Safety and analgesic efficacy of marine lipid precursors of specialized pro-resolving mediators in adults with chronic temporomandibular pain

NIDCR Protocol Number: 25-016-E

NIDCR Grant Number: 1UG3DE033354

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Grantee Institution: University of North Carolina at Chapel Hill

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Draft or Version Number: 1.0

20 August, 2026

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice (GCP) (ICH E6) and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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Signed: Anne E. Sanders Date: August 20, 2026

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LIST OF ABBREVIATIONS

AE	Adverse Event/Experience
ASOD	Adams School of Dentistry
cGMP	Current Good Manufacturing Practices
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CRT	Controlled Room Temperature
CRF	Case Report Form
CROMS	Clinical Research Operations and Management Support
DC/TMD	Diagnostic Criteria for Temporomandibular Disorders
DSD	Daily Symptom Diary
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
g	Gram
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
GRAS	Generally Recognized as Safe
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IP	Investigational product
IRB	Institutional Review Board
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MCT	Medium-chain triglycerides
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIDCR	National Institute of Dental and Craniofacial Research, NIH
NIH	National Institutes of Health
NRS	Numeric rating scale
OCTOM	Office of Clinical Trials Operations and Management, NIDCR, NIH
OHRP	Office for Human Research Protections
PI	Principal Investigator
PP	Per-protocol population
PUFA	Polyunsaturated fatty acid
RCT	Randomized clinical trial
SAE	Serious AE/experience

SAP	Statistical Analysis Plan
SPM	Specialized pro-resolving mediators
SOC	System Organ Class
TEAE	Treatment emergent Adverse Event
TMD	Temporomandibular disorder
TMJ	Temporomandibular joint
TARDIS	Teleform-Access Research Data Intelligence Service
UNC-CH	University of North Carolina at Chapel Hill
UP	Unanticipated Problem
WHO	World Health Organisation

PROTOCOL SUMMARY

Title:	Safety and analgesic efficacy of marine lipid precursors of specialized pro-resolving mediators (SPM) in adults with chronic temporomandibular pain
Short title:	M**a**rine lipi**d**s e**a**se **p**ainful **T**MD (**ADAPT**)
Précis:	This single-site, phase 2b proof of concept, randomized, triple-masked, placebo-controlled, parallel-group clinical trial will evaluate the analgesic efficacy and safety of a marine oil dietary supplement enriched with SPM precursors compared to placebo, administered orally twice daily over 8 weeks in 100 adults with examiner verified chronic temporomandibular disorder (TMD) myalgia and/or arthralgia. The active intervention is an SPM Active® softgel dietary supplement. The placebo is a medium-chain triglyceride oil softgel. Both are manufactured and supplied to this trial by Metagenics LLC.
Primary Objectives and Outcomes	**Primary Clinical Objective** To evaluate whether the marine oil dietary supplement affects average weekly pain intensity compared with placebo during the 8-week intervention. **Primary Clinical Outcome** Net change in average weekly pain intensity from baseline to Week 8, measured on a 0–100 numeric rating scale (NRS) [0 = “no pain,” 100 = “the most intense pain imaginable”] using the Daily Symptom Diary (DSD). **Primary Safety Objective** To evaluate whether the marine oil dietary supplement differs from placebo in the rate of treatment-emergent adverse events (AE) during the 8-week intervention. **Primary Safety Outcome** Rate of treatment-emergent AEs, defined as an AE that first appears or worsens after a participant begins taking the study intervention and up to 7 days after the last dose.

Secondary Objective and Outcomes:

Secondary Objective

To evaluate whether the marine oil dietary supplement, compared with placebo, alters experimental pain sensitivity and the multidimensional impact of chronic TMD pain, including clinical pain severity, duration and interference, psychosocial distress, headache impact, TMD quality of life, and pain in other body regions, over 8 weeks of treatment.

Secondary Outcomes

Clinical Pain

- Change from baseline to Week 8 in pain severity, pain duration (DSD) and pain interference scores (Graded Chronic Pain Scale scores (GCPS)), headache impact scores (HIT-6), and pain in other body regions (anterior and posterior body manikin) determined by questionnaires.

Experimental Pain Sensitivity

- Change from baseline to Week 8 in pressure pain thresholds at standardized orofacial and extra-orofacial sites.
- An additional assessment at Week 4 will capture early changes to support causal mediation analyses.

Psychosocial and Quality of Life

- Change from baseline to Week 8 in the state anxiety score (State-Trait Anxiety Inventory) and depression score (SCL-90R Depression Scale). An additional assessment at Week 4 will capture early changes to support causal mediation analyses.
- Change from baseline to Week 8 in Oral Health Impact Profile, modified for TMD (OHIP-TMD) scores as well as sense of overall change (Global Impression of Change).

Tertiary Objective and Outcome

Tertiary Objective

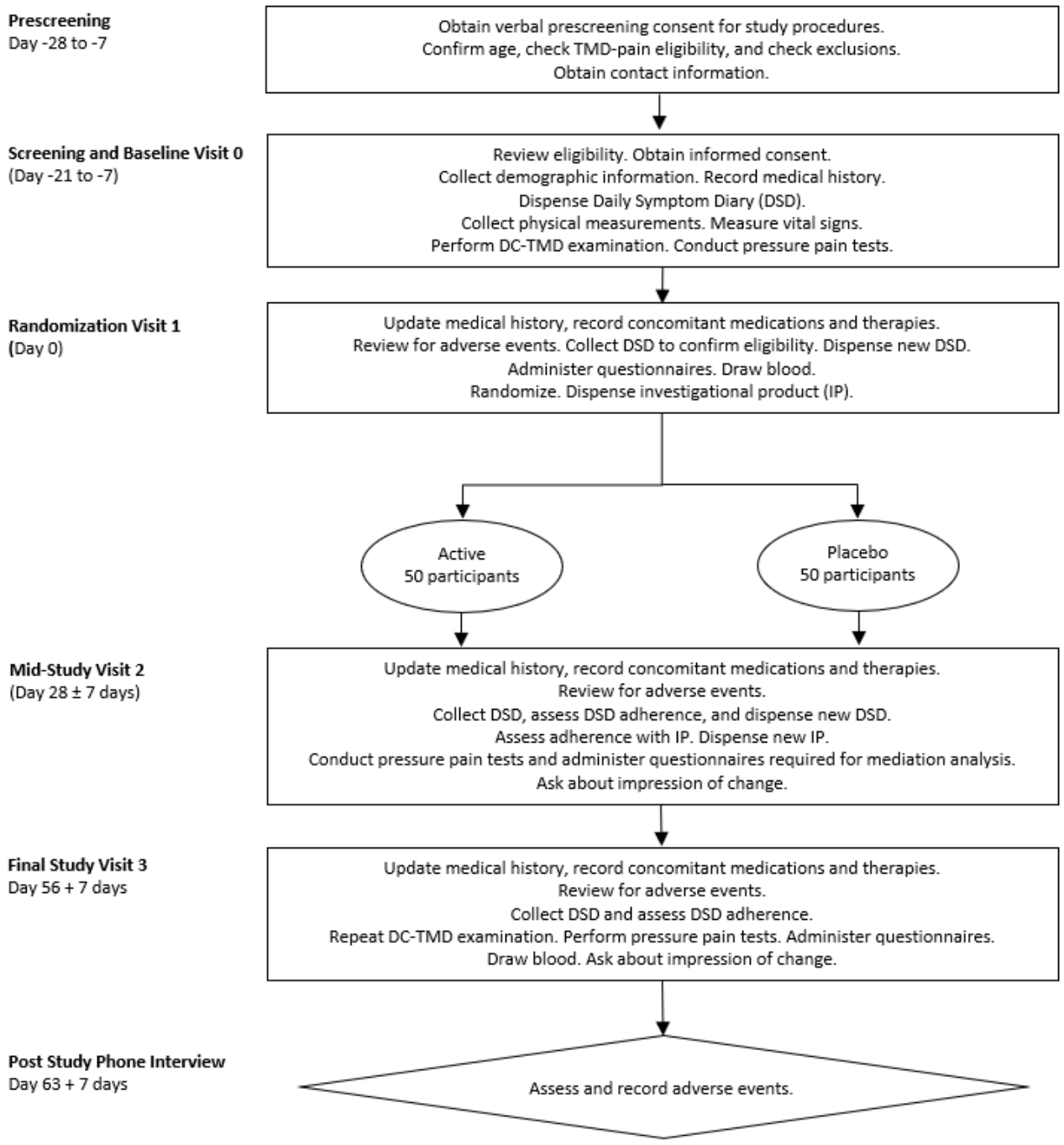
Compare differences between the active and placebo study arms in biochemical changes in circulating polyunsaturated fatty acids (PUFAs) and their derived oxylipins after 8 weeks of treatment.

Tertiary Outcome

Change in the ratio of omega-6 PUFAs to omega-3 PUFAs, with lower omega-6 and higher omega-3 levels considered beneficial.

Population:	The target population consists of 100 adults aged 18 years or older, of any race or ethnicity, with examiner-verified TMD myalgia and/or arthralgia. Participants will be recruited from Chapel Hill, Durham, and surrounding areas in North Carolina. Based on historical experience recruiting individuals with TMD at UNC–Chapel Hill, we anticipate that the study sample will reflect the demographic distribution of individuals reporting TMD in the U.S. population, with approximately 77% female, 6% Hispanic, 83% White, 8% African American, and 9% identifying as other races.(1)
Phase or Stage:	Phase 2b
Number of Sites:	Single-site study conducted at the University of North Carolina Adams School of Dentistry (ASOD) in Chapel Hill, NC.
Description of Intervention:	At Visit 1, participants will be allocated at random to either the active or the placebo group. The active group receives an orally administered marine oil dietary supplement enriched with SPM precursors: 18-hydroxyeicosapentaenoic acid (18-HEPE), 17-hydroxydocosahexaenoic acid (17-HDHA), and 14-hydroxydocosahexaenoic acid (14-HDHA). Each active softgel contains 1 gram (g) of a marine oil fraction with demonstrated pro-resolving activity covered by the patent family PCT/US2013/040313. The placebo group receives an identical bottle of medium-chain triglyceride (MCT) oil softgels. Each placebo softgel contains 1 g of MCT, with a purity of 100%. The daily dose of active and placebo interventions is 2 g, administered as 1 g taken twice daily.
Study Duration:	56 Months
Subject Participation Duration:	Up to 12 weeks comprising: up to 3-week pre-screening period, 8-week intervention period, and a follow-up phone call 1 week after the end of intervention period.
Estimated Time to Complete Enrollment:	48 months

Schematic of Study Design



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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Health problem. Like all pain conditions, TMDs have sensory and emotional components. The sensory component involves arthralgia in the temporomandibular joint/s and/or myalgia in masticatory muscle. The 2.8% of males and 6.3% of females with TMD (2) rate the pain intensity as 4.3, on average, on a 0 to 10 scale. (3) The emotional component of TMD is characterized by depression, anxiety, and somatic complaints, and is both a risk factor for incident TMD and a contributor to pain persistence.(4) Although drugs offer temporary relief of both sensory and emotional components, these drugs often come with severe side effects.(5)

Role of diet in TMD. Features of the modern Western diet can influence pain. This diet is characterized by an excessive intake of omega-6 (n-6) polyunsaturated fatty acids (PUFAs), obtained from seed oils, and a deficient intake of omega-3 (n-3) PUFAs,(6) obtained from fatty fish. The metabolic derivatives of these two fatty acid groups have generally opposing effects on inflammation, nociception, sleep quality, and psychological health. In general, the n-6 derivates exacerbate inflammation, pain sensitivity, sleep disturbance, (7) and psychological distress, (8, 9) whereas n-3 PUFAs and their lipid derivatives, known as specialized proresolving mediators (SPMs), resolve inflammation and confer antinociceptive, analgesic, and anxiolytic benefits and promote good sleep. (10-14) We propose that a dietary supplement of n-3 PUFAs will shift the balance in PUFAs in favor of n-3 PUFAs thereby allowing their protective effects against pain to dominate.

