 17 days before the Screening Visit will be recorded in the case report form.

Concomitant use of the following medications or therapies could influence the evaluation of the study drug's efficacy and safety and are prohibited throughout the study:

- Antidepressants (except for selective serotonin reuptake inhibitors)
- Ketamine
- Opioid agonists
- Mast cell stabilizers (e.g., cromolyn sodium, ketotifen, hydroxyurea)
- Mast cell inhibitors (e.g., montelukast, zafirlukast, zileuton, petosan)
- Chemotherapeutic agents (e.g., imatinib, masitinib, dasatinib, nilotinib)
- Intravenous immune globulin (IVIG)
- NSAIDs
- Cannabinoids
- Herbal remedies/supplements containing palmitoylethanolamide

Procedures that may have efficacy in reducing chronic musculoskeletal nociplastic pain are prohibited unless stable for 4 weeks before the Screening Visit, for example, nerve block,

iontophoresis, laser therapy, acupuncture, spinal cord stimulation therapy, transcutaneous electrical nerve stimulation. Stable procedures should be continued for the duration of the study.

The following medications are permitted if they have been at a stable dose (defined as no change to the regimen and the subject reports taking the medication as prescribed) for at least 4 weeks before the Screening Visit, and the dose will remain unchanged during the study:

- Sedatives (e.g., zopiclone, zolpidem, benzodiazepines except lorazepam, temazepam, oxazepam, midazolam);
- Aspirin (low dose, ≤325 mg once daily, for cardio prophylaxis)
- Histamine blockers
- Naltrexone (opioid antagonist)
- Gabapentinoids and other anticonvulsants
- Muscle relaxants
- Local anesthetics
- Topical pain mediations

Stable doses of the selective serotonin reuptake inhibitors (SSRIs) are allowed to treat depression if the dose is stable for 60 days before Screening Visit.

8.2.3. Treatment Duration

Each subject will participate in the study for a maximum of 80 days, including a screening period of up to 17 days, a 56 day double-blind treatment period, and a 1-week post-treatment follow-up period.

After their last study drug intake (Day 56), a safety follow-up assessment 7 days (7 ± 2 days) will occur. Follow-up on SAEs and AEs will continue until resolution of the event or until a stable condition is reached. Any SAEs occurring within 7 days after the last IMP (Investigational Medicinal Product) intake will be collected.

9. Materials

The Sponsor will provide at no cost the investigational medicinal product to be used. In addition, the App will be provided at no cost. Patients can choose to have the App installed on their own device, or a device can be provided by the site at no cost.

10. Selection and Withdrawal of Subjects

10.1. Inclusion Criteria

1. The subject is ≥ 18 and ≤ 75 years of age at the time of signing ICF

2. Clinical diagnosis of idiopathic MCAS (in the presence or absence of a generalized hypermobility spectrum disorder (G-HSD) or Ehlers-Danlos Syndrome (EDS)) as per the global consensus diagnostic criteria (consensus-2 criteria (Afrin et al., 2021);
    a) Medical history shows a constellation of clinical complaints attributable to pathologically increased mast cell (MC) activity (MC mediator release syndrome)
    b) Medical history of symptomatic response to inhibitors of MC activation or MC mediator production or action
3. Adults with widespread chronic nociplastic pain (in three or more body regions)
4. Chronic pains of intensity ≥4.0 but ≤9.0 on a Numeric Pain Rating Scale, symptom duration of >6 months
5. Subject signed a Research Ethics Board (REB) or Institutional Review Board (IRB) approved written informed consent and privacy language (Health Insurance Portability and Accountability Act (HIPAA) and Personal Information Protection and Electronic Documents Act (PIPEDA) authorization before performing any study-related procedures
6. The subject is considered reliable and capable of adhering to the protocol (e.g. able to understand and complete forms and questionnaires, visit schedule, or medication intake according to the judgment of the investigator
7. Subject agrees to use only acetaminophen (up to 1000 mg per dose and not to exceed 3000 mg/day) or diphenhydramine (up to 300 mg/day) as rescue medication for chronic widespread musculoskeletal nociplastic pains throughout the trial
8. The subject is willing to maintain current activity and exercise levels throughout the study
9. During the study, the subject agrees not to initiate or change any non-pharmacologic interventions (including chiropractic care, physical therapy, psychotherapy, and massage therapy). Any ongoing non-pharmacologic intervention must be stable for at least 4 weeks before screening and should be continued for the duration of the study
10. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Randomization Visit
11. Female subjects of childbearing potential must use an acceptable method of birth control. Acceptable birth control includes total abstinence from heterosexual intercourse, a vasectomized partner, intrauterine device, or double barrier method including condoms, sponge, diaphragm, contraceptives (oral, parenteral, or transdermal), or vaginal ring with spermicidal jellies or cream. Subjects considered not of childbearing potential must be surgically sterile (total hysterectomy, bilateral salpingo-oophorectomy, or tubal ligation) or be more than one year post-menopausal, defined as a complete cessation of menstruation for at least one year. Male subjects who are sexually active must use an acceptable method of birth control. Acceptable birth control includes total abstinence from heterosexual intercourse, or use of a double barrier method including condoms sponge, diaphragm, contraceptives (oral, parenteral, or transdermal), or vaginal ring with spermicidal jellies or cream used by partner. Periodic abstinence and withdrawal are not acceptable methods of contraception.
12. The subject is in good health as judged by the investigator, based on medical history, physical examination, serum chemistry, hematology, and urine analysis

13. At the screening visit, the body mass index (BMI) is between 18 and 39 kg/m^2
14. The subject is sufficiently fluent in English language to answer the questionnaires in clinic and on the App.

