RESEARCH PROTOCOL

Study Number:

Title:	A Randomized, Double Blind, Placebo-Controlled Single Center Phase 2 Pilot Study to Assess the Safety and Efficacy of Off-label Subcutaneous Administration of Erenumab-aooe in Patients with Temporomandibular Disorder
Sponsor:	Indiana University*
Investigation Site:	Oral Health Research Institute Indiana University School of Dentistry
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List of Abbreviations

AE	Adverse Event
BPI	Brief Pain Inventory
CFR	Code of Federal Regulations
CGRP	Calcitonin Gene Related Peptide
CM	Chronic Migraine
COPCs	Chronic Overlapping Pain Conditions COPCs
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
DC/TMD	Diagnostic Criteria/Temporomandibular Disorder
EREN	Erenumab-aooe
EREN-P	Placebo
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IRB	Institutional Review Board
IUPUI	Indiana University Purdue University Indianapolis
IUSD	Indiana University School of Dentistry
JFLS	Jaw Function Limitation Scale
NIH/NIDCR	National Institutes of Health/National Institutes of Dental and Craniofacial Research
PEG	Pain, Enjoyment, General Activity Scale
PGIC	Patient Global Impression of Change
PHQ-4	Patient Health Questionnaire
PI	Principal Investigator
SAE	Serious Adverse Event
s.c.	Subcutaneous
SOP	Standard Operating Procedure
SSS-8	Somatic Symptom Scale
TGV	Trigeminovascular Pathway
TMD	Temporomandibular Disorder
UmMa(s)	Human Monoclonal Antibody(s)

1. Background & Rationale

Aimovig® [erenumab (EREN)] is a first in class FDA-approved human monoclonal antibody (UmAb) for the prevention of migraine in adults. It selectively targets and blocks the calcitonin gene-related peptide (CGRP) receptor, disrupting a key component of migraine pathophysiology (Hargreaves & Olesen, 2019). Several studies have provided evidence of the safety and efficacy of Aimovig® in reducing the frequency of migraine compared to placebo (Goadsby et al., 2017; Tepper et al., 2017). Furthermore, an open-label longer-term study found that Aimovig® was safe and well-tolerated with a safety profile consistent with shorter-term placebo-controlled studies (Ashina et al., 2020), through 5-years of treatment. Aimovig® has rapidly become a widely accepted prescription drug for the prevention of migraines, including episodic migraine and chronic migraine (CM) along with other anti-CGRP monoclonal antibody-based therapies (Yuan et al., 2019).

Temporomandibular Disorders (TMD) are known to be co-morbid with the medical diagnosis of CM (Speciali, 2015). TMD symptoms are numerous and chronic in nature (see appendix A) and TMD treatments are more numerous than symptoms and are predictable only in their unpredictability (see Appendix B). Most patients experiencing TMD find it to be a chronic, untreatable condition. In the US alone, TMDs are the second most commonly occurring musculoskeletal conditions resulting in pain and disability (after chronic low back pain), affecting approximately 5 to 12% of the population, with an annual cost estimated at $4 billion (NIH/NIDCR). There is increasing interest in the concept of Chronic Overlapping Pain Conditions (COPCs), which include TMD, fibromyalgia, irritable bowel syndrome, vulvodynia, myalgic encephalomyelitis/chronic fatigue syndrome, interstitial cystitis/painful bladder syndrome, endometriosis, chronic tension-type headache, migraine headache, and chronic lower back pain that may have common biopsychosocial factors (Maixner et al., 2016).

Co-Principal Investigator, Dr. Harold C. Avila, has treated several patients that presented with chronic TMD pain and a history of migraines headaches, which have responded positively to off-label administration of Aimovig®. Anecdotally, five of Dr. Avila's TMD patients were treated with Aimovig® along with his standard therapy. Of these, three patients experienced substantial life-changing relief of TMD pain symptoms. Another patient initially experienced substantial pain relief, which declined slightly over two months. The last patient stopped taking Aimovig® due to elevated blood pressure, which is not an adverse event associated with Aimovig® in the published clinical trials (Goadsby et al., 2017; Tepper et al., 2017); however, the development of hypertension and worsening of pre-existing hypertension have been reported following the use of AIMOVIG in the postmarketing setting (FDA-approved Patient Labeling).