Preclinical research. In reviewing molecular mechanisms and pathways of n-3 PUFA-derived SPMs in chronic pain, Osthues & Sisignano (15) and Chávez-Castillo et al., (16) concluded that n-3 PUFA derivatives modulate opioid signaling and inhibit proinflammatory signals, transient receptor potential channels, and central and peripheral sensitizations. Fattori et al., (17) described SPMs as “powerful non-immunosuppressive and non-opioid analgesic” agents. Chávez-Castillo et al., (16) predicted that SPMs will become “the future of chronic pain therapy” because of their potent, long-lasting, antinociceptive and analgesic effects, without immunosuppression and without side effects.

Clinical research. Goldberg & Katz’s meta-analysis of the analgesic effects of n-3 PUFA supplements on overall chronic inflammatory joint pain in humans, primarily in rheumatoid arthritis, using total tender joint counts, without specifying individual joints.(18) They found that n-3 PUFA supplementation significantly reduced joint pain intensity, number of painful or tender joints, and NSAID consumption.

Our team showed that lower levels of circulating n-3 PUFAs were associated with higher odds of TMD pain (19) and that each unit increase in the circulating n-6/n-3 PUFA ratio corresponded to greater pain intensity from TMD, headache, low back pain, and fibromyalgia. (20) In quantitative sensory testing, we showed that higher levels of n-6 arachidonic acid were significantly associated with lower pressure pain thresholds at five of six tested anatomical sites. (21) Additionally, elevated circulating levels of n-6 linoleic acid and arachidonic acid were associated with poor sleep quality.(22) Regarding the emotional component of TMD pain, we showed that lower levels of n-3 PUFAs were associated with greater psychological distress. (23)

Only one clinical trial has studied the analgesic effects of SPM precursors. In this non-randomized, open-label trial, Callan et al. (24) administered the Metagenics SPM Active® supplement for 4 weeks to 44 adults with chronic moderate or severe pain anywhere in the body. It produced statistically significant reductions in pain intensity, pain interference, depression and anxiety, as well as an improvement in mobility and physical activity, therefore translating to a better quality of life. (24) Inferences are limited, however, because there was no comparison group.

Overall goal. The overall goal is to perform a clinical trial to evaluate the analgesic efficacy and safety of a marine lipid dietary supplement enhanced with SPM precursors in adults with chronic TMD pain.

2.2 Rationale

TMD shows limited response to conservative therapies (25, 26) and splint therapy.(27, 28) Furthermore, a Cochrane review of randomized controlled trials (RCTs) comparing various drug groups—non-steroidal anti-inflammatory drugs, anticonvulsants, muscle relaxants, corticosteroids, and benzodiazepines—against placebo found insufficient evidence to support their analgesic efficacy for TMD.(29) In addition, some of these drugs lead to the development of analgesic tolerance, immunosuppression, addiction, and other harmful side effects.

An SPM precursor-enriched marine oil supplement has not been evaluated for analgesic efficacy under rigorous randomized controlled conditions in TMD, providing rationale for this phase 2b proof of concept clinical trial. The route of administration of the investigational product (IP) is by mouth and therapeutic dose of 2 g per day for 8 weeks in adults with examiner-verified painful TMD.

The therapeutic dose and duration of the trial were guided by two clinical studies. One was a dose-finding, pharmacokinetic trial (30) that tested three doses (1.5 g, 3 g, or 4.5 g per day) of SPM Active® versus placebo. The other study was a dose titration trial, in which SPM Active® was administered to adults with chronic pain to assess reduction in pain intensity.(24) These studies demonstrated that daily doses at or above 2 g yielded favorable pharmacokinetic profiles and reductions in pain intensity, supporting selection of the 2-g daily dose for the ADAPT trial.

We selected an 8-week duration based on IMMPACT recommendations,(31) which suggest that when a proof-of-concept trial is expected to achieve maximal effects within several weeks, at least 4 weeks of follow-up is appropriate. Given that our trial extends beyond initial efficacy to include exploratory aims—such as mechanistic and psychological outcomes—we chose a longer 8-week period to allow sufficient time for these additional effects to emerge.

We hypothesize that a dietary supplement of n-3 PUFAs enhanced with SPM precursors will reduce pain intensity in adults with TMD arthralgia and/or myalgia. We will also investigate whether elevation of pressure pain thresholds, and alleviation of psychological distress and headache (secondary outcomes) are potential pathways through which effect may occur.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Investigational Product. Known adverse events (AEs) related to the active intervention are similar to those reported for other high-quality fish oils and are uncommon (generally <0.5%). These AEs may include minor gastrointestinal distress such as loose stools, nausea, abdominal discomfort, and belching. The placebo, a medium-chain triglyceride (MCT) oil at a 2 g daily dose with 100% purity (manufactured by Metagenics LLC.), also has an excellent safety profile (32) and is commonly used as a placebo in lipid clinical trials. When taken orally, MCT-related AEs are uncommon (generally <0.5%) and may include diarrhea, vomiting, irritability, nausea, stomach discomfort, intestinal gas, and bloating. The study team will monitor AEs. A treatment-emergent AE (TEAE) is an AE that first appears or worsens after the participant begins taking the study intervention and up to 7 days after the last dose. Steps to mitigate risks include informing participants of these side effects at the time of informed consent and explaining that they are free to discontinue from the study at any time.

Questionnaires. A participant may experience discomfort associated with being asked personal questions about her or his health history, symptoms, or emotions. Participants will be told that they may choose not to answer any questions that cause discomfort.

TMD Examination and Pressure Pain Thresholds. Assessments of muscle and temporomandibular joint (TMJ) sensitivity to digital palpation during the TMD examination, and algometry assessment of pressure pain thresholds are designed to evoke brief pain or discomfort during application of the stimulus. However, none of these assessments are expected to result in lasting discomfort or damage to affected tissues: a chosen range of stimulus intensities produces a level of pain or discomfort that is acceptable to the participant. No test will exceed this range, and all tests will end upon completion of the modality or upon the participant's request, whichever comes first.

Blood Collection. Blood collection can cause mild pain and/or bruising. Trained and experienced personnel will perform the blood collection using standard procedures.

Breach of Confidentiality. The risk of accidental disclosure of private information exists because study participants are providing personal information. Strategies to minimize this potential risk include collecting only minimal identifying information, using unique study codes for participants, and storing data collection documents on secure, password-protected servers or in a locked private office within locked filing cabinets. Password-protected computers will be used, and only individuals involved in the study will have access. Compliance with all IRB regulations concerning data collection, data analysis, data storage, and data destruction will be strictly observed.

2.3.2 Potential Benefits

Participants may or may not benefit from receiving the investigational drug by experiencing decreased pain and improved functionality. In the absence of any approved TMD medication, this search for an efficacious, safe, and affordable treatment may benefit many TMD patients in the future. The potential for a cost effective, non-invasive pain reduction treatment outweighs the minor risks associated with this study.

3 OBJECTIVES AND OUTCOME MEASURES

The primary purpose of this phase 2b randomized tripled-masked, placebo-controlled study is to evaluate the analgesic efficacy and safety of a marine oil supplement enriched with n-3 SPM precursors compared with placebo in adults with chronic TMD.

3.1 Primary clinical endpoint and safety outcome measure

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
To evaluate whether the marine oil dietary supplement, compared with placebo, affects average weekly facial pain intensity during the 8-week intervention.	The primary efficacy endpoint is net change in average weekly facial pain intensity over 8 weeks of treatment, from the week prior to randomization through the week before Visit 3. This primary endpoint is in keeping with the 2016 IMMPACT consensus panel recommendations for clinical trials of chronic pain, (33) where participant-assessed pain is the first-recommended outcome.	Daily pain intensity is measured on 0-100 NRS where 0 = "no pain" and 100 = "the most intense pain imaginable" as reported in the DSD. A higher score means *a worse outcome.*	Visit 1 (Randomization, Day 0) Visit 3 (Final visit, Day 56±7)
To evaluate whether the marine oil dietary supplement differs from placebo in the rate of treatment-emergent AEs during the 8-week intervention.	AEs classified as treatment-emergent (TEAEs) will be summarized, including the proportion of participants in active and placebo groups experiencing TEAEs. TEAEs are defined as any AEs that first appear or worsen in severity after initiation of the investigational product and up to 7 days after the last dose, compared to baseline. This measure ensures safety monitoring according to regulatory standards.	All TEAEs will be collected from the Screening and Baseline Visit through the last clinic visit. Investigators will document onset, duration, severity, relatedness to study treatment, and expectedness based on the known risk profile described in the protocol using standardized case report forms. All emergent AEs from first dose through follow-up will be considered TEAEs.	Visit 3 (Final visit, Study Day 56±7)

3.2 Secondary

The secondary outcomes align with core outcome domains in the 2016 IMMPACT consensus panel recommendations for clinical trials of chronic pain. (33)

Overall objective for all secondary outcomes
To evaluate whether the marine oil dietary supplement, compared with placebo, affects the multidimensional impact of chronic TMD pain over 8 weeks. Outcomes will include clinical pain severity, pain duration, and interference, headache impact, pain in other body regions, experimental pain sensitivity, psychosocial distress, TMD quality of life, and overall patient-reported change. Secondary outcomes are grouped into three domains: (1) clinical pain outcomes; (2) experimental pain sensitivity; and (3) psychological distress and quality of life.

Clinical pain outcomes		
Brief Description/ Justification of Outcome Measure	**Outcome Measured By**	**Time Frame**
While the primary endpoint determines change in facial pain intensity, this outcome determines change in the duration of TMD pain. The percentage of waking day with facial pain (0-100) is recorded daily.	Daily Symptom Diary	Visit 1 (Randomization, Day 0) Visit 3 (Final visit, Day 56±7)
Published scoring algorithms will classify TMD pain severity (current, worst, average) and pain interference with life activities (0-10 scale).	Graded Chronic Pain Scale (37)	Visit 1 (Randomization visit Study Day 0) Visit 3 (Follow-up visit Study Day 56 (±7)
Published scoring algorithms will be used to compute the total score for headache impact (range=36 to 78).	HIT-6 questionnaire (36)	Visit 1 (Randomization visit, Study Day 0) Visit 2 (Mid-study visit Study Day 28 (±7) Visit 3 (Follow-up visit Study Day 56 (±7)
The summed number of anatomical locations in which aches or pains were depicted in line drawings of a body manikin (range=0 to 42).	Anterior and posterior views of a Body Manikin	Visit 1 (Randomization visit Study Day 0) Visit 3 (Follow-up visit Study Day 56 (±7)

Experimental pain sensitivity outcomes		
Brief Description/ Justification of Outcome Measure	**Outcome Measured By**	**Time Frame**
Pressure pain thresholds recorded in kg, will be measured bilaterally at each of five anatomical locations: a) temporalis muscle, b) masseter muscle; c) TM joint; d) trapezius muscle; and e) lateral epicondyle eminence.	Pain threshold is defined as the amount of algometer pressure at which the participant first perceives the stimulus to be painful. Up to 5 trials can be performed on each site until the difference between 2 trials is ≤0.2 kg.	Visit 0 (Screening and Baseline visit, 7-28 days prior to Visit 1) Visit 2 (Mid-study visit Study Day 28 (±7) Visit 3 (Follow-up visit, Study Day 56 (±7)

Psychological distress and quality of life outcomes		
Brief Description/ Justification of Outcome Measure	**Outcome Measured By**	**Time Frame**
Published scoring algorithms will be used to compute the state anxiety subscale (range=20 to 80) and total score for depression (range=0 to 48).	State Trait Anxiety Inventory Form Y (State subscale) (34) SCL-90 Depression subscale (35)	Visit 1 (Randomization visit Study Day 0) Visit 2 (Mid-study visit Study Day 28 (±7) Visit 3 (Follow-up visit Study Day 56 (±7)
Quantifies adverse impact of TMD on daily activities, pain levels, psychological well-being, and other aspects of TMD-related quality of life (range=0 to 88).	OHIP-TMD questionnaire (38)	Visit 1 (Randomization visit Study Day 0) Visit 3 (Follow-up visit Study Day 56 (±7)
Report of perceived change (since baseline) in activities, symptoms, emotions and quality of life as it relates to their facial pain using a 7-point rating scale.	Patient Global Impression of Change questionnaire (39)	Visit 2 (Mid-study visit Study Day 28 (±7) Visit 3 (Follow-up visit Study Day 56 (±7)

3.3 Tertiary/Exploratory

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
Compare biochemical changes in circulating PUFAs and derived oxylipins between active and placebo study arms after 8 weeks of treatment.	Individual PUFAs and oxylipin derivatives are thought to mediate primary and secondary endpoints by regulating specific pain-related biochemical pathways. Lower omega-6 and higher omega-3 levels are considered beneficial. These endpoints are considered exploratory and hence do not alter protection against type I error for the primary objective.	Ultra-high performance liquid chromatography tandem mass spectrometry method will be used to assess 65 PUFAs and oxylipins measured in peripheral blood samples • Ratio of n-6/n-3 PUFAs	Visit 1 (Randomization visit Study Day 0) Visit 3 (Follow-up visit Study Day 56 (±7)

4 STUDY DESIGN

Overview of Study Design and Procedures. This is a single site, phase 2B, proof of concept, randomized, triple-masked (participants, study staff and data analysts), placebo-controlled, parallel-group design to evaluate the safety and analgesic efficacy of a SPM precursor-enriched marine oil supplement compared to placebo, orally administered over 8 weeks in 100 adults with examiner-verified TMD myalgia and/or arthralgia.