10.2. Randomization Criteria

1. The subject is compliant with daily App entries during the baseline period, as defined by the completion of a minimum of 5 of 7 daily NPRS scores
2. The average daily pain intensity scores on the NPRS are ≥ 4.0 and ≤ 9.0 over the last seven days before the Randomization Visit

10.3. Exclusion Criteria

1. The subject has pain that cannot be clearly differentiated from or that could interfere with the assessment of chronic musculoskeletal nociplastic pain secondary likely to idiopathic MCAS (e.g.post-herpetic neuralgia, traumatic injury, prior surgery, complex regional pain syndrome)
2. Adults with chronic cancer pain
3. Adults with inflammatory connective tissue disorder or rheumatological disorder-related pain, e.g. rheumatoid arthritis
4. Adults with focal musculoskeletal pain
5. Adults with skin diseases (e.g., chronic urticaria, pemphigus, lupus, rosacea etc.)
6. Adults with endocrinological disorders (e.g., acute hypothyroidism, acute adrenal insufficiency etc.)
7. Adults with systemic gastrointestinal conditions (e.g., Inflammatory bowel disease)
8. Significant psychological comorbidities: PHQ-9 score >20; and GAD-7 score >15 (indication of severe anxiety that could interfere with accurate logging of pain ratings)
9. Current or recent (within 12 months of screening) history of a substance use disorder including cannabinoid or alcohol use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (5th edition; DSM-5)
10. Subject has neurologic disorder unrelated to chronic widespread musculoskeletal nociplastic pains (e.g., phantom limb from amputation, vitamin B12 deficiency, chronic inflammatory demyelinating polyneuropathy), circulatory disorder (e.g., peripheral artery disease), a skin condition in the area of neuropathy that could alter sensation (e.g., plantar ulcer), or other painful conditions (e.g., arthritis) that, in the judgment of the investigator, could interfere with reporting of pain due to chronic widespread musculoskeletal nociplastic pains
11. Current severe or uncontrolled major depressive disorder or anxiety disorders. Mild to moderate major depression or anxiety disorders are permitted provided that the investigator assesses the patient as clinically stable and appropriate for entry into the study. Stable doses of SSRIs are allowed for the treatment of depression if the dose is stable for 60 days before Screening Visit

12. Subject has a history of suicide attempt or suicidal behaviour within the last 12 months or has suicidal ideation within the previous 12 months or who is at significant risk to commit suicide, as judged by the Investigator at Screening or during the treatment period
13. The subject is currently using protocol-specified prohibited medications.
14. Positive urine drug screen for illegal or non-prescribed drugs at the Screening Visit or during the treatment period
15. Pregnant or lactating females or females planning to become pregnant during the study or within 28 days following the last dose of study medication
16. Male patients planning a partner pregnancy or sperm donation during the study or within three months following the last dose of study medication
17. Patients with active malignancy or history of malignancy, except for basal cell or squamous cell carcinoma and actinic keratosis. Basal cell carcinoma and small squamous cell carcinoma of the skin which have been excised according to guidelines within the last 5 years or in situ cervical carcinoma that has been fully treated and shows no evidence of recurrence are allowed
18. Positive human immunodeficiency virus (HIV), hepatitis B or hepatitis C laboratory result
19. Any clinically significant unstable medical abnormality or acute or chronic disease of the cardiovascular, gastrointestinal, respiratory, hepatic, or renal systems. Subject with aspartate transferase or alanine transferase > 2.5 times the upper limit of normal (ULN) or alkaline phosphatase > 3.0 times ULN
20. Any clinically significant deviation from normal in physical examination, vital signs, or clinical laboratory tests, as determined by the investigator
21. Known history of seizure disorder, epilepsy, convulsions, or increased intracranial pressure anytime during the subject's life except for pediatric febrile seizures
22. Subject has received an investigational therapy of any kind within 28 days or 5 half-lives, whichever is longer, before Screening Visit
23. Subject has had known hypersensitivity or intolerance to the use of PEA, diphenhydramine (e.g. Benadryl) or acetaminophen (e.g. Tylenol) and/or their associated formulation components
24. The subject is a member of the site staff or relative of a staff member
25. Individuals with high baseline serum tryptase levels suggestive of Primary or Secondary MCAS (defined as above the normal range of 2.2 to 13.2 µg/L)

10.4. Subject Withdrawal or Replacement

A subject can withdrawal at any time for any reason. Subjects will be withdrawn if they are unable to receive a dose.

10.5. Planned Sample Size

The planned sample size for this study is based on making a Go/No-Go evaluation, focussing on the percentage of patients achieving the reduction in NPRS score, that is, using the binary responder endpoint. A decision criterion is applied with possible decision outcomes being ‘Go’

(suggests FSD201 warrants further development), 'Stop' (or no-Go, suggests further development of the FSD201 should stop), and 'Pause' (inconclusive, additional investigation should be performed before a decision is made). This decision framework was published by Lalonde et al., (2007) and Frewer et al., (2016). Note that these decision criteria will not be definitive as the final decision to continue development will be based on more than just the responder endpoint.