CM is thought to originate within the trigeminovascular pathway (TGV) (Noseda & Burstein, 2013). TMD is also considered to originate within the TGV (de Leeuw, 2018). Thus, our working hypothesis is that a CGRP receptor antagonist for treatment of CM will also be effective in reducing TMD pain and related symptoms. To test this hypothesis, we applied several validated measures: Brief Pain Inventory (BPI) (Kean et al., 2016); PEG (Pain, Enjoyment, General Activity) Scale (Krebs et al., 2009); an assessment of daily pain medication; Patient Global Impression of Change (PGIC) (Kroenke et al., 2018); Jaw Function Limitation Scale (JFLS) (Ohrbach et al., 2008); Patient Health Questionnaire (PHQ-4) (Kroenke et al., 2009); and Somatic Symptom Scale (SSS-8) (Toussaint et al., 2017).

The purpose of this proof of concept study was to evaluate the safety and efficacy of the off-label use of Aimovig® (EREN) in reducing Temporomandibular Disorder (TMD) pain compared to placebo.

2. Study Objectives and Outcome Measures

2.1 Primary Objective and Outcome Measure

To assess the effects of Aimovig® (EREN) compared to placebo (EREN-P) based on the change in mean between-group difference in pain using the Brief Pain Inventory (BPI) 4-item pain severity/intensity scale during the 20-week trial. The BPI is a validated and widely used outcome measures in chronic pain trials (Kean et al., 2016; Kroenke et al., 2019). *We postulated that Aimovig® will be superior to placebo in reducing pain intensity/severity over 20 weeks*.

2.2 Secondary Objective and Outcome Measures

To assess the effects of Aimovig® (EREN) compared to placebo (EREN-P) based on the change in mean between-group difference in secondary outcomes during the 20-week trial and after 24 weeks (two months after the last treatment). The outcome measures are based on consensus recommendations for research assessments in chronic pain and TMD research (Ohrbach et al., 2016; Kroenke et al., 2019). *We postulated that Aimovig® will be superior to placebo in improving several secondary outcomes including:*

a) Pain interference as measured by the BPI interference scale

b) Trajectory of pain improvement based on changes in daily reporting of pain using the PEG (Pain, Enjoyment, General Activity) Scale as measured using an app downloaded on the subject's smartphone or for individuals without smartphones at baseline and every 4 weeks over the 24-week study period

c) Days of use of TMD pain-specific medication per month

d) Global improvement in pain as measured by the Patient Global Impression of Change (PGIC)

e) Jaw function as measured by the Jaw Function Limitation Scale (JFLS-8)

f) Depressive and anxiety symptoms as measured by the Patient Health Questionnaire (PHQ-4)

g) Somatic symptom severity as measured by the Somatic Symptoms Scale (SSS-8)

h) Safety and tolerance as measured by incidence of AEs and SAEs

3. Study Design

This was a 24-week, randomized, double-blinded, placebo-controlled, parallel group proof-of-concept study with two arms (active and placebo). The plan was to enroll 30 subjects. There was a four-week screening period to identify subjects that meet the diagnostic criteria (DC/TMD) for "myalgia", recommended by the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group (Schiffman et al., 2014). The Diagnostic Criteria for Temporomandibular Disorders Symptom Questionnaire and DC/TMD Examination Form (Ohrbach, 2016) was used during Screening and Baseline visits to confirm the TMD diagnosis and determine whether subjects met the inclusion/exclusion criteria.

Subjects attended a Screening visit followed by Baseline visit to randomize eligible subjects to active (EREN) or placebo (EREN-P). During the Baseline visit and Wks 4, 8, 12, and 16, subjects received treatment with either 140 mg of EREN or Placebo administered by subcutaneous injection. At Baseline and Wks 4, 8, 12, 16, 20, and 24 subjects were instructed to complete the Brief Pain Inventory (BPI) (Kean et al., 2016); PEG (Pain, Enjoyment, General Activity) Scale (Krebs et al., 2009); pain mediation assessment; Patient Global Impression of Change (PGIC)

(Kroenke et al., 2018) (except for Baseline visit); Jaw Function Limitation Scale (JFLS) (Ohrbach et al., 2008); Patient Health Questionnaire (PHQ-4) (Kroenke et al., 2009); and Somatic Symptom Scale (SSS-8) (Toussaint et al., 2017). These visits also included review of continuance criteria and adverse event collection.

At the Screening and Baseline visits the subjects were instructed on how to use the PEG Scale and pain use assessment app, which was downloaded on their smartphone, to provide a daily assessment of their pain intensity and interference with enjoyment and general activity (PEG) and their daily used of pain medications. Subjects who did not own a smartphone or were unwilling to use the app on a daily basis only completed the PEG and pain medication assessment at the Baseline visit and all subsequent visits using the app onsite.