Rationale for study design. This is a conventional parallel group design because, unlike a crossover design, the parallel group design is not biased by participant fatigue, loss to follow-up, or potential carryover effects. A phase 3 trial is premature at this time because an SPM precursor-enriched marine oil supplement has not been evaluated for analgesic efficacy under rigorous randomized controlled conditions in adults with TMD. A phase 2B, proof-of-concept RCT provides a useful interim step to evaluate safety and gauge efficacy. It will demonstrate whether the supplement is safe and sufficiently active to detect a preliminary analgesic efficacy signal. If we find no efficacy signal, we will avoid investment in an intervention that is unlikely to succeed. If we find a signal, the proof-of-concept clinical trial will establish the basis for a larger-scale phase 3 trial confirming efficacy.

Target Population. Participants will be 100 adults who meet diagnostic criteria (DC/TMD) for TMD myalgia and/or arthralgia.(40) Following a pre-screening phase, study participants who complete a minimum of 4 of 7 DSD entries prior to Visit 1 (Randomization visit) and whose weekly average pain score on this DSD is ≥30 or ≥30 on at least 2 days during that week will be eligible for randomization. Eligible participants will be randomly allocated in a 1:1 ratio within fixed permutated blocks of 4 to the active or placebo group, using sex-stratified randomization. They will attend 4 clinic visits (V0, V1, V2, and V3) during the screening period and the 8-week intervention plus a post-study phone call to evaluate primary and secondary outcomes and to monitor AEs.

Active intervention and the placebo. The active intervention is a marine oil dietary supplement softgel enriched with n-3 SPM precursors: 18-hydroxyeicosapentaenoic acid (18-HEPE), 17-hydroxydocosahexaenoic acid (17-HDHA), and 14-hydroxydocosahexaenoic acid (14-HDHA). It is manufactured by Metagenics LLC. Gig Harbor, WA using Good Manufacturing Practices (cGMP) and sold commercially as SPM Active®. Each softgel contains 1 g of a marine oil fraction with demonstrated pro-resolving activity covered by the patent family PCT/US2013/040313.

The placebo is a medium-chain triglyceride (MCT) oil packaged in a bottle of softgels. MCT oil has an excellent safety profile (32) and is commonly used as a placebo in lipid clinical trials. (41) Each placebo softgel contains 1 g of MCT, with a purity of 100%. The placebo is also manufactured by Metagenics LLC. Gig Harbor, WA using cGMP.

Both products will be enclosed in an identical softgel shell (gelatin, glycerin, water), to be indistinguishable in appearance and weight, and will be dispensed in a brown glass bottle. Instructions on the product label on each bottle are to take one softgel orally, twice daily, for 8 weeks. Thus, the daily dose of the active agent and placebo is 2 g.

Dose justification. The dose was guided by two previous clinical studies. One was a dose-finding, pharmacokinetic trial (30) (that tested three doses (1.5 g, 3 g, or 4.5 g per day) of

SPM Active® versus placebo. The other study was a dose titration trial, in which SPM Active® was administered to adults with chronic pain to assess reduction in pain intensity. (24)

End of study definition. A participant is considered to have completed the study when he or she has completed all phases of the study including the last visit and the follow-up safety phone call shown in the Schedule of Events, *Appendix A*.

5 STUDY POPULATION

5.1 Participant Inclusion Criteria

Pre-screening inclusion criteria:

a. Aged ≥18 years
b. Has had pain in jaws, temples, ears or in front of ears every month for the last 3 months, and for at least 5 days of the last 30 days
c. The pain is not caused by toothache or ear infection
d. The pain intensity is rated ≥30 on a 0-100 NRS for the week preceding pre-screening
e. Is willing to provide signed and dated informed consent
f. Is willing to follow all study procedures and be available for the study duration
g. Provides contact information

Visit 0 Screening and Baseline inclusion criteria:

- Fulfils the pre-screening TMD pain criteria (item b. above)
- Meets examiner-verified DC-TMD diagnostic criteria for TMD myalgia or arthralgia
- If currently using an omega-3 supplement, agrees to discontinue its use prior to Randomization and refrain from use for the duration of the study.
- Agrees not to initiate occlusal splint therapy during the study. Participants already using a splint for ≥30 days prior to enrollment may continue its use.
- Maintains a stable facial pain management regimen, defined as meeting all of the following criteria: (1) no change in the dose or frequency of regularly scheduled daily pain medications; (2) no initiation of new facial pain treatments (pharmacologic, injectable, or non-pharmacologic) during the study period; and (3) discontinuation of episodic prescription pain medications prior to randomization, with the exception of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and low-dose (“mini”) aspirin. Episodic prescription pain medications will remain discontinued for the duration of the trial to ensure stability of the pain management regimen.

Visit 1 Randomization inclusion criteria:

- Completes ≥4 of 7 DSD entries before Visit 1, with an average weekly pain score ≥30 on a 0-100 NRS or a score ≥30 on at least 2 days that week.

5.2 Participant Exclusion Criteria

All exclusion criteria will be assessed at pre-screening and/or screening using participant self-report and review of current medications, as appropriate. No vital signs or clinical measurements will be collected as part of eligibility determination.

- **Participant self-report** will be used to assess:
  - Allergy or hypersensitivity to fish or seafood
  - Receipt of botulinum toxin (Botox) injections for facial pain within the past 3 months

- Facial trauma or orofacial surgery within the past 6 weeks
- History of renal failure or dialysis treatment
- History of hyperthyroidism
- Immunocompromised state or autoimmune disorder
- History of seizure disorder and seizure control status
- Use of opioid medications within the past 30 days
- Pregnancy

- **Medication review and self-report** will be used to assess:
  - Current use of prescribed anticoagulant therapy (excluding low-dose aspirin)

Visit 0 Screening and Baseline exclusion criteria:

Participants will be excluded from randomization if they have currently:

- Class II obesity (BMI > 35 kg/m²); renal failure/dialysis; hyperthyroidism; immune compromise; autoimmune disorder; uncontrolled seizures; fish/seafood allergy; prescribed anticoagulant use; or opioid use within 30 days before screening
- Initiated new daily prescription pain medication within 30 days; commenced occlusal splint therapy for facial pain within 30 days; had injection therapy (tender/trigger point or steroid) for facial pain within 2 weeks; had onabotulinumtoxinA injections for facial pain within 3 months; or had acupuncture/biofeedback for facial pain within 2 weeks before screening
- Major depression or other major psychiatric disorder requiring hospitalization within the past 6 months
- Had treatment for drug or alcohol abuse within the past year
- Are undergoing chemotherapy or radiation therapy
- Had treatment with an investigational drug or therapy within 30 days before screening
- Self-reported pregnancy
- Have anything that, in the opinion of the investigator, would place the participant at increased risk or preclude their full compliance with or completion of the study

5.3 Strategies for Recruitment and Retention

Multimodal recruitment strategies will be used as described in detail in Section 2.5 of the HSS record. In summary, recruitment strategies will include:

- Direct contact with patients who have relevant diagnoses recorded in electronic health records or patient registries at UNC-CH (e.g., the Carolina Data Warehouse for Health, ASOD records, and Dr. Tchivileva's Orofacial Pain and Headache Research Participant Registry)
- Direct contact with participants from previous TMD studies (e.g., OPPERA and SOPPRANO)
- Recruitment through Research for Me@UNC, a recruitment and research registry platform operated by UNC-CH's NC TraCS Institute

- Recruitment from the Adams School of Dentistry (ASOD) Orofacial Pain Clinic
- Distribution of recruitment flyers by staff at the Duke Hospital Orofacial Pain Clinic, featuring a QR code linking to a UNC-CH pre-screening form. Additionally, Duke IT will send mass emails to consenting TMD registry patients, with the UNC-CH team monitoring responses for eligibility
- A public study website (adapt.study) provides information about the ADAPT clinical trial, including the purpose of the study, study procedures, eligibility criteria, frequently asked questions, study contact information, directions to the UNC Adams School of Dentistry, and links to the National Institutes of Health, UNC Adams School of Dentistry, ClinicalTrials.gov, the study protocol, and the current IRB-approved informed consent document. The website includes an "Are you eligible?" button that links directly to the existing IRB-approved Qualtrics prescreening survey. The website does not collect research data or personal information directly. Interested individuals who choose to proceed are redirected to the existing IRB-approved prescreening survey.
- Conventional advertising (e.g., flyers and print media) and advertising on UNC-CH list-serves

We have significant experience recruiting participants with TMD for clinical research studies. Based on our most recently completed RCT of people with TMD, (42) we anticipate 75% of enrolled participants to be female, 23% to be non-White, and 10% to be Hispanic.

In the SOPPRANO randomized controlled trial of adults with TMD myalgia, pre-screening data from the UNC site show that 547 individuals were prescreened, of whom 148 (27%) passed pre-screening, corresponding to a screen-to-pass ratio of approximately 3:1. The most common reasons for prescreen failure were failure to meet facial pain eligibility criteria and age ineligibility, with relatively few exclusions for medical or safety reasons. We are confident that enrollment of 100 eligible participants is feasible because ADAPT allows a longer enrollment period (4 years vs. 3 years in SOPPRANO) and includes fewer exclusion criteria than SOPPRANO.

Projected rate of randomization in UH3 years 1 through 4

	Y1	Y2	Y3	Y4	Y5	Total
# Screened	32	56	56	16	0	160
# Randomized	20	35	35	10	0	100

With an average enrollment of 3 participants per month beginning in UH3 year 1, 100 participants will be randomized early in year 4.

This resembles the rate of enrollment in SOPPRANO.
Participants will be compensated up $320 for completion of all study activities as per this schedule:

- $60 for Visits 0 and 2;
- $75 for visits 1 and 3, and
- $50 bonus for completion of all study visits.

To promote retention beyond remuneration, we will offer flexible scheduling, parking vouchers, transportation support if required, and continuity with the same study staff to build rapport. Visits will be streamlined to minimize participant burden, and we will use reminder

calls, texts, and emails to reduce missed appointments. We will also emphasize each participant's contribution to advancing scientific knowledge and regularly assess barriers to continued participation, addressing them as needed.

If a participant fails to return for a scheduled study visit, the following procedures will be implemented:

- Study staff will attempt to contact the participant to reschedule the missed visit within 1 week, counsel the participant on the importance of adhering to the visit schedule and determine whether the participant wishes to and/or should continue participation in the study.
- Prior to classifying a participant as lost to follow-up, the investigator or designee will make reasonable and documented efforts to re-establish contact, including up to three telephone calls and, if necessary, a certified letter sent to the participant's last known mailing address or other locally approved contact methods.
- All contact attempts and outcomes will be documented in the participant's study record. Should the participant continue to be unreachable, he or she will be considered lost to follow-up and excluded from the per-protocol analysis population (see Section 12.4.1).