For this decision framework, a lower reference value (LRV) and a target value (TV) are defined for the treatment effect (i.e., difference in the drug response rate between FSD201 and placebo) as follows:

• LRV: The minimum treatment effect below which there is no desire to continue development the compound.
• TV: The targeted treatment effect above which the compound is expected to replace the current standard of care in terms of efficacy

The Go/No-Go calculations are based on the TV of a 30% difference between FSD201 and placebo, and the minimum difference to be considered for further development being 10% (LRV). Furthermore, the calculations have been made such that there is at most 30% probability of a false-go, i.e., there is at least 70% desired confidence that the treatment effect is better than a 10% improvement (LRV), given that a Go decision is made. Similarly, there is a maximum of 10% false-stop risk, i.e., a maximum probability that the treatment effect is better than a 30% improvement (TV), given a Stop decision is made. Finally, it is assumed that the placebo response rate is 20%.

2:1 randomisation

A total sample size of 60 patients (40 on FSD201 and 20 on placebo) has been chosen to balance the needs to minimize the probability of 'Pause' whilst maintaining reasonable recruitment cost and time. Table 4 shows the probabilities of making a Go, Pause or Stop decision.

True Treatment Effect	Go	Pause	Stop
TV (30%)	85.2%	4.3%	10.4%
LRV (10%)	25.7%	7.5%	66.8%

Sum of the probabilities may not be 100% due to rounding for display

Table 4 Probabilities of Go, Pause or Stop Given the True Treatment Difference

11. Efficacy

Subjects will report daily average Numerical Pain Rating Scale (NPRS), their Daily Sleep Interference Scale (DSIS), their rescue medication and Investigational Compliance each day using the App.

The questionnaires on efficacy to be performed during the clinic visits include:

Patients Health Questionnaire (PHQ-9), Generalized Anxiety Disorder (GAD–7), Patient Global Impression of Change (PGIC), Anxiety – Short Form 8a (PROMIS), Sleep Disturbance – Short Form 8a (PROMIS), Pain Interference – Short Form 8a (PROMIS), Fatigue – Short Form 8a (PROMIS), General Life Satisfaction – Short Form 5a (PROMIS), Pain Catastrophizing Scale (PCS). Refer to the Study Procedures and Evaluations to determine which questionnaires are performed at each visit.

12. Safety

The safety and tolerability of FSD201 will be evaluated based on an assessment of treatment-emergent adverse events (TEAEs), clinical laboratory evaluations and physical examinations.

12.1. Biomarkers

Blood samples for analysis of inflammatory cytokines will be collected at Visit 2, Visit 4, Visit 6 and Visit 10. Blood sample collection will be captured in the source and recorded into the Electronic Case Report Form (eCRF).

12.2. Exploratory FSD201 plasma concentration

Blood samples for analysis of FSD201 will be collected on Visit 2, Visit 4, Visit 6 and Visit 10. Blood sample collection and processing times will be captured in the source and recorded into the eCRF, along with time of last test article intake (by patient recall). Blood samples should be processed according to the provided procedure as soon after collection as possible.

12.3. Definitions of Adverse Events

Per International Council for Harmonization (ICH) E2A: An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is considered to be related to the medicinal product.

Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs, but the action taken to treat the medical condition. They should be recorded as treatment of the AEs.

Use the following categories for assigning the certainty of the relatedness:

- **Not Related:** A causal relationship between the study drug and the AE can be easily ruled out (e.g., based on the temporal sequence, absence of a reasonable pathophysiological mechanism, or direct evidence of actual cause).
- **Unlikely Related:** A clinical event, including a laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and for which other drugs, chemicals, or underlying disease provide plausible explanations.
- **Possibly Related:** A clinical event, including a laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Probably Related:** A clinical event, including a laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal. Rechallenge information is not required to fulfill this definition.
- **Definitely Related**: A clinical event, including a laboratory test abnormality, which is a known effect of the drug, follows an obvious sequence of time from the drug's administration, and ceases with discontinuation of the drug. Rechallenge information is not required to fulfill this definition.

12.4. Severity of Adverse Events

Each AE will be assessed for its severity or for its intensity as experienced by the subject and according to the most recent MedDRA Version.

- **Grade 1 – Mild**
- **Grade 2 – Moderate**
- **Grade 3 – Severe**
- **Grade 4 – Life Threatening**
- **Grade 5 – Death**

12.5. Adverse Events Outcomes

The Investigator will categorize the outcome of AEs according to the definitions below:

- **Resolved:** The subject recovered from the AE.
- **Not Resolved/Ongoing:** At the time of the last assessment, the event is ongoing, with an undetermined outcome. Note: Ongoing AEs are not considered resolved as a result of death. No AE stop date will be recorded with an AE that is ongoing.

- **Chronic/Stable:** At the time of the last assessment, the event is ongoing and stabilized, with no change to the event outcome anticipated.
- **Death:** The AE directly caused death.
- **Unknown:** There is an inability to access the subject or the subject's records to determine the outcome (i.e., subject withdraws consent or is lost to follow-up).