4. Study Population

The study population consisted of male and female subjects diagnosed as having pain-related TMD using the diagnostic criteria (DC/TMD) for "myalgia", recommended by the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group (Schiffman et al., 2014). The goal was to recruit 30 subjects that fulfill the inclusion and exclusion criteria. It was anticipated that 24 subjects (12 in each treatment group) will complete all aspects of the study.

4.1 Inclusion Criteria

Subjects eligible for inclusion in the study must have met all of the following criteria:

1. Signed the informed consent;
2. Have a history of head, face, neck and/or shoulder pain for longer than 3 months;
3. Have a diagnosis of myalgia based on clinical examination using DC/TMD criteria;
4. Age 18 years and younger than 60 years;
5. Have a good knowledge of the English language;
6. Able to understand and comply with the study requirements; and
7. If taking prescription pain medications, the dose regimen must be stable for at least 2 months prior to the screening visit.

4.2 Exclusion Criteria

Subjects that met any of the following criteria were not eligible for inclusion:

1. Lacking stable bilateral posterior occlusion;
2. Currently uses a complete maxillary or mandibular prosthetic denture;
3. Currently pregnant or plan to become pregnant;
4. Breastfeeding or plan to breastfeed;
5. Allergic to erenumab-aooe or any of the ingredients in Aimovig® (acetate, polysorbate 80, and sucrose);
6. Allergic to rubber or latex;
7. Currently undergoing TMD treatment elsewhere. Exception: patients undergoing TMD treatment involving the use of oral orthotics for a minimum of 3 months prior to Screening can be considered eligible for the study;

8. Started orthodontic treatment during the 3 months prior to Screening;
9. Currently included in other experimental protocols within the last 30 days or 5 half-lives before enrollment;
10. Having 8 or more migraine days during the past 4 weeks;
11. Started receiving massage, acupuncture or physical therapy treatment of the head, neck or shoulders during the previous 3 months prior to Screening;
12. History of unstable or acute severe non-head, neck or shoulder pain;
13. History of traumatic brain injury;
14. History of surgical treatment or recommended surgical treatment for TMD;
15. History of ongoing, unresolved disability litigation;
16. History of drug abuse;
17. Started treatment for moderate to severe sleep apnea requiring CPAP or oral mandibular repositioning appliance during the previous 3 months prior to Screening;
18. Anything that would place the subjects at increased risk or preclude the individual's full compliance with or completion of the study (e.g., medical condition, laboratory finding, physical exam finding logistical complication);
19. History of previously receiving erenumab-aooe or other anti-CGRP pathway therapies, including anti-CGRP and anti-CGRP receptor monoclonal antibodies and small molecule CGRP receptor antagonists (gepants);
20. History of chronic constipation and/or using medication associated with decreased gastrointestinal motility; and
21. History of uncontrolled hypertension or risk factors for hypertension.

4.3 Enrollment Procedures

Subjects were recruited using fliers and advertisements placed in the Indiana University (IU) School of Dentistry (IUSD) and other locations on the Indiana University Purdue University Indianapolis (IUPUI) campus including IU Health facilities. Fliers may also be posted on Facebook.

Dr. Avila may send approved study information to persons who may have TMD and he may also mention the study during planned radio interviews about TMD. Dr. Avila's website will not mention research.

Persons responding to an advertisement will be given a brief description of the study and asked a series of questions related to the inclusion/exclusion criteria using an IRB approved phone script. Those who are interested and appear to meet the study requirements will be scheduled for a screening visit at the Oral Health Research Institute (OHRI).

Additionally, contact information was obtained from Regenstrief for IU Health patients who have indicated they have TMJ problems and are willing to be contacted for future studies. Once contact information was obtained, the OH study coordinator contacted the potential subjects by telephone to see if they were interested in attending a screening visit.

5. Treatments

5.1 Study Treatments

Investigational drug: erenumab-aooe (EREN) 140 mg, for s.c. injections, provided by Amgen

Placebo: liquid placebo (EREN-P), for s.c. injections provided by Amgen

Amgen provided the active and placebo free of charge through the Investigator Sponsored Studies (ISS) Program (CAMG334AUS01T).