5.4 Treatment Assignment Procedures

5.4.1 Randomization Procedures

At Visit 1, study participants will be randomly allocated to the active or placebo group in a 1:1 ratio within fixed permutated blocks of 4 and stratified by sex. The allocation sequence will be generated using the "plan" procedure in SAS v9.4 software and implemented with a module of the Teleform-Access Research Data Intelligence Service (TARDIS) that will also conceal the allocation sequence to users of TARDIS. While the unmasked data manager and (as backup) the study biostatistician will create the allocation sequence table, upload it to the TARDIS and have access to it in the TARDIS, those individuals will not be involved in the process of randomizing individuals. Instead, at the time of randomization, other study staff will access the TARDIS, enter the participant's study identification number, and verify that the participant is eligible for randomization. The TARDIS will store the study group assignment in a data record that will also contain the study participant's 3-digit identification code. The TARDIS will generate a verification code that will be recorded in the participant's casebook providing an audit trail to signify that the study participant was randomized; however, the TARDIS will not reveal the study participant's study group assignment to TARDIS users. The study group allocation will therefore be concealed from study personnel who perform the randomization procedure.

The randomization table will be linked in a 1:1 relationship to a second table in the same split-section containing only the randomization tables' sequence number. That second table will be mirrored in the masked split-section of the TARDIS database to be used by masked study personnel who interact with study participants.

No planned or unplanned breaking of randomization codes is expected until the end of the study.

5.4.2 Masking Procedures

Both the active and placebo interventions will be encapsulated in identical softgel shells composed of gelatin, glycerin, and water, rendering them indistinguishable in appearance and weight. The softgels are oval, translucent, and have a smooth, glossy surface, with a pale amber or light golden hue, and each weighs approximately 1 g. Both interventions will be dispensed in identical brown glass bottles containing 70 softgels per bottle (to cover 28+7 days). The first bottle will be provided at the randomization visit (Visit 1), and the second bottle will be provided at the mid-study visit (Visit 2).

All study participants and research personnel will remain masked to treatment allocation, and the allocation sequence will be concealed. The only exceptions are the unmasked statistician (Dr. John Preisser) and the unmasked data manager (Dr. Gary Slade), who will have no participant contact or role in outcome assessment, with the exception of any necessary follow-up with participants concerning AEs where unmasking is required, in which case Dr. Slade will do that contact (see Section 9.4).

The adequacy of participant masking will be assessed at Visit 3 by asking participants to report their perceived treatment assignment. In the SOPPRANO trial of propranolol, in which expected and well-described side effects were readily apparent, agreement between perceived and actual treatment assignment was low (kappa = 0.22; 95% CI, 0.09–0.36), indicating effective participant masking.

Any inadvertent unmasking of study staff or participants will be promptly documented and reported as a protocol deviation, although the participant will continue in the study. The study team will conduct a systematic review of the circumstances surrounding the unmasking to identify contributing factors and implement corrective actions to minimize the risk of recurrence.

5.5 Participant Withdrawal or Discontinuation from Study Procedures/Intervention

5.5.1 Reasons for Participant Withdrawal or Discontinuation from Study Procedures/Intervention

Participants are free to withdraw from participation in the study at any time upon request. Participants may choose to discontinue the intervention or study procedure but continue to be followed. An investigator may discontinue the intervention but allow the participant to continue with the study for the following reasons:

- Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued intervention would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- Self-reported pregnancy

An investigator may withdraw a participant from the study if the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.5.2 Handling of Participant Withdrawals from Study or Participant Discontinuation of Study Intervention

Complete withdrawal from the trial.

- Participants who withdraw from the study after randomization will not be replaced. Participants who withdraw prior to randomization may be replaced in order to achieve the target sample size.
- If a participant withdraws due to an AE, the study intervention will be discontinued, and the PI or a qualified designee will determine the clinical significance of the AE and its relatedness to the study intervention. Withdrawals for reasons other than an AE will, with the participant's permission, be managed through an Early Termination Visit conducted during a scheduled or unscheduled visit. If permission to conduct an Early Termination Visit is not granted, the reason for participant discontinuation or withdrawal will be documented on the Discontinuation Case Report Form.
- Participants whose study intervention is discontinued prematurely will be encouraged to remain in the study for continued data collection through Visit 3, unless the participant withdraws consent. In such cases, the Early Termination Visit will follow the procedures outlined for Visit 3.

Discontinued intervention with continued participation. There may be circumstances in which it is in the best interest of the participant to discontinue the intervention (e.g., because of mild but persistent gastrointestinal symptoms), but to continue with study procedures and data collection. In such cases a participant would discontinue the intervention while continuing to attend study visits so that safety and outcome data can still be collected.

5.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the PI, funding agency (NIDCR), and regulatory authorities. The PI will also promptly inform the IRB and NIDCR and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data that are insufficiently complete and/or evaluable.

6 STUDY INTERVENTION

6.1 Study Product Description

Metagenics, the manufacturer, will provide both active and placebo intervention products to the study at no cost.

Each SPM Active™ softgel contains 1 g of a marine lipid fraction (Lipinova®-Solutex) with demonstrated pro-resolving activity covered by the patent family PCT/US2013/040313. For the purposes of this clinical trial, the softgels will be repackaged into bottles of 70 softgels to cover 28 days, with an additional 7-day buffer. A product label will provide instructions on use and the name of the PI. The product has a shelf life of 24 months. This information can be found in the Product Information sheet.

As described in the supplement's clinical brochure [SPM Clinical Brochure_ INTERACTIVE MET3029.pdf], an expert panel granted Generally Recognized as Safe (GRAS) status to this proprietary SPM Supplement following procedures specified in 21 CFR§170.3(b). The expert scientific panel studying the proprietary SPM precursors with standardized content ascertained that the intended use of the SPM precursors has been determined to be safe through scientific procedures as set forth in 21 CFR§170.3(b). The panel determined the proprietary SPM-precursors with standardized content are appropriately characterized, meet product specifications, and have a proven stability profile.

The safety analysis included a detailed review of the existing scientific literature (through June 2018) on the safety of the pro-resolving mediators 17-hydroxy-docosahexaenoic acid (17-HDHA), 14-hydroxydocosahexaenoic acid (14-HDHA) and 18-hydroxy-eicosapentaenoic acid (18-HEPE) standardized in this supplement and their specific properties. Based on this independent, critical evaluation of all the available information as well as discussions by the expert panel, they unanimously concluded that this proprietary SPM formula is GRAS. The SPM formula is a fraction of marine oil. The SPM-precursor products are shown to be manufactured following current Good Manufacturing Practice regulations (cGMP). Analytical (chemical) results for the SPM products confirm that the finished product formulations meet the proposed specifications as demonstrated by the consistency of production, the lack of impurities/contaminants (e.g., heavy metals, polychlorinated dibenzo-p-dioxins (PCDDs), polycyclic aromatic hydrocarbons (PAHs), and polychlorinated biphenyls (PCBs)), and their stability over a 6-month period. The full panel of purity evaluations is available at https://www.metagenics.com/truquality – enter lot number B09190428). Known and expected side effects are similar to other high-quality fish oils and are quite uncommon (generally <0.5%). These may include minor gastrointestinal distress, such as loose stools, nausea, abdominal discomfort, and belching.

The placebo, also manufactured by Metagenics LLC., is a medium-chain triglyceride (MCT) oil. Each placebo softgel contains 1 g of MCT, with a purity of 100%. MCT oil has an excellent safety profile (32) and is commonly used as a placebo in lipid clinical trials.(41) Although MCT oil is not biologically inert, the MCT softgels were selected as the placebo because they match the marine oil dietary supplement in appearance, taste, and fat content. Moreover, their anti-inflammatory potential is modest relative to the marine lipid–derived SPM precursors under investigation. Furthermore, they are less likely to influence inflammatory pathways than other commonly used placebo oils, such as olive oil, soybean oil, and corn oil.

Both active and placebo interventions are enclosed in an identical softgel shell (gelatin, glycerin, water) to be indistinguishable in appearance and weight.

6.1.1 Acquisition

The active IP and the placebo will be delivered to Dr. Slade (the unmasked data manager) at the UNC-CH ASOD directly from the manufacturer's primary headquarters in Aliso Viejo, California.

6.1.2 Investigational Product Management

The PI, acting as the authorized delegate, will assume overall responsibility for IP management activities, including receipt, storage, accountability, dispensing, and documentation, in accordance with the study protocol, Good Clinical Practice (GCP), and 21 CFR Parts 50, 56, and 312.7. Day-to-day management of the IP will be carried out by the unmasked investigator, Dr. Gary Slade, and the Study Coordinator through the UNC Clinical Research Support & Operations (CRSO).

The study team will maintain secure, temperature-controlled, access-restricted storage for the IP and will perform regular accountability checks. Detailed records of IP receipt, dispensing, and returns will be maintained and reconciled throughout the study. The study team will also oversee destruction of unused IP.

All IP management procedures, including labeling, packaging, masking, and dispensing will be conducted by the study team in accordance with the protocol and institutional requirements, ensuring compliance with all applicable regulatory standards. The FDA is exercising enforcement discretion, allowing the study to proceed without an IND while maintaining compliance with 21 CFR Parts 50, 56, and 312.7.

6.1.3 Formulation, Packaging, and Labeling

IP will be dispensed in brown glass light-resistant containers. The containers will be labeled with the following information:

- Name of the institution
- Protocol number
- Name of the PI
- Date dispensed
- Name of the IP labeled as "SPM Active or placebo" to protect the masking
- Strength of the IP (1 g SPM Active and 1 g placebo)
- Number of softgels dispensed
- Instructions for use
- Participant name
- Participant date of birth
- Lot number
- Expiration date
- Prescription number
- The following statement: "Caution: New drug limited by U.S. Federal Law to Investigational Use Only"

6.1.4 Product Storage and Stability

The IP will be stored under Controlled Room Temperature (CRT) conditions, in accordance with the United States Pharmacopeial Convention (USP) standards. CRT is defined as maintaining temperatures between 20°C and 25°C (68°F to 77°F), with allowable brief excursions between 15°C and 30°C (59°F to 86°F), provided such excursions do not adversely affect product quality. Room temperature will be monitored continuously with temperature logged at hourly intervals. The log will be reviewed daily and downloaded for monthly QC reports. Any excursion outside 15–30 °C will be reported as a Protocol Deviation.

6.2 Accountability Procedures for the Study Product

During the study, Dr. Slade will be responsible for verification of IP shipment from the manufacturer, documentation of IP receipt, and IP provisioning. All necessary records will be entered in the Site IP Accountability Log within TARDIS. The Study Coordinator will be responsible for inventory control of the IP dispensation to and return by participants. The Study Coordinator will request dispensation of the individual participant's IP electronically within TARDIS and receive an assigned bottle with IP at the visit. The staff will record the number of dispensed and returned softgels at all relevant visits in the Participant IP Accountability Log. All returned bottles with unused IP will be kept until inspection by the study monitor. Then we will dispose of returned, unused, or expired products.

Dr. Slade and designated study staff will be responsible for monitoring IP expiration. Upon receipt of each shipment, Dr. Slade will record the lot number and expiration date in the Site IP Accountability Log within TARDIS. Expiration dates will be verified and cross-checked against the Certificate of Analysis or product label. The study staff will additionally monitor the expiration date when dispensing the IP to a participant.

The study team will review IP inventory at least monthly to ensure that no product is expired or nearing expiration. TARDIS will be used to generate alerts for products within 60 days of expiration. Any approaching IP expiration will be clearly flagged and segregated from the active supply to prevent dispensing. Expired IP will be immediately quarantined, labeled "Do Not Use," and disposed of according to UNC-CH institutional policies and sponsor requirements.

All activities related to expiration monitoring, including verification, segregation, and destruction, will be documented in TARDIS and maintained as part of the IP accountability records. The study sponsor will notify the PI promptly of any updated expiration or retest dates.

6.3 Assessment of Participant Compliance with Study Product Administration

The number of softgels consumed per day will be recorded by study participants in the DSD. In addition, participants will be asked to return their IP bottles at Visits 2 and 3, and study staff will record the number of unused softgels in the Participant IP Accountability Log.

Participant compliance with the study IP will be defined as taking 70% or more of the study IP for the duration of the study.

6.4 Concomitant Medications/Treatments

Prior and concomitant medication information will be collected for all participants for the 30 days prior to the Screening and Baseline Visit and during the study. Concomitant therapies comprise prescription medications, over-the-counter medications, supplements, occlusal splint therapy and complementary/alternative therapies.