12.6. Serious Adverse Events

An SAE or reaction is any untoward medical occurrence that at any dose:

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or congenital disability
- Is a significant medical event (e.g., intensive treatment in an emergency room or for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse; malignancy)
- Is life-threatening
- Results in death

12.7. Abnormal Laboratory Values

Any abnormality in a laboratory value that is new in onset, or which has worsened in severity or frequency from the baseline condition and meets 1 of the following criteria will be recorded on the AE pages of the eCRF:

- Is judged by the investigator as clinically significant
- Leads to discontinuation of the investigational product
- Requires therapeutic intervention or diagnostic tests
- Has accompanying or inducing symptoms or signs

12.8. Pregnancy

The Sponsor should report all pregnancies and pregnancies in the partners of subjects to the REB/IRB and Regulatory Authorities per institutional and/or regulatory guidelines.

Women who become pregnant during the study will be immediately discontinued from the study; if the woman was taking a double-blind treatment, the blind will be broken to determine whether the woman was taking placebo or FSD201; in the latter case, the woman will be regularly followed during the pregnancy until the child is born. Male participants whose partners become pregnant during the study will be immediately discontinued from the study; if the man was taking a double-blind treatment, the blind will be broken to determine whether he was taking placebo or FSD201.

Subjects should be instructed to immediately notify the investigator of any pregnancies and the investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

A Pregnancy Reporting Form should be completed by the investigator and submitted to Ozmosis Research Inc. either by email (ozmsafety@ozmosisresearch.ca) or via fax (416-637-8333) within 24 hours after learning of the pregnancy. Pregnancy should not be recorded on the Adverse Event eCRF but the date of pregnancy will be recorded in the database on the Pregnancy Report form CRF.

13. Reporting Procedures and Requirements

Any Adverse Events (AEs) occurring before the start of treatment (i.e., before the first dose of the investigational product) will be recorded in the medical history. The AE reporting period for this study begins when the subject received the first dose of study drug on trial and ends at the last follow-up visit. All AEs must be recorded in the eCRFs. The sign, symptoms, or diseases present before starting the treatment period are only considered AEs if they worsen after starting the treatment period.

13.1. Reporting of Serious Adverse Events

All serious adverse events (SAE) defined per ICH guidelines must be recorded on case report forms. In addition, all serious adverse events must be reported, whether or not considered causally related to treatment using the SAE form to Ozmosis Research Inc. within 24 hours of becoming aware of the event. The SAE must be completely described in the case report form. The reporting period for SAEs is the period immediately following the time of first dose through the last follow-up visit. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

Serious Adverse Event Reporting Instructions

All serious adverse events must be reported as follows:

Within 24 hours: Report initial information (on trial specific SAE report form) by fax or e-mail to:

Ozmosis Research Inc.
Email: ozmsafety@ozmosisresearch.ca
Fax: 416-864-8333

The initial information should always contain:

- Name of Reporter/Investigator

- Subject identification
- SAE Term
- Study drug dose and start/stop dates

On the next working day: Fax or e-mail completed trial-specific Serious Adverse Event form.

All SAEs must be followed until resolved, become chronic, or stable unless the subject is lost to follow up. Resolution status of such an event should be documented on the CRF.

13.2. Procedures for Expedited Reporting

Responsibility for Reporting Serious Adverse Events to Regulatory Authorities

Ozmosis Research Inc. will provide expedited reports SAEs to Intrinsik for submission to Health Canada and FDA according to applicable guidelines and regulations, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a casual relationship with protocol treatment cannot be ruled out).

Reporting Serious Adverse Events to Local Ethics Boards

Ozmosis Research Inc. will notify all Investigators of all Serious Adverse Events that are reportable to regulatory authorities from this trial or from other clinical trials as reported to the Sponsor. This includes all serious events that are unexpected and related to protocol treatment. Investigators must notify their Research Ethics Board (REB) / Institutional Review Board (IRB) and file the report with their Investigator Site File. Documentation that serious adverse events (SAEs) have been reported to REB/IRB must be kept on file at Ozmosis Research Inc.

Documentation can be any of the following:

- Letter from REB/IRB acknowledging receipt
- Stamp from the REB/IRB, signed and dated by REB/IRB chair, acknowledging receipt
- Letter demonstrating the SAE was sent to the board

All expedited serious adverse events occurring within a centre should also be reported to local REB/IRB.

14. Statistical Methods and Planned Analyses

The intent-to-treat (ITT) population will consist of all randomized subjects. The safety population will include all randomized subjects who receive at least one dose of the study drug. The per-protocol population will consist of all subjects in the ITT population who have no major protocol deviations that would have a significant effect on the efficacy of the study treatment. The ITT

population will be the primary population for all efficacy analyses. All safety data will be summarized based on the safety population. The per-protocol population will be used as the population for sensitivity analyses of the primary and key secondary efficacy endpoints.

All efficacy and safety will be summarized descriptively.

14.1. Efficacy Analysis

As the primary analysis, the change from baseline in the weekly average of the daily pain intensity measured by NPRS will be analyzed using the mixed model for repeated measure (MMRM) with the treatment as a factor, visit, the interaction between treatment and visit, and baseline as a covariate. The analysis of covariance (ANCOVA) will also be used as an additional analysis. The change in the weekly average of the daily sleep score on Daily Sleep Interference Score (DSIS) and the change in the NPRS score will be analyzed using the same methods for primary endpoint analysis. The percentage of subjects achieving ≥30% and ≥50% reduction in NPRS score at Day 28 and Day 56 will be analyzed using Fisher's exact test and the logistic regression model. The change in Patient Global Impression of Change (PGIC) and other continuous efficacy endpoints will be analyzed using ANCOVA.