5.2 Treatment Arms

Subjects were assigned at baseline to one of the two treatment arms:

- Arm A: erenumab-aooe (EREN) 140 mg s.c. administered every four weeks for a total of five treatments
- Arm B: placebo (EREN-P) s.c. administered every four weeks for a total of five treatments

5.3 Treatment assignment and randomization

Subjects were randomized and stratified based on gender into two groups using block randomization based on a schedule provided by the study statistician, George Eckert, Indiana University School of Medicine Department of Biostatistics.

The randomization code was provided to Amgen as part of the ISS contract agreement.

5.4 Treatment blinding

Subjects, investigators and study staff will remain blind to the identity of the treatment from the time of randomization until database lock. The randomization code will be kept strictly confidential and the identity of the study drug treatments will be concealed using identical packaging and labeling. The blind will only be broken in an emergency where it is essential to know which treatment a subject received in order to give the appropriate medical care.

5.5 Dispensing of study drug

The investigational products (EREN and EREN-P) supplied in prefilled syringes will be shipped by Amgen to the attention of the unblinded IU Health Investigational Drug Services Pharmacy. The IU Health Pharmacy will dispense the investigational products according to a randomization schedule provided by the study statistician, George Eckert. A written prescription order form will be completed by the licensed study dentist and submitted to the pharmacy each time study drug is requested for a subject. Doses will be administered in the upper arm, thigh, or abdomen by a study dentist qualified in s.c. drug administration.

Study product will be stored and handled according to labeling instructions: store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use; do not freeze; and do not shake; leave the prefilled syringe at room temperature for at least 30 minutes before injecting. The investigational products will be stored in a secured area of the IU Health Investigation Drug Services Pharmacy to which only the pharmacy staff have access.

The IU Health pharmacy will maintain adequate records documenting the receipt, use, loss, or other disposition of the products on the electronic Investigational Agent Accountability Record. The log will identify the products and account for the disposition including specific dates and

quantities used/dispensed and returned, as applicable. The log will capture the electronic signatures of the site designees who dispensed and verified the products.

The clinical site, OHRI, working with the pharmacy will also maintain a Drug Administration Form documenting the date and time of transport to the blinded site staff, the date and signature of the blinded site staff receiving the study drug, the date and time the study drug was received from the pharmacy, the date and time the study drug was administered, and the injection site body location.

6. Visit Schedule and Assessments

Study Schedule

Period	**Screening**	**Treatment Period**						**Post-Treatment**
Visit Name	**Screening**	**Baseline**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**
Days	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**
Weeks	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**
Informed consent	X							
Randomization		X						
Study drug administration		X	X	X	X	X		
Inclusion / Exclusion criteria	X							
Demography	X							
Medical history/current medical conditions	X							
Prior therapy for TMD	X							
Adverse Events	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Familiarize with PEG App	X	X						
BPI, PEG and pain medication assessment (daily), JFLS-8, PHQ-4, SSS-8		X	X	X	X	X	X	X
PGIC			X	X	X	X	X	X

Screening Visit: Subjects will complete the informed consent process, being given ample time to review the consent and to ask any questions they have before deciding if they wish to participate. Those interested will sign and date their informed consent and the consent will also

be signed and dated by the person reviewing the consent process with them. Subjects will receive a signed copy of their consent before leaving this visit. A Study Dentist qualified to diagnosis TMD will review the potential subject's health history, medications and TMD history for the inclusion and exclusion criteria.

The Diagnostic Criteria for Temporomandibular Disorders Symptom Questionnaire (Appendix C) and DC/TMD Examination Form (Ohrbach, 2016) will be used to confirm the TMD diagnosis and determine whether subjects meet the inclusion/exclusion criteria. To meet the diagnostic criteria for TMD Myalgia (IDC-9 729; ICD-10 M79.1) (Schiffman et al., 2014), subjects must have a history of pain of muscle origin that is affected by jaw movement, function, or parafunction, and demonstrate replication of this pain with provocation testing of the masticatory muscles. The specific criteria (Schiffman et al., 2014) include having a positive history for both pain in the jaw, temple, in the ear, or in front of ear and pain modified with jaw movement, function or parafunction. During clinical examination, subjects must have a confirmation of pain in the temporalis or masseter muscle(s) and report familiar pain in the temporalis or masseter muscle(s) with at least one of the following provocation tests: palpation of the temporalis or masseter muscle(s) or maximum unassisted or assisted opening movement(s).

Subjects with smartphones will be asked to download the MyCap app and will then be trained on completing the PEG Scale and the pain medication assessment questions using their smartphone. The subject will be scheduled to return to the study site for their Baseline visit.