Concomitant therapies at follow-up visits that represent protocol deviations will be recorded in case report forms by study staff at Visits 0, 1, 2 and 3. Information collected will include medication, total daily dose, start date, stop date (if applicable), and primary reason for use. While such protocol deviations are considered when defining the per-protocol analysis population (see Section 12.4.1) they do not constitute reasons for early termination or intervention discontinuation.

During the trial, non-steroidal anti-inflammatory drugs (NSAIDS), acetaminophen, and low-dose (“mini”) aspirin will be permitted as rescue medications with specified limits: up to 5 consecutive days of NSAIDs usage (with a maximum of 16 days during the treatment period) will be regarded as within the protocol. Participants will record frequency and doses of rescue medication used in the DSD. Participants whose use of rescue medication exceeds those limits will be excluded from the per-protocol analysis population.

7 STUDY SCHEDULE

The Schedule of Events table, which provides an overview of the study phases, timeline, and events by visit, is provided in *Appendix A*. In the following section, events are listed by study phase and visit, though the order of events listed within a visit does not imply the order in which the events will occur. A description of the procedures is provided in Section 8.

7.1 Pre-screening (Day -49 to Day -7)

Potential participants may first learn about the study through the recruitment methods described in Section 5.3, including the public study website (adapt.study). Individuals who select the “Are you eligible?” button on the website are directed to the existing IRB-approved Qualtrics prescreening survey. Prescreening will begin with a questionnaire completed online by potential study participants:

- A QR code on recruitment flyers will direct potential study participants to a Qualtrics pre-screening questionnaire. The landing page provides the Study Coordinator’s contact information, the IRB number, and the UNC-CH IRB email address.
- The questionnaire, which takes 2–3 minutes to complete, first confirms that respondents are 18 years or older, then collects contact information.
- Screening questions assess symptoms of painful TMD and determine if any exclusion criteria apply.
- Any response that renders a respondent ineligible triggers a message thanking them for their interest and explaining that they will not be invited to join the study.
- Eligible respondents are asked to confirm that they understand and agree to attend four in-person visits over eight weeks, complete two blood draws, record daily pain ratings, communicate via text with the study team, and submit weekly photos of their pain diary. They are then thanked and informed that the Study Coordinator will contact them.

People who are eligible based on the Qualtrics questionnaire will be phoned by study staff to verify eligibility and to schedule a Screening and Baseline Visit. During the phone call:

- Study staff will obtain verbal consent for the telephone interview
- They will then ask about symptoms of painful TMD and determine if any exclusion criteria apply, as per the Eligibility CRF.
- For participants who meet eligibility criteria, staff will schedule a Screening and Baseline Visit to occur within 28 days of the interview.
- For participants who do not meet eligibility criteria due to some transient condition, the eligibility can be re-assessed up to two times after the condition that precluded eligibility resolves.

7.2 Screening and Baseline Visit 0 (Day -21 to -7)

The visit will begin with the process of obtaining informed consent:

- Obtain informed and signed consent for study participation

- Obtain signed Health Insurance Portability and Accountability statement (as applicable)
- Check contact information recorded at pre-screening
- Collect demographic information as per the Enrollment CRF

Participants will then complete interviews and examinations:

- Obtain medical history using the TARDIS Baseline Medical History module
- Study staff will record concomitant medications and therapy using the TARDIS Medications module
- Study staff will perform TMD examination as per the DC-TMD CRF
- Study staff will collect physical measurements
- Conduct eligibility review
- Dispense DSD CRF to be completed prior to next visit
- Schedule next visit

7.3 Randomization Visit 1 (Day 0)

The following procedures and assessments will be conducted at Visit 1:

- Update medical history using the TARDIS Follow-up Medical History module
- Record concomitant medications and therapy using the TARDIS Medications module
- Assess and record adverse events using the Adverse Event CRF
- Collect and assess eligibility with DSD entries. If the criterion for randomization is not met, eligibility can be re-assessed at up to two subsequent visits scheduled within the window
- Conduct eligibility review
- Participants will complete CRFs to measure baseline values for secondary outcomes: GCPS-TMD, HIT-6, ID-Migraine, OHIP-TMD, Pain Manikin, SCL-90 and STAIY-1
- Perform randomization, if eligible, using the TARDIS Randomization module
- Dispense new DSD
- Dispense IP
- Administer outcome measure questionnaires as per Schedule of Events
- Draw blood
- Schedule next visit

7.4 Intermediate Visit

Visit 2 (Day 28 [± 7 days])

The following procedures and assessments will be conducted at Visit 2:

- Update medical history for any changes in health or treatment since last visit
- Record concomitant medications and therapy
- Assess and record AEs
- Dispense new DSD

- Participants will complete CRFs to measure values for secondary outcomes: PGIC, HIT-6, SCL-90 and STAIY-1
- Assess compliance with IP (e.g., count returned medication)
- Dispense IP
- Perform pressure pain tests
- Schedule next visit

7.5 Final Study Visit

Visit 3 (Day 56 [+ 7 days])

The following procedures and assessments will be conducted at Visit 3:

- Update medical history for any changes in health or treatment since the last visit
- Record concomitant medications and therapy
- Assess and record AEs
- Participants will complete CRFs to measure values for secondary outcomes: PGIC, GCPS-TMD, HIT-6, OHIP-TMD, Pain Manikin, SCL-90 and STAIY-1
- Collect DSD and assess compliance with DSD
- Assess compliance with IP (e.g., count returned medication)
- Study staff will perform TMD examination as per the DC-TMD CRF
- Study staff will collect pressure pain thresholds as per the PPT CRF
- Draw blood

Post-study Phone Interview (Day 63 [+ 7 days])

The following procedures and assessments will be conducted at Post-study Phone Interview:

- Assess and record AEs

7.6 Early Termination/Withdrawal Visit

If a participant is discontinued before study completion, prior to the withdrawal of consent and with the participant's permission, an Early Termination Visit may be conducted, either during a scheduled or unscheduled visit. Each of the procedures and assessments described for Visit 3 (Section 7.5) will be conducted at the Early Termination Visit.

7.7 Unscheduled Visit

An unscheduled visit may occur at the discretion of the investigator. Reasons for an unscheduled visit would include, but are not limited to, an AE, or the need for an Early Termination Visit. All activities conducted during the visit will be documented in the study database.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Study Procedures/Evaluations

8.1.1 Clinical Procedures/Evaluations and Specimen Collection

- Physical Measurements (Visit 0). A physical examination is performed at the Screening and Baseline Visit (Visit 0) to measure height and weight.
- Medical History (all visits). A full medical history will be obtained by interview for each participant at the Screening and Baseline Visit (Visit 0) and entered into the case report form. Any change to medical history will be recorded at Visits 1, 2 and 3.
- TMD Diagnostic Criteria (Visits 0 and 3). The trained study examiner will determine presence of TMD myalgia/arthralgia using the established examination protocol and validated Diagnostic Criteria for Temporomandibular Disorder (DC/TMD). (40) In brief, the examiner will assess the presence of pain reported in the cheeks, jaw muscles, temples, or jaw joints. To be classified as having TMD, participants must have all four of the following findings: a) history of orofacial pain in examiner-verified locations of masseter, temporalis, submandibular or temporomandibular joint area; b) evoked pain in the same muscles and/or temporomandibular joint(s) following palpation of those structures or jaw maneuver; c) reported familiarity of evoked pain to facial pain symptoms during the preceding 30 days; and d) pain that was modified by jaw function (i.e., chewing, opening the mouth, or jaw habits).
- Pressure pain algometry (Visits 0, 2 and 3). Trained staff will conduct the pressure pain threshold (PPT) tests using a pressure algometer at five anatomical sites, bilaterally, in the following order: (1) the center of the temporalis muscle, (2) the center of the masseter muscle, (3) overlying the temporomandibular joint, (4) the center of the trapezius muscle, and (5) overlying the lateral epicondyle. The PPT will be defined as the amount of pressure at which the participant first perceives the stimulus to be painful. One pre-trial assessment will be performed at each site followed by additional assessments until 2 measures differing by less than 0.2 kg are obtained, or 5 assessments are administered. In either case, the mean of the 2 closest values will be recorded as the threshold estimate. Pressure stimuli will be delivered at an approximate rate of 1 kg/s. The cutoff pressure for all sites will be 5 kg. The values from the right and left sides will be averaged to obtain a single PPT value per anatomical site.
- Pregnancy (Visit 0). Participants who report being pregnant at baseline will be excluded. This exclusion is intended to avoid withholding a supplement that is currently recommended to improve pregnancy outcomes, rather than due to safety concerns. A 2024 clinical practice guideline, supported by multiple medical and scientific organizations, recommends that pregnant individuals with low omega-3 intake receive 600–1000 mg/day of DHA and/or EPA beginning by 20 weeks' gestation to reduce the risk of preterm birth.(43) These recommendations are supported by strong evidence from randomized controlled trials. Including pregnant participants at baseline could therefore expose individuals randomized to placebo to potential harm by withholding a clinically recommended intervention.

- Consistent with this rationale, and as described in Section 9.4.5, participants who become pregnant after randomization will be asked to discontinue the study intervention but remain in the trial.
- Assessment of AEs (All visits). Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participants is the preferred method to inquire about AE occurrences. Common Terminology Criteria for AEs (CTCAE version 6) will be used for grading of AEs and the Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding of AEs.
- Daily Symptom Diary (collected at Visits 1, 2 and 3). Participants will be asked to complete the DSD at the end of each day starting at Visit 0 and ending at Visit 3. Participants who complete at least 4 out of the 7 entries within 7 days prior to Visit 1 will be considered eligible for study participation. The diary requests information about the participant's pain intensity (reported on a 0-100 NRS) and percent of waking days with pain (reported on a 0-100 percentage scale). It also records the number of study medication softgels taken, and the name and dose of any pain medication taken. Participants will return paper-based diaries either by mail or in person on study visits. Compliance with the DSD will be defined as completion of at least 4 daily entries within 7 days prior to Visits 1, 2, and 3. Any noncompliance found during Visits 2 and 3 will be reported as protocol deviations.
- Biological specimen collection (Visits 1 and 3). Participants will undergo a non-fasting blood draw for lipidomic profiling. Study personnel trained in phlebotomy will collect up to 10 mL of blood by venipuncture. To assess fatty acids and their derivatives that may be modulated by the SPM precursor-enriched supplement, samples will be collected at Randomization (Visit 1) and at Follow-up (Visit 3). Plasma and red blood cells will be aliquoted into 1.5mL cryovials and stored at −80°C in freezers located at the UNC-CH ASOD, until shipment to the UNC-CH Mass Spectrometry Core Laboratory.

8.1.2 Outcome Measure Questionnaires.

The primary outcome is pain intensity recorded in the DSD (see above). Secondary outcomes will be assessed with questionnaires and measurements listed in the Schedule of Events (*Appendix A*) and are briefly described below. Copies of the questionnaires are reproduced in the attachments. Several questionnaires are self-administered, and others will be administered by trained study staff. For outcome-measure questionnaires, responses will be recorded on paper Teleform case report forms, which will be scanned as described in the study's MOP.

- Pain duration. Participants will record, in the DSD, the percentage of their waking day during which facial pain is present.
- Graded Chronic Pain Scale (GCPS). Developed by Von Korff et. al., (37) the GCPS measures the severity and impact of pain. Ohrbach et al. (44) adapted the GCPS for the OPPERA study by restricting the index condition to facial pain. Participants rate current, worst, and average facial pain on 0–10 numeric scales (0 = no pain; 10 = pain as bad as it could be), report the number of days pain limited usual activities, and rate interference with daily, social/recreational, and work activities (0 = no interference; 10

= unable to carry on any activities). We will shorten the reference period to one month to reflect the time between study visits.