No multiplicity adjustment will be used in this study. The missing data imputation methods and sensitivity analyses for primary and key secondary efficacy endpoints will be included in Statistical Analysis Plan (SAP).

14.2. Exploratory Analysis

The change in CRP, serum tryptase, and plasma cytokines will be summarized descriptively by treatment group in the ITT (Intention-To-Treat) population. A further exploratory endpoint of FSD201 plasma exposure will be performed by analyzing plasma samples.

14.3. Safety Analysis

The safety analysis population includes subjects who received at least 1 dose of study medication. Safety endpoints include adverse events, vital signs, and clinical laboratory data. Safety endpoints will be listed and/or summarized descriptively by treatment group.

All adverse events (AEs) will be coded using the most recent MedDRA Version. The incidence of TEAEs, SAEs, and AEs leading to treatment discontinuation will be summarized by system organ class and preferred term. Summaries in terms of severity and relationship to study drug will also be provided. SAEs will be summarized separately in a similar manner. Subject listings of AEs causing discontinuation of study medication and SAEs will be produced.

Clinical laboratory data and vital signs will be summarized, including absolute values and changes from baseline values and numbers of subjects with clinically significant values. The incidence and

severity of treatment-emergent changes in laboratory values will be summarized separately; Summary tables will be provided for physical examination by treatment group and visit where appropriate. Vital signs analysis will include the mean, standard deviation, minimum, maximum, and quartiles at baseline and at the end of treatment, and the change from baseline to the end of treatment. Concomitant medications will be analyzed descriptively.

14.4. Methods for Handling Missing Data

Reasonable efforts will be made to obtain complete data for all subjects; however, missing observations may occur due to subjects lost to follow-up or non-adherence to required assessments. The reasons for missing data will be evaluated. In addition, the distribution of prognostic factors between subjects with data and those without data will be examined to evaluate any potential sources of bias. In the absence of any apparent systematic loss, data will be analyzed assuming that these observations are missing at random.

For efficacy endpoints, missing data will be adjusted in the analysis by using the method of last observation carried forward (LOCF). A sensitivity analysis will be carried out using the baseline observation carried forward (BOCF).

15. Investigational Obligations

15.1. General considerations

The end date for the study overall will be defined as the date of last contact or final contact attempt for the last subject completing or withdrawing from the study. If the Sponsor were to suspend or terminate the study prematurely for any reason, prompt notification would be given to investigators, REBs, IRBs, and regulatory authorities in accordance with regulatory requirements.

The Sponsor should be notified promptly if the study is terminated by the investigator or the REB/IRB at the applicable study site. A particular study site may be terminated from this study at the discretion of the investigator, Sponsor, or REB/IRB (e.g., for nonenrolment of subjects or noncompliance with the protocol).

15.2. Ethical Guidelines for the Conduct of the Study

The investigator is responsible for ensuring that the study is conducted in accordance with the clinical protocol and is in full compliance with FDA regulatory requirements; the basic principles outlined in 21 CFR Parts 50, 54, 56 & 312, the ICH-Guidelines for Good Clinical Practice as published in the Federal Register on May 9, 1997, and the Declaration of Helsinki (ICH 1996; FDA Regulation 2021).

15.3. Written Informed Consent

A written informed consent form will be provided to each subject describing this information. The investigator will inform the subject of the nature, risks, and purpose of the study. This form must

be reviewed and approved by the Sponsor and the REB/IRB before its use in the study. Each volunteer must sign and date this form prior to their participation in the study. A signed original consent form for each subject will be kept on file at the clinical site. A copy will also be given to the subject signing the form.

15.4. Confidentiality

The Principal Investigator at each site and designees, employees and agents involved with this study will comply with relevant provincial/state and federal laws relating to the confidentiality, privacy and security of the subject's health information. They will only create, maintain, use or disclose any data that is generated by this study or other information disclosed to the Principal Investigator or their employees or agents during the course of the study to the Sponsor, REB/IRB, Health Canada, FDA or other authorized recipients as appropriate for the execution, analysis, review and reporting of this study. Such information shall not be used for any other purposes and will remain confidential.

16. Study Management

16.1. Approval and Consent

16.1.1. Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and all relevant regulations as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the United States Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation and GCP guidelines and according to the appropriate regulatory requirements in the countries where the study was conducted.

16.1.2. Research Ethics Board or Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted REB or IRB/IEC. Approval is required for the study protocol, protocol amendments (if applicable), IB, informed consent form (ICFs), recruitment material and patient information sheets, and other patient-facing material.

16.1.3. Informed Consent

For each subject (or the patient's Legally Authorized Representative (LAR)), informed consent will be obtained before any protocol-related activities. As part of this procedure, the principal investigator (PI) or designee must explain the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The subject (or the subject's LAR) should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and guidelines for International Council for Harmonisation. The PI will provide the sponsor or its representative with a copy of the REB or IRB/IEC-approved ICF before the start of the study.