- State-Trait Anxiety Inventory-Y (STAI-Y), State Subscale. The State Anxiety Subscale evaluates the current state of anxiety using 20 items that measure subjective feelings of apprehension, tension, nervousness, worry, and activation of the autonomic nervous system.(34)
- Symptom Checklist 90-Revised (SCL-90) Depression Subscale. The Symptom Checklist 90 (SCL-90) depression subscale is a 12-item section of the SCL-90, a self-report questionnaire that measures a range of psychological and psychiatric symptoms.(35)
- Headache Impact Test (HIT-6). The HIT-6 evaluates the factors contributing to the burden of headache and consists of 6 items: pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. (36) The participant answers each question using responses ranging from “never” to “always.” These responses are summed to produce a total HIT-6 score.
- Oral Health Impact Profile for TMDs. OHIP-TMDs is a 22-item questionnaire with good psychometric properties that assesses quality of life in people with TMDs.(38)
- Pain Manikin (anterior and posterior views of a body manikin). To assess the distribution and extent of bodily pain, participants will complete a standardized pain mapping task using paper-based body manikins that display both anterior (front) and posterior (back) views of the human body. These manikins provide a comprehensive visual representation that allows participants to indicate exactly where they are experiencing pain. At designated study visits, participants will be asked to shade the areas of the body where they have felt pain over a specified recall period (e.g., past 7 days). Instructions will encourage careful attention to both the front and back of the body to ensure accurate capture of widespread or localized pain patterns. This method enables quantification of pain location, symmetry, and potential referral patterns, and can help distinguish between localized and generalized pain presentations
- ID-Migraine. The ID-Migraine screener is a quick, three-question tool used to identify people who are likely to have migraine. It asks about headaches in the past three months and whether they were accompanied by disability (interference with activities), nausea, and sensitivity to light. If two or more answers are “Yes,” it suggests a high likelihood of migraine.(45)
- Patient Global Impression of Change (PGIC). The PGIC is a participant-rated instrument that measures change in participant’s overall status on a scale ranging from 1 (“very much improved”) to 7 (“very much worse”). The PGIC is based on the Clinical Global Impression of Change, which is a validated scale. (39)

8.2 Laboratory Procedures/Evaluations

8.2.1 Clinical Laboratory Evaluations

In this study, clinical laboratory tests are not needed for the monitoring of safety or the evaluation of study objectives; therefore, none will be performed.

8.2.2 Special Assays or Procedures

Dr. Ehrmann's laboratory will employ a rigorously optimized ultra-high-performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) method to quantify targeted n-6 and n-3 PUFAs and their lipid derivatives in erythrocytes and plasma. This method enables simultaneous profiling and quantification of 65 targeted oxylipins, including specialized pro-resolving mediators (SPMs), in a single analytical run. The targeted analytes include n-6 oxylipins such as oxidized linoleic acid metabolites (OXLAMs), arachidonic acid–derived prostaglandins, thromboxanes, and hydroxyeicosatetraenoic acids (HETEs), as well as n-3 oxylipins such as EPA- and DHA-derived hydroxy, epoxy, and dihydroxy fatty acids, along with D-series and E-series resolvins, protectins, and maresins.

Due to their low endogenous concentrations (46) and chemical instability(47), direct measurement of these lipid mediators presents significant analytical challenges. These challenges necessitate meticulous extraction procedures to ensure compound stability and analytical fidelity. Our extraction protocol integrates multiple liquid-liquid extraction steps with solid-phase extraction (SPE) to maximize analyte recovery and integrity.

The mass spectrometry method has been carefully developed to include validated quantifier and qualifier ion transitions, ensuring unambiguous identification and accurate quantitation of each oxylipin. Liquid chromatography parameters will be further evaluated and extended as needed to optimize chromatographic retention, resolution, and separation of closely eluting compounds. Our laboratory personnel bring extensive expertise in lipidomics and complex biofluid extraction, ensuring high reproducibility and analytical rigor throughout the workflow.

8.2.3 Specimen Preparation, Handling, and Storage

Preparation, handling, and storage of specimens are described in detail in the study's Manual of Procedures (MOP). In brief, nonfasting venous blood samples will be collected from each participant at two time points (V1 and V3) for targeted mass spectrometry-based profiling of oxylipins. Because our protocol involves collection only of human blood in a clinical research setting, with no on-site processing or manipulation, BSL-2 laboratory designation is not required for the collection space. Any downstream handling of specimens will occur in appropriately designated facilities operating under BSL-2 conditions and associated safety plans. Collected samples will be transferred for prompt processing in the Adams School of Dentistry analytical laboratory to isolate plasma and erythrocyte fractions, handled using standard biospecimen safety procedures, and stored at –80 °C until analysis. For this shipment, samples will be packed with sufficient dry ice to maintain frozen conditions and transferred to the analytical laboratory in another building on campus. Biospecimens will be assessed in bulk after all biospecimens have been collected. Detailed instructions for the shipment are provided in the study's MOP.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Participants in this study will undergo close follow-up. Risks related to participation include: 1) risks related to the administration of a marine oil supplement enriched with SPM precursors; 2) risks associated with questionnaires; 3) risks associated with TMD examinations and psychophysical tests; 4) well-known and anticipated minor risks from venous phlebotomy; and 5) risks related to study participation such as loss of confidentiality of collected data.

9.1.1 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.1.2 AEs

An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

9.1.3 Serious AEs

A serious AE (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical

judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2 Time Period and Frequency for Event Assessment and Follow-Up

Safety events will be recorded in the data collection system throughout the study. The PI or her delegate(s) will record all events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. If follow-up any other aspect of participant safety requires unmasking of the participant, the unmasked data manager, Dr. Slade, will perform that aspect of follow-up.

9.3 Characteristics of an AE

Each event will be recorded on an appropriate case report form that includes assessment of the characteristics defined below. These characteristics, along with the frequency of an event's occurrence, will be considered in determining if the event is a UP. AEs will be encoded numerically using the MedDRA Coding system accessed through UNC's web-based browser (mssotools.com/mssoweb/wbb3/wbb3_index.html). Other characteristics of the AE will be classified using the National Cancer Institute *Common Terminology Criteria for AEs* (v 6.0), which may be found in its entirety at:

https://dctd.cancer.gov/research/ctep-trials/trial-development/ctcae-v6.0.xlsx

Determining whether a particular AE is unexpected by virtue of an unexpectedly higher frequency can only be done through an analysis of appropriate data on all participants enrolled in the research. If the investigator determines that an AE is not an unanticipated problem, but the NIDCR Medical Monitor subsequently determines that the AE does represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the oversight board or NIDCR Medical Monitor will report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB.

9.3.1 Relationship to Study Intervention

To assess the relationship of an event to study intervention the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study active or placebo investigational product, and/or
    b. There is a temporal relationship between the investigational product and event onset and/or
    c. The event abates when the investigational product is discontinued, and/or
    d. The event reappears upon a re-challenge with the investigational product.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the investigational product and event onset, and/or

b. An alternate etiology has been established.

9.3.2 Expectedness

The study PI and/or study-appointed, clinically responsible individual will determine whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IP.

AEs associated with the administration of the marine oil dietary supplement and placebo are described in Section 2.3.1. They will be characterized and monitored to protect the safety of participants. In addition, the study has been designed to minimize risks. Participants will be monitored closely for AEs with frequent visits. AEs will be managed by the site investigators depending on the nature of the event.

In this study, the following expected events will not be recorded as AEs:

- Minor bleeding or bruising resulting from the blood draw
- Temporary pain or temporary increases in existing pain elicited during the TMD clinical examination or tests of pressure pain sensitivity
- Worsening of TMD signs and symptoms during the study

9.3.3 Severity of Event

AEs will be graded on a scale from 1 to 5 according to the following standards from the National Cancer Institute's *Common Terminology Criteria for AEs* (v 6.0), which may be found in its entirety at *https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50*:

- Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 = moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3 = severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self- care ADL
- Grade 4 = life-threatening consequences; urgent intervention indicated
- Grade 5 = death related to AE

9.4 Reporting Procedures

9.4.1 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that

investigators include the following information when reporting an AE, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the AE, incident, experience, or outcome;
- an explanation of the basis for determining that the AE, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious AEs will be reported to the IRB within 7 days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB within 14 days of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

All unanticipated problems will be reported to NIDCR concurrently with reporting to the IRB. These reports will be made to NIDCR's centralized reporting system via the NIDCR CROMS contractor.

9.4.2 Serious AE Reporting

Any AE meeting the specified Serious AE criteria will be submitted on an SAE form to NIDCR's centralized safety system via the NIDCR CROMS contractor.

Dr. Tchivileva will complete a Serious AE Form and submit via email within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious AE Form and submitted to NIDCR within 24 hours of site awareness.
- Serious AEs (AEs) other than death and immediately life-threatening events, regardless of relationship, will be reported within 72 hours of site awareness.
- All SAEs will be followed until resolution or stabilization.
- All SAEs will be reported to NIDCR concurrently with reporting to the IRB.

SAEs will be reported to the NIDCR concurrently with reporting to the IRB. In addition, the PI will report to Metagenics LLC. any adverse event suspected to be attributable to the IP or placebo within three business days, and any serious adverse event suspected to be attributable to the IP or placebo within one business day. The determination that an AE is

"suspected" of being attributable to IP will be determined in a masked manner by Dr. Tchivileva. If the IRB, NIDCR or Metagenics LLC require unmasked information, it will be provided by Dr. Slade.

9.4.3 Reporting of Safety Events to FDA

As the study hasn't raised safety concerns, FDA exercised enforcement discretion to allow the study to proceed without an IND. Therefore, the study is not expected to comply with the IND reporting requirements of safety events to FDA.

9.4.4 Reporting of Pregnancy

Pregnancy status will be determined by participant self-report during eligibility screening and throughout the trial. Should a participant become pregnant during the study, the event will be reported to the NIDCR in oversight reports.

9.5 Halting Rules

There are no *a-priori* stopping rules based on study endpoints. However, interventions for individuals or the study itself will be halted if a safety review by the Medical Monitor or IRB finds sufficient grounds to do so. See also Section 5.6 regarding premature termination or suspension of the study.

10 STUDY OVERSIGHT

In addition to oversight by the Principal Investigator (PI), independent safety oversight will be provided by the NIDCR Medical Monitor. Routine AEs will be summarized in a Medical Monitor Oversight Report submitted to the NIDCR Medical Monitor every 6 months. This report will also summarize study enrollment and retention, unanticipated problems, protocol deviations, biospecimen disposition, outcome measures, quality management findings, and other relevant study metrics. SAEs and UPs will be reported to the NIDCR Medical Monitor and the IRB according to the expedited reporting timelines specified in this protocol and applicable regulatory requirements and will not await the routine Medical Monitor Oversight Report. The NIDCR Medical Monitor may recommend additional actions as needed to ensure participant safety, data integrity, and protocol compliance. The Medical Monitor Oversight Report will also be submitted as an attachment to the annual IRB continuing review.

11 CLINICAL SITE MONITORING

No outside clinical site monitoring will be employed for this study. The Principal Investigator(s) and staff will closely monitor the subjects as they progress through the study. They will monitor and evaluate study processes and documentation based on the International Council for Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP), and internal quality management plans. The NIDCR reserves the right to conduct independent clinical site monitoring as necessary.

12 STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

Primary Objective

Hypothesis: Participants randomized to the active group will demonstrate a statistically significantly greater reduction in mean pain intensity over 8 weeks compared to those in the placebo group. This superiority hypothesis will be tested using a two-tailed test with a significance threshold of $P < 0.05$.

Primary Safety Objective

Hypothesis: The proportion of participants experiencing TEAEs over 8 weeks will differ significantly between the active treatment and placebo groups.

Key Secondary Objectives

Hypothesis (Clinical pain): Participants in the active treatment group will exhibit a statistically significantly greater reduction in pain duration, pain severity, pain interference with life activities, headache impact, and pain in other body regions over 8 weeks compared to those in the placebo group.

Hypothesis (Experimental pain): Participants in the active group will exhibit a statistically significantly greater increase in experimental pressure pain threshold.

over 8 weeks compared to those in the placebo group.

Hypothesis (Psychological and quality-of-life): Participants in the active treatment group will exhibit a statistically significantly greater reduction in psychological distress, as well as a statistically significant improvement in TMD-related quality of life, and greater global impression of change from baseline to 8 weeks compared to the placebo group.

12.2 Sample Size Considerations

The proposed sample of 100 randomized participants (50 per group) provides at least 80% power (after allowing 14% dropout) to detect a hypothesized study group-difference in TMD pain intensity reduction (primary endpoint) of 34% in the active group versus 11% in the placebo group. This corresponds to reductions in mean pain intensity, measured on a 0-100 scale of 16.2 and 5.0, respectively, assuming mean pain intensity of 47.5 at baseline, as observed earlier in our SOPPRANO trial.(42) This study is not powered to address secondary endpoints or exploratory analyses.

In calculating power, we assumed a standard deviation of 18.6 for change in pain intensity (as observed in SOPPRANO), and we specified conventional two-tailed type I error ($P<0.05$). Likewise, 14% loss to follow-up is equivalent to the rate seen in the SOPPRANO study.(42) Calculations were made using the POWER procedure with SAS 9.4 which is applicable to the simplified situation where the study hypothesis is tested using a t-test.

12.3 Planned Interim Analyses (if applicable)

There will be no interim analysis.

12.4 Final Analysis Plan

A Statistical Analysis Plan will expand on details summarized in this document by describing procedures for creating analytic variables and details of statistical analysis.

12.4.1 Analysis of populations

Analysis populations are defined in the Statistical Analysis Plan. In summary:

- The modified intention-to-treat (ITT) sample is defined as all study participants who have at least one valid post- randomization measurement of the primary endpoint (i.e., at least 4 daily reports of pain intensity collected in the 7-day period prior to Visit 2 or Visit 3).

- The per-protocol (PP) population is a subset of the ITT population, excluding any assessments made at or after a visit at which the participant is found to have any major protocol deviation and excluding all assessments for participants whose compliance with study medication is less than 70% over all the study visits.

- The safety sample will include all randomized participants who received at least one dose of study medication.

12.4.2 Creation of analytic datasets

Datasets created from case report forms and from Dr. Ehrmann's lab will be cross-validated. Intention-to-treat and per-protocol study samples will be defined, prior to database lock and unmasking. Missing data will be imputed in specific situations using methods described in the SAP. Data will be imported into SAS v9.4 for statistical analysis of specific aims described below.

12.4.3 Statistical analysis for the primary objective

The primary efficacy endpoint is change in facial pain intensity, evaluated by testing for efficacy at Visit 3 (8 weeks after randomization). Facial pain intensity is rated by participants in DSDs on a 0 to 100 NRS. The primary endpoint is computed as change in average weekly facial pain intensity over 8 weeks of treatment, from the week prior to randomization through the week before Visit 3. Values are based on at least 4 daily reports of pain intensity collected in the 7-day period prior to the visit. If there are fewer than 4 ratings in a 7-day period, the variable will be coded as missing for that visit. Change is defined as the difference between the participant's mean pain intensity at Visit 1 and each subsequent visit. Efficacy is defined as the difference between the marine oil dietary supplement and placebo groups in mean change in facial pain intensity. Post-baseline change in average weekly facial pain intensity is calculated in the 7 days prior to randomization and at each follow-up visit (Visits 2 and 3 - the latter is for the primary endpoint).

The primary analysis will use a modified ITT study sample, defined as randomized participants who have at least one valid measurement of the primary endpoint after randomization (i.e., Visit 2 or Visit 3). A linear mixed model will use the net change in the mean pain intensity as the dependent variable. The model's independent variables will be fixed effects for sex, race-ethnicity, the mean pain intensity at Visit 1 (as a baseline covariate), visit sequence (Visit 2 and Visit 3), treatment allocation (active versus placebo), and a visit by treatment interaction. Participants will be included as a random effect in the mixed model. Efficacy will be evaluated statistically at Visit 3 applying 2-tailed tests with a type I error threshold of $P<0.05$ to evaluate the null hypotheses that study groups have equivalent change in pain.

For descriptive purposes (and regardless of the P-value for efficacy at Visit 3), responder analyses will be performed by dichotomizing the primary endpoint to represent the proportion of participants with clinically significant pain reductions of ≥30% and ≥50% relative to their pain intensity at Visit 1. The binary variable will be used in a generalized linear mixed model to estimate odds ratios for clinically significant pain reduction in the active versus placebo groups. The model will use the same fixed- and random-effect covariates described above for the linear mixed model to estimate proportions and ratios of the proportions between active and placebo groups along with their 95% confidence intervals. The inverse of the ratio estimate will be reported as the number needed to treat (NNT). To avoid misinterpretations that might be drawn from the arbitrary thresholds of ≥30% and ≥50% reductions, the cumulative proportion of responders will be graphed over a range of thresholds from 20% to 70%, and associated NNTs reported.(48)

As secondary efficacy analyses, the primary hypothesis analyses will be repeated on the per-protocol (PP) population. The results of the ITT and PP analyses will be reported separately.

If it appears reasonable to assume that the results of the primary hypothesis are independent of choice of the analysis population (ITT or PP), then all subsequent analyses will be performed on the ITT population only. The analysis will be descriptive, reporting means and 95% confidence intervals. There will be no hypothesis tests of efficacy within demographic subgroups because of the expected small numbers of groups of interest.

12.4.4 Statistical analyses for the secondary objectives

The secondary endpoints are summarized in Section 3.2. They will be analyzed in the ITT population. Secondary endpoints will be analyzed statistically using linear mixed models that follow the approach described for the primary endpoint. Namely, the participant's net change at Visit 2 and Visit 3 will be calculated by subtracting the value of the secondary endpoint at Visit 1 (baseline) from the value at each of the follow-up visits. The linear mixed model will use the computed net change as the dependent variable, and independent variables will be fixed effects for sex, race-ethnicity, the mean value of the secondary endpoint at Visit 1 (as a baseline covariate), visit sequence (Visit 2 and Visit 3), treatment allocation (active versus placebo), and a visit by treatment interaction. Participants will be included as a random effect in the mixed model. Outcomes will be estimated statistically using a SAS "lsmestimate" statement to estimate the mean and 95% confidence interval for between-group differences in the secondary endpoint at Visit 2 and Visit 3. Other "lsmestimate" statements will estimate the mean and 95% confidence interval for the mean value of the secondary endpoint within each group at each follow-up visit.

Patients' Global Impression of Change is the one secondary-efficacy measure that was not measured at Visits 0 or 1, so the test for treatment group differences in that outcome will be evaluated using the Wilcoxon rank sum.

Consistent with the philosophy of Phase 2b trials, (49) secondary endpoints are being investigated in this investigator-initiated study to test scientific concepts, independent of the investigation of the primary endpoint. It is not intended that results from these secondary endpoints would be used as evidence in support of a labeling claim of effects of the marine oil dietary supplement on TMD. For that reason, statistical evaluation of each secondary endpoint will be determined at the threshold of $P<0.05$ using a two-tailed test, with no adjustment for multiple tests. For each hypothesis, the alternative hypothesis is that there is a statistically significant difference between active and placebo groups.

Changes in pressure pain thresholds, anxiety, depression and headache impact will be explored for their potential to mediate effects of the intervention on the primary endpoint (pain intensity). First, univariate linear regression models will test for associations between change (Visit 2 minus Visit 1) in each mediator and the primary endpoint. Then, if Objective 1 demonstrates efficacy, formal tests for mediation will use the counterfactual framework implemented in the SAS "causalmed" procedure to estimate direct and indirect effects of the intervention on the primary endpoint.

12.4.5 Baseline descriptive statistics

Demographic and other baseline characteristics will be summarized descriptively for both the ITT and the PP populations. While no formal statistical testing will be done, all demographic

and baseline characteristics will be assessed for clinically significant differences between the study groups. P-values from these comparisons will be considered descriptive.

All prior and concomitant medications will be coded to preferred drug names and therapeutic drug class using the WHO Drug Dictionary. Use of concomitant medications will be summarized for each therapeutic drug class and each preferred drug name. Concomitant medications will include medications reported on the Concomitant Medications page of the CRF.

12.4.6 Sub-group analyses

Consistent with NIH guidelines requiring reporting of sex as a biological variable (NOT-OD-15-102), sex stratified analysis of the primary endpoint will estimate efficacy for males and females separately. The estimates will be made within a linear mixed model that extends the model for primary analysis by adding a three-way interaction term between sex, treatment allocation, and visit sequence. Efficacy for each sex will be estimated at Visit 3 to generate the point estimate and 95% confidence limits. There will be no test for statistical significance of the interaction terms.

12.4.7 Exploratory analyses

Mixed linear models will be used to compare study groups for biochemical changes in circulating PUFAs and derived oxylipins, hypothesizing that the intervention increases anti-inflammatory, anxiolytic, anti-nociceptive oxylipin derivatives, and decreases levels of n-6 derivatives. Because the panel will be finalized during the first year of the project, we label these analyses to be exploratory. Given that up to 65 PUFAs and oxylipins will be measured, we will guard against type I error by focusing on n-6/n-3 ratio as the primary variable summarizing biochemical changes between visits and evaluate group differences at the threshold of $P<0.05$. We further justify that focus based on results from our preliminary studies where the n-6/n-3 ratio was more consistently associated with pain intensity than any individual constituent of the ratio.(20) However, hierarchical clustering and principal components have proven to be useful for data visualization and data reduction with panels of oxylipins measured with LCMS, (50) and we will therefore explore those methods for analysis of all 65 PUFAs and oxylipins.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source documents for data that will be used for assessing the study's safety and efficacy aims are paper case report forms that have been completed either by study participants, as self-reported questionnaires, or by study staff, from their measurements and recordings. For other data that are being collected to manage participants' progress through the study, the source documents are electronic data records in Access. It is acceptable to use case report forms as source documents. For this study, some clinical examination and questionnaire data may be recorded directly from the participant onto the Teleform case report forms (paper), with the case report form being the source document.

Biospecimen-derived data will not be considered source documents. Oxylipin concentrations will be measured by the mass spectrometry laboratory and transmitted to the study team as electronic spreadsheets. These laboratory output files will be treated as analytical results rather than source documentation.

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. Study staff will permit authorized representatives of NIDCR, including CROMS clinical monitors, and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

14 QUALITY CONTROL AND QUALITY ASSURANCE

Quality control (QC) refers to the ongoing, concurrent review of data collection forms to ensure completeness, internal consistency, and adherence to study procedures. Quality assurance (QA) is a comprehensive, retrospective evaluation of all components of the research records to assess compliance with the protocol, standard operating procedures, and applicable regulations, as well as to verify the accuracy and integrity of the data. Quality management encompasses both QC and QA processes and focuses on assessing and improving the quality of all operational procedures within the study system.

The PI and team are responsible for ensuring all investigational product activities follow FDA regulations (21 CFR Part 312), GCP guidelines, UNC-CH policies, and the IRB-approved protocol. This includes secure, temperature-monitored storage; accurate labeling and accountability; trained staff handling; and complete, audit-ready documentation using approved templates. The ADAPT Study Quality Management Program will include, but is not limited to, the following components:

- Training of study personnel on the protocol, study procedures, and use of all data collection instruments and systems.
- Quality checks of the Consent Document and process, including documentation that the consent process was reviewed
- Quality checks at or after each study visit to ensure complete and accurate data collection
- QC procedures for biospecimens, including logs for processing, transport and analysis
- Programmed checks within the electronic data management system (TARDIS)
- A study start-up checklist documenting all tasks that must be completed and approved by the NIDCR program officer before enrollment of the first participant.
- Preparation for the baseline pre-enrollment audit conducted by the UNC-CH *Clinical Trials Quality Assurance* (CTQA) team to assess procedures, documentation, and storage facilities
- Documentation and tracking of training for each staff member.
- A Clinical Quality Management Plan outlining periodic monitoring visits to ensure participant rights are protected, study activities follow the approved protocol, and data integrity is maintained.
- A Data Management Plan that defines procedures for data entry and completion, data security safeguards, and data quality control and validation procedures.

14.1 Training study personnel on the Clinical Protocol

Prior to performing any study-related activities, personnel must be trained by the PI on the protocol and the Manual of Procedures (MOP). Completion of training will be documented in the Training Log.

The Study Coordinator will complete training and calibration in the DC-TMD protocol, including the TMD examination and pressure pain threshold (PPT) techniques, and will be trained to perform all TMD assessments according to standardized procedures.