16.1.4. Data Handling

Clinical data will be entered by site personnel on eCRFs for transmission to the sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site. All study forms and records transmitted to the sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by eClinical Services. Access to the EDC system is available only to authorized users via the study's internet website, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of data clarification forms or queries in the EDC system. When all missing and/or incorrect data have been resolved, eCRFs will be considered complete.

16.1.5. Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of study-related monitoring, audits, review by REBs or IRB/IECs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

16.1.6. Record Retention

Study records and source documents must be preserved for at least 25 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 Privacy Regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with Health Insurance Portability Accountability Act (HIPAA) Privacy Regulation and in a form satisfactory to the sponsor.

16.1.7. Monitoring

The study will be monitored to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements. Ozmosis Research Inc. will organize remote/on-site monitoring of this study to be conducted as per the Monitoring Plan.

As this trial is conducted under both a CTA with Health Canada and an IND with the United States' Food and Drug Administration, your site may be subject to an inspection by the Health Products and Food Branch Inspectorate or FDA. Other audits may be conducted by the study sponsor, Ozmosis Research Inc.

16.1.8. Quality Control and Quality Assurance

The sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the sponsor lies with the investigator generating the data.

The sponsor may arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

16.2. Investigator Selection

The Investigator must be of good standing as an Investigator and knowledgeable in relevant areas of clinical research to ensure adherence to the requirements of the protocol, including the protection of human subjects. Other site personnel must have appropriate research experience and infrastructure to ensure adherence to the protocol and enrollment of sufficient numbers of evaluable subjects. The curriculum vitae of the Investigator will be maintained in the Sponsor files as documentation of previous medical training, and federal databases will be searched to ensure that the Investigator and/or the site are not prohibited from engaging in federally sponsored clinical research. The Principal Investigator will sign the signature page of this protocol, agreeing to comply with all applicable government regulations and the requirements of this study.

16.3. Protocol Amendment and Protocol Deviation

16.3.1. Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of patients or the conduct of the study will be classed as administrative amendments and will be submitted to the REB or IRB/IEC for information only. The sponsor will ensure that acknowledgment is received and filed. Amendments that are classed as substantial amendments

must be submitted to the appropriate regulatory authorities and the REB or IRB/IECs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

16.3.2. Protocol Deviations

Should a protocol deviation occur, the sponsor/Ozmosis Research must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the CSR. Reporting of protocol deviations to the REB or IRB/IEC and in accordance with applicable regulatory authority mandates is the investigator's responsibility. All REB or IRB/IEC correspondence is to be forwarded to Ozmosis Research Inc.

16.4. Administrative Requirements

16.4.1. Drug Accountability

The study drug may only be used for subjects enrolled in this study under the supervision of the Investigator and under the terms of the clinical protocol. The Investigator may not provide study drug to any person not authorized to use it. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual. The Investigator, or delegate, will also ensure that the drugs are maintained under secure storage and that the drug accountability record is maintained. This may include:

- Product code
- Lot number
- Receipt dates
- Dates and quantities dispensed, including subject number
- Return date to the clinical site (if any)
- Return date to the Sponsor (if any)
- Any drugs that have not been used will be returned to the Sponsor.

The Sponsor will supply the Investigator with an adequate amount of the investigational drug for completion of the study. All unused or expired study drug will be returned to the Sponsor or the Sponsor's designee or, if authorized, disposed of at the study site per the site's Standard Operating Procedures and documented. Study drug is expected to be dispensed to the subject at the study site.

Unblinding envelopes will also be provided with the drug product shipments, and should be kept in a controlled, restricted cabinet. These envelopes must be kept sealed and only used if the PI determines unblinding to be necessary. Accountability on these envelopes will be performed at the end of the clinical trial.

16.4.2. Communication with the Sponsor

Although the Investigator and his/her staff may have contact with other key individuals at the Sponsor throughout the course of the study, all communications regarding conduct of the study must be channeled through the Sponsor's clinical affairs personnel or their designees.

16.4.3. Required Documentation

An Investigator may not screen or enroll subjects until authorized to do so by the Sponsor. At a minimum, the following documentation must be received by the Sponsor prior to study commencement:

- Curriculum vitae for the Principal Investigator and Sub-investigators
- Signed Investigator Agreement
- Signed Confidentiality Statement for Investigator and Sub-investigators
- Signed "Protocol Agreement Page" (page 2 of this protocol)
- IRB/REB's written approval of both the protocol and the ICF
- Signed Financial Disclosure Statement, if applicable
- Signed Qualified Investigator Undertaking form, if applicable
- IRB Assurance of Compliance Form or equivalent

16.4.4. Termination of Study

The Sponsor reserves the right to suspend enrollment or terminate the study at any time as set forth in the Clinical Study Agreement. Written notice will be submitted to the Investigator in advance of such termination.

The Sponsor may suspend enrollment or terminate the study at a specific site for reasons including, but not limited to, inadequate data collection, low subject enrollment rate, achievement of the total enrollment, or noncompliance with the protocol or other clinical research requirements.

The REB or IRB/EC will be informed promptly and provided with a detailed written explanation for the termination or suspension.

As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

16.4.5. Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312,

Subpart D, of Title 21 of the CFR; EU 536/2014, Annex 1, D, 17 (a); and in compliance with GCP guidelines.

REB or IRB/IECs will review and approve this protocol and the ICF. All patients (or the patient's LAR) are required to give informed consent before participation in the study.