14.2 Quality checks of the consent document and process

Quality checks for informed consent will confirm that the consent process is conducted and documented using the UNC-CH Informed Consent Process Checklist template adapted for the ADAPT study. Documentation will verify that participants or legally authorized representatives (LARs) received a copy of the consent form, were given adequate time to review it, and had all questions addressed by the PI or designated study team member before providing written consent. QC procedures will also ensure that no study procedures occurred prior to consent, that signed copies were provided to participants or LARs, and that finalized consent documents were appropriately filed in the participant's medical record. These elements will be reviewed during routine monitoring to confirm compliance with the approved consent process.

14.3 Quality checks at or after each study visit to ensure complete and accurate data collection

The TARDIS data management system incorporates the following quality checks:

- The schedule of person visits for each study participant will be generated by the Data Management System at the time of randomization. The schedule will be exported to an Outlook calendar created for study staff to help ensure that interactions with study participants are completed within the planned timeframe.
- Barcode readers will be used to scan identification codes printed onto labels used with CRFs, specimens and study products. This will reduce human error in reading and writing identification codes.
- Validation edits will be applied to data entered using CRFs. Four levels of edits will be applied, as applicable:
    a) Item-level input edits will utilize pre-coded checklists for most categorical responses, while other numeric responses will be restricted to acceptable ranges. These input edits will be implemented with Teleform.
    b) CRF-level input edits will validate data from two or more items in a single CRF (e.g. to verify skip sequences and assure completeness of data within the CRF). These input edits will be implemented with Teleform.

c) CRF-level output edits will apply algorithms and verify user decisions (for example, to determine the eligibility criterion regarding pain intensity measured using the daily symptoms diary). These edits will be implemented with Access.

d) Casebook-level edits will cross-validate data from two or more CRFs and/or time points for a specific study participant to verify data required for key processes (e.g., randomization, IP dispensing and tracking). These edits will be implemented with Access.

14.4 QC procedures for biospecimens

QC procedures for biospecimens include maintaining detailed logs that document each step of specimen handling, from collection through processing, transport, and analysis. Processing logs capture timelines, handling conditions, and any deviations from protocol. Transport logs record chain-of-custody, temperature control, and shipment details to ensure sample integrity. Analytical logs track laboratory procedures, instrument calibration, and assay performance. Together, these QC measures ensure traceability, consistency, and reliability of all biospecimen data for the ADAPT study.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The PI will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

15.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

15.3 Informed Consent Process

Informed consent is an ongoing process that begins prior to an individual's agreement to participate and continues throughout study participation. Before enrollment, the investigator or a qualified designee will explain the study purpose, procedures, risks, potential benefits, and alternatives, and will answer any questions from the prospective participant and, if applicable, their family or surrogate.

An IRB-approved informed consent document describing the study procedures, risks, and participant rights will be provided. Participants will be required to read and review the document or have it read to them and will be given adequate time to consider participation and to discuss the study with others, if desired.

Written informed consent will be obtained prior to the initiation of any study-specific procedures or assessments. Participants may withdraw consent at any time without penalty or loss of benefits to which they are otherwise entitled. A copy of the signed informed consent document will be provided to participants.

Participants will be informed that refusal to participate or withdrawal from the study will not adversely affect the quality of their current or future medical care. The informed consent process will be documented in the research record.

15.4 Exclusion of Women, Minorities, and Children (Special Populations)

The proposed study will enroll individuals 18 years or more; thus, no children will be recruited. No other special populations will be excluded from the study.

The rationale for excluding individuals younger than 18 years is as follows: chronic TMD is rarely seen in children; many of the questionnaires and measurements to be used, although validated in adults, have not been validated for use in children; pain pressure testing is wisely and safely used in adults, but may be inappropriate

or even unsafe for use in children; and individuals younger than 18 may not possess the level of comprehension required to follow complex instructions and schedules, or to complete questionnaires.

The active agents of the marine oil dietary supplement comprise n-3 marine lipid concentrates of SPMs that regulate multiple pain-related biochemical pathways. Although clinical trials of n-3 supplements have been conducted for children, SPMs have not. Hence, the dosing, pharmacokinetics and safety of the investigational product have not been established for children.

The exclusion of children aged less than 18 years meets the following criteria (NOT-OD-18-116):

- A separate, age-specific study in children is warranted and preferable.
- Prevalence of TMD is less common in children than adults

15.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the NIDCR and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the study sponsor.

The study monitor or other authorized representatives of the NIDCR may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

Research information about the participants will be collected on either paper or electronic forms that will contain a study identification number rather than a name or any other information that could be used to identify the participant. Only the study staff will have access to the list that links the name and identification number. All paper research forms will be kept under lock and key.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical, or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (*https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when

federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

NIH Data Sharing Policies

As described in section 17, it is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). PIs and funding recipient institutions will ensure that all mechanisms used to share data include proper plans and safeguards to protect the rights and privacy of individuals who participate in NIH-sponsored research.

15.6 Future Use of Stored Specimens and Other Identifiable Data

Not applicable. Biological specimens collected for lipidomic analyses will be destroyed after testing is completed and will not be stored for future use.

16 DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making corrections, the original entry will be crossed out with a single line, and the correction will be initialed and dated. No entries will be erased or overwritten. Data reported on case report forms (CRFs) will be consistent with the source documents or the discrepancies will be explained and documented. For this study, CRFs (paper or electronic) may serve as the source document for the collection of some types of data, such as questionnaire data or clinical examination findings.

16.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the PI. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and AEs must be reviewed by the PI or designee.

16.2 Data Capture Methods

Data recorded on paper CRF source documents will be scanned using Teleform to create electronic records in tables of the Access database. Other electronic records will be entered directly into Access tables using e-forms designed for manual data entry. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator.

All data will be managed with TARDIS, a custom-built data management system designed to manage enrollment, randomization, masking, and data collection. The main functions performed by TARDIS are:

- Pre-screening questionnaire will be completed electronically, using Qualtrics software, and the date exported to a table in TARDIS.
- Participants' self-completed questionnaires will be recorded on paper CRFs which will then be scanned and encoded with Teleform software and stored as a read-only electronic CRF in TARDIS.
- Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will likewise be entered into paper CRFs that will be scanned by Teleform and stored electronically in TARDIS.
- The randomization allocation table used to allocate study participants to intervention arms will be created using the PLAN procedure in SAS, exported to a split-section of the TARDIS that is accessible only to the unmasked data manager.
- A Diary Creation module will use Teleform Automerge to print paper CRFs that are pre-filled with dates for recording symptoms, customized according to each participant's schedule of visits.
- A Visit Schedule module will generate dates and windows for all study visits, with the data exported to a Microsoft Outlook group calendar to be used by study staff.

- Electronic copies of paper CRFs will be created by Teleform which will encode and store the data in Microsoft Access tables designed for TARDIS. Teleform will also make a digital image of the paper CRF and store it as a read-only electronic CRF in TARDIS. In this way, each electronic CRF record will also have a corresponding read-only scanned image of the paper CRF. The term “read-only” means that users cannot change the stored data using TARDIS.
- Mass spectrometry measures of blood lipids made at Dr. Ehrmann’s laboratory will be exported from Excel files and uploaded to TARDIS as a read-only table and linked to other tables in the database.

All data tables are linked to create the relational structure of the TARDIS database. This means that data from several tables for a specific subject can be viewed in one screen, while maintaining necessary separation of tables and/or data items such as personal identifiers or pre-screening information obtained prior to signed consent.

16.3 Types of Data

Clinical examination findings, physical measurement, safety data, quantitative sensory testing results, demographic and medical history data, outcome measures obtained from questionnaires, and circulating PUFAs and derived oxylipins data will be collected in this study.

16.4 Schedule and Content of Reports

The data manager will generate study progress reports (i.e., screening, enrollment, and study progress reports) periodically throughout the study period, as determined by the NIDCR program official and the PI. Study enrollment/retention reports will be provided to NIDCR monthly. The data manager will also post data management reports that contain measures of data quality, such as the number of outstanding data queries and data completion rates. Study reports will be provided to the IRB prior to their periodic meetings. No interim statistical analyses are planned.

16.5 Study Records Retention

Study records will be maintained for at least three years from the date that the last grant federal financial report (FFR) is submitted to the NIDCR. No records will be destroyed without the written consent of the NIDCR.

16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or Good Clinical Practice requirements. The noncompliance may be on the part of the participant, the investigator, or study staff. Protocol deviations will be assessed for their impact on safety, study operations, and data integrity. Appropriate corrective and preventive actions will be implemented, if warranted.

These practices are consistent with investigator and sponsor obligations in ICH E6.

All deviations from the protocol must be addressed in study participant source documents, and any deviation from the IRB-approved protocol must be explained. Protocol deviations will be promptly reported to the IRB, according to their requirements. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

17 PUBLICATION/DATA SHARING

This study will comply with all applicable NIH Data Sharing Policies. See *https://grants.nih.gov/policy/sharing.htm* for policies and resources.

NIH Public Access Policy

The NIH *Public Access Policy* requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to *PubMed Central* immediately upon acceptance for publication. This ensures that the public has access to the published results of NIH funded research.

NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

The study is a clinical trial and will comply with the NIH policy that establishes the expectation that all investigators conducting clinical trials funded in whole or in part by the NIH will ensure that these trials are registered at ClinicalTrials.gov, and that results of these trials are submitted to ClinicalTrials.gov.

Food and Drug Administration Amendments Act of 2007 (FDAAA) and the Final Rule for Clinical Trials Registration and Results Information Submission

This study is an applicable clinical trial and will comply with *U.S. Public Law 110-85* (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 and *42 CFR Part 11* (HHS Final Rule for Clinical Trials Registration and Results Information Submission), which mandate that a "responsible party" (i.e., the sponsor or designated investigator) register and report results of "applicable clinical trials."

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APPENDICES

Appendix A Cover Page: Schedule of Events

Protocol title: Safety and analgesic efficacy of marine lipid precursors of specialized pro-resolving mediators in adults with chronic temporomandibular pain

NIDCR Protocol Number: 25-016-E

NIDCR Grant Number: 1UG3DE033354

Brief description: The Schedule of Events outlines all study activities from pre-screening through post-study follow-up, including eligibility assessments, randomization, clinical examinations, blood draws, administration and monitoring of the investigational product, collection of daily symptom diaries, and administration of outcome questionnaires at specified visits.

APPENDIX A: SCHEDULE OF EVENTS

Study Phase[a]	**Pre-screen** [(b)]	**Screening & baseline**	**Random-ization** [(c)]	**Mid-study**	**Follow-up**	**Safety Follow-up** [(d)]
Clinic Visit		**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	
Study Day	**≤21 days prior to V0**	**7-28 days prior to V1**	**0**	**28 (±7)**	**56 (±7)**	**63 (±7)**
Procedure						
Pre-screening interview	X					
Informed consent		X				
Demographic information		X				
Contact information		X				
Medical history		X	X	X	X	
Concomitant medications and therapy		X	X	X	X	
Eligibility review		X	X			
AE review			X	X	X	X
Dispense daily symptom diaries (DSD)		X	X	X		
Scan and review completed DSD pages			X[(e)]	X	X	
Randomization			X			
Dispense investigational product (IP)			X[(f)]	X		
Assess compliance with IP				X	X	
Clinical Examinations and Tests						
Physical measurements		X				
TMD examination		X			X	
Pressure pain tests (algometer)		X		X	X	
Blood draw			X		X	
Outcome Measure Questionnaires						
State-Trait Anxiety Inventory (State only)			X	X	X	
SCL-90 Depression Subscale			X	X	X	
Headache Impact Test-6			X	X	X	
Graded Chronic Pain Scale			X		X	
Oral Health Impact Profile for TMDs			X		X	
Body Manikin pain			X		X	
ID Migraine			X			
Patient Global Impression of Change				X	X	

(a) If early termination is required, an ET CRF will be completed in addition to any of the activities tabulated for the visit at which ET occurs
(b) Conducted by phone or at the Screening and Baseline Visit (Visit 0). The pre-screening interview is limited to basic eligibility criteria.
(c) The timing of subsequent Visits and their windows is established from the date of Randomization (Visit 1).
(d) The post-study safety follow-up is conducted by phone.
(e) If DSD criterion for randomization is not met, up to 2 additional visits can be scheduled within the window.
(f) The first dose of study drug will be administered at the evening of Day 0