16.4.6. Financing and Insurance

Before the study commences, the sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

16.4.7. Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the sponsor or their designee. With respect to such rights, the sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the sponsor or its designee, as will be set forth in the clinical study agreement.

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18. Appendixes (Scales)

18.1	Anxiety – Short Form 8a (PROMIS)
18.2	Body Mass Index (BMI)
18.3	Daily Sleep Interference Scale (DSIS)
18.4	Fatigue – Short Form 8a (PROMIS)
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18.1 Anxiety Short Form - PROMIS

Emotional Distress – Anxiety – Short Form 8a

Date:_____ **Subject Number:**_____

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
EDANX01	I felt fearful.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX46	I felt nervous.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX07	I felt like I needed help for my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX05	I felt anxious.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX54	I felt tense	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

31May2019

Confidential

18.2 Body Mass Index Table

Body Mass Index Table

	Normal						Overweight					Obese										Extreme Obesity																
BMI	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
Height (inches)	Body Weight (pounds)																																			
58	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167	172	177	181	186	191	196	201	205	210	215	220	224	229	234	239	244	248	253	258
59	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173	178	183	188	193	198	203	208	212	217	222	227	232	237	242	247	252	257	262	267
60	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179	184	189	194	199	204	209	215	220	225	230	235	240	245	250	255	261	266	271	276
61	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185	190	195	201	206	211	217	222	227	232	238	243	248	254	259	264	269	275	280	285
62	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191	196	202	207	213	218	224	229	235	240	246	251	256	262	267	273	278	284	289	295
63	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197	203	208	214	220	225	231	237	242	248	254	259	265	270	278	282	287	293	299	304
64	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204	209	215	221	227	232	238	244	250	256	262	267	273	279	285	291	296	302	308	314
65	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210	216	222	228	234	240	246	252	258	264	270	276	282	288	294	300	306	312	318	324
66	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216	223	229	235	241	247	253	260	266	272	278	284	291	297	303	309	315	322	328	334
67	121	127	134	140	146	153	159	166	172	178	185	191	198	204	211	217	223	230	236	242	249	255	261	268	274	280	287	293	299	306	312	319	325	331	338	344
68	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230	236	243	249	256	262	269	276	282	289	295	302	308	315	322	328	335	341	348	354
69	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236	243	250	257	263	270	277	284	291	297	304	311	318	324	331	338	345	351	358	365
70	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243	250	257	264	271	278	285	292	299	306	313	320	327	334	341	348	355	362	369	376
71	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250	257	265	272	279	286	293	301	308	315	322	329	338	343	351	358	365	372	379	386
72	140	147	154	162	169	177	184	191	199	206	213	221	228	235	242	250	258	265	272	279	287	294	302	309	316	324	331	338	346	353	361	368	375	383	390	397
73	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265	272	280	288	295	302	310	318	325	333	340	348	355	363	371	378	386	393	401	408
74	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272	280	287	295	303	311	319	326	334	342	350	358	365	373	381	389	396	404	412	420
75	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279	287	295	303	311	319	327	335	343	351	359	367	375	383	391	399	407	415	423	431
76	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287	295	304	312	320	328	336	344	353	361	369	377	385	394	402	410	418	426	435	443

Source: Adapted from *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report.*

18.3 Daily Sleep Interference Scale (DSIS)

DAILY SLEEP INTERFERENCE SCALE:

☐ **NOT DONE**

Please complete the following upon awakening:

Today's Date:
(yyyy-mm-dd) |_|_|_|_|-|_|_|-|_|_|

Time of Day:
(24 hour clock) |_|_|:|_|_|

Select the number that best describes how much your pain has interfered with your sleep during the past 24 hours. (Check one number only)

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
Did not interfere with sleep										Completely interferes (Unable to sleep due to pain)

18.4 Fatigue Short Form 8a (PROMIS)

Fatigue – Short Form 8a

Date:_____ **Subject Number:**_____

Please respond to each question or statement by marking one box per row.

	During the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
HI7	I feel fatigued.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…					
FATEXP41	How run-down did you feel on average? ..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP35	How much were you bothered by your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP49	To what degree did your fatigue interfere with your physical functioning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
FATIMP3	How often did you have to push yourself to get things done because of your fatigue?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP16	How often did you have trouble finishing things because of your fatigue?..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

English
16 March 2020

Generalized Anxiety Disorder (GAD–7) Scale

Date:_____ **Subject Number:**_____

1. Over the last two weeks how often have you been bothered by any of the following problems?

	Not at all (0)	Several days (1)	More than half the days (2)	Nearly every day (3)
a. Feeling nervous, anxious or on edge	☐	☐	☐	☐
b. Not being able to stop or control worrying	☐	☐	☐	☐
c. Worrying too much about different things	☐	☐	☐	☐
d. Trouble relaxing	☐	☐	☐	☐
e. Being so restless that is hard to sit still.	☐	☐	☐	☐
f. Becoming easily annoyed or irritable	☐	☐	☐	☐
g. Feeling afraid as if something awful might happen	☐	☐	☐	☐

Total Score: _____

18.6 General Life Satisfaction - Short Form 5a (PROMIS)

General Life Satisfaction – Short Form 5a (PROMIS)

Date:_____ **Subject Number:**_____

Please respond to each question or statement by marking one box per row.

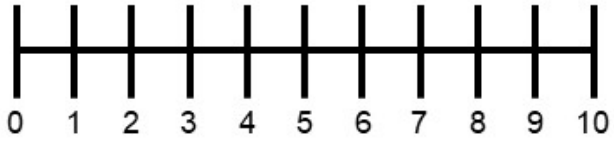
	Indicate how much you agree or disagree…	Strongly disagree	Disagree	Slightly disagree	Neither agree nor disagree	Slightly agree	Agree	Strongly agree
PAD45m	In most ways, my life is close to perfect	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
PAD46	If I could live my life over, I would change almost nothing.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
PAD47	I am satisfied with my life.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
PAD48	So far I have gotten the important things I want in life.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
PAD49m	My life situation is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

English
16 March 2020

Page 1 of 1

Numeric Pain Rating Scale

Please rate your pain by indicating the number that best describes your pain on average in the last 24 hours



No Pain

Pain as bad as you can imagine

Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113(1-2):9-19.

18.8 Pain Catastrophizing Scale (PCS)

Date:_____ Subject Number:_____

Pain Catastrophizing Scale (Copyright 1995, 2001, 2004, 2006, 2009 Michael JL Sullivan, PhD) Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feeling that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
I worry all the time about whether the pain will end	0	1	2	3	4
I feel I can't go on	0	1	2	3	4
It's terrible and I think it's never going to get any better	0	1	2	3	4
It's awful and I feel that it overwhelms me	0	1	2	3	4
I feel I can't stand it anymore	0	1	2	3	4
I become afraid that the pain will get worse	0	1	2	3	4
I keep thinking of other painful events	0	1	2	3	4
I anxiously want the pain to go away	0	1	2	3	4
I can't seem to keep it out of my mind	0	1	2	3	4
I keep thinking about how much it hurts	0	1	2	3	4
I keep thinking about how badly I want the pain to stop	0	1	2	3	4
There's nothing I can do to reduce the intensity of the pain	0	1	2	3	4
I wonder whether something serious may happen	0	1	2	3	4

Pain Intensity Numeric Rating Scale (PI-NRS)

Date:_____

Subject Number:_____

1. On a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable, how would you rate your pain RIGHT NOW.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

2. On the same scale, how would you rate your USUAL level of pain during the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

3. On the same scale, how would you rate your BEST level of pain during the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

4. On the same scale, how would you rate your WORST level of pain during the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Imaginable

Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2005; 113(1-2): 9-19.

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18.10 Pain Interference - Short Form 8a (PROMIS)

Pain Interference – Short Form 8a (PROMIS)

Date:_____
Subject Number:_____

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ12	How much did pain interfere with the things you usually do for fun?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ36	How much did pain interfere with your enjoyment of social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ3	How much did pain interfere with your enjoyment of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ13	How much did pain interfere with your family life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PATIENT'S GLOBAL IMPRESSION OF CHANGE (PGIC)

Date:_____

Subject Number:_____

Since beginning treatment at this facility, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS and OVERALL QUALITY OF LIFE, related to your condition?

Choose ONE.
___No change (or condition has gotten worse) (1)
___Almost the same, hardly any change at all (2)
___A little better, but no noticeable change (3)
___Somewhat better, but the change has not made any real difference (4)
___Moderately better, and a slight but noticeable change (5)
___Better and a definite improvement that has made a real and worthwhile difference (6)
___A great deal better and a considerable improvement that has made all the difference (7)

Reference: Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. ***J Manipulative Physiol. Ther.*** **2004; 27; 26-35.**

FSD PHARMA

18.12 Patient Health Questionnaire (PHQ-9)

Subject Number: _____ ***Date:*** _____

Patient Health Questionnaire (PHQ–9)

1. Over the last two weeks how often have you been bothered by any of the following problems?

	Not at all (0)	Several days (1)	More than half the days (2)	Nearly every day (3)
a. Little interest or pleasure in doing things.	☐	☐	☐	☐
b. Feeling down, depressed, or hopeless.	☐	☐	☐	☐
c. Trouble falling/staying asleep, sleeping too much	☐	☐	☐	☐
d. Feeling tired or having little energy	☐	☐	☐	☐
e. Poor appetite or overeating.	☐	☐	☐	☐
f. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down.	☐	☐	☐	☐
g. Trouble concentrating on things, such as reading the newspaper or watching TV.	☐	☐	☐	☐
h. Moving or speaking so slowly that other people could have noticed. Or the opposite; being so fidgety or restless that you have been moving around more than usual.	☐	☐	☐	☐
i. Thoughts that you would be better off dead or of hurting yourself in some way.	☐	☐	☐	☐

Total Score: _____

2. If you checked off <u>any</u> problem on this questionnaire so far, how <u>difficult</u> have these problems made it for you to do your work, take care of things at home, or get along with other people?

☐Not difficult at all ☐Somewhat difficult ☐Very difficult ☐Extremely difficult

18.13 Sleep Disturbance – Short Form 8a (PROMIS)

Sleep Disturbance – Short Form 8a (PROMIS)

Date:_____ **Subject Number:**_____

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Very poor	Poor	Fair	Good	Very good
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep116	My sleep was refreshing.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep108	My sleep was restless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep72	I tried hard to get to sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep67	I worried about not being able to fall asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep115	I was satisfied with my sleep.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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