Baseline, Wk 4, 8, 12, and 16 Visits: The subject's medical history, medications and continuance criteria will be reviewed to assure the subject still qualifies to participate in the study. The Diagnostic Criteria for Temporomandibular Disorders Symptom Questionnaire (Appendix C) and DC/TMD Examination Form will be used to confirm the TMD diagnosis and determine whether subjects meet the inclusion/exclusion criteria. In addition, the subjects will be assessed using the Brief Pain Inventory (BPI) (Appendix D), PEG (Pain, Enjoyment, General Activity) Scale and pain medication assessment (Appendix E), Jaw Function Limitation Scale (JFLS) (Appendix G), Patient Health Questionnaire (PHQ-4) (Appendix H), and Somatic Symptom Scale (SSS-8) (Appendix I). Starting at week 4 the subjects will also be assessed using global improvement in pain as measured by the Patient Global Impression of Change (PGIC) (Appendix F).

The subject will receive their assigned treatment (EREN or EREN-P) based on the randomization scheme at baseline and Wk 4, 8, 12, and 16.

The procedure for texting each day will be reviewed with the subject and a practice text will be sent to assure communication is accurate. Subjects without smartphones will only be required complete the PEG Scale and pain medication assessment questions using the app onsite at Baseline and at all subsequent study visits.

Adverse events will be assessed and documented, and the subjects will be schedule for their next visit.

Wk 20 End of Treatment Period Visit: Subjects will be assessed using the BPI, PEG and pain medication assessment (app), PGIC, JFLS, PHQ-4, and SSS-8. Adverse events will be assessed and documented, and the subjects will be schedule for their next visit.

Wk 24 Post-Treatment Follow-up Visit: Subjects will return for follow-up examination and assessed using the BPI, PEG and pain medication assessment (app), PGIC, JFLS, PHQ-4, and SSS-8. Adverse events will be assessed and documented.

7. Safety Monitoring

This study will be conducted in compliance with the US Code of Federal Regulations (CRF) governing informed consent (21 CFR 50), Institutional Review Board (IRB) (21 CFR 56), and with applicable regulations governing Investigator conduct (21 CFR 312).

This study will be performed according to GCPs. SOPs for all procedures are on file with the Quality Assurance staff of the Oral Health Research Institute.

All study staff who have direct subject contact will be required to review the WARNINGS AND PRECAUTIONS for Hypersensitivity Reactions, Constipation with Serious Complications and Hypertension found in Section 5 of the US Prescribing Information (USPI) for Aimovig®. https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/aimovig/aimovig_pi_hcp_english.ashx

7.1 Adverse Events

Subjects will be questioned regarding any general health or oral complaints and symptoms they have experienced during each visit. Any findings will be documented on the AE CRF. In the event of subjects reporting AEs outside the scheduled clinical visit, the Investigator will assess them at the earliest opportunity.

All AEs, regardless of severity or relationship to the treatments, will be recorded. Serious AEs include any events resulting in death, decreased life expectancy, life-threatening situations, persistent or permanent disability/incapacity, hospitalization, or congenital anomaly/birth defect. In addition, other important medical events that are deemed clinically important/serious based on PI judgement will be recorded as AEs. Within 24 hours, the Investigator will submit a written report to Amgen documenting the circumstances of the serious AE.

7.2 Serious Adverse Events

Safety monitoring for this study will focus on adverse events related to treatment use and unanticipated problems involving risks to participants, including unanticipated problems that meet the definition of a serious adverse event. At each visit, subjects will be queried about any adverse events that may have occurred since their last visit, regardless of direct relationship to treatment use. Adverse events will be recorded on an Adverse Event form. Abnormalities, or worsening of pre-existing conditions, observed by the examiner or reported by the subject that occur at any visit will be recorded on the AE CRF. All AEs will be transcribed onto a log, which will be monitored by the PI to determine if the nature, frequency, or severity of an event meets the criteria for prompt reporting. All adverse events will be reported to the IRB during annual review.

The PI will be notified immediately if a serious adverse event occurs. All serious adverse events that meet the prompt reporting requirements will be reported to the IRB within 5 business days. Serious adverse events include: any event resulting in death, is life-threatening, requires hospitalization, results in disability/permanent damage, congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage, and/or other medical events.

The study site will be responsible for reporting SAEs to Amgen in accordance with the Amgen ISS Program contract requirements.

The study site will be responsible for reporting all safety information to Amgen in accordance with their reporting requirements (Table 1).

7.3 Study Withdrawal/Discontinuation

Subjects may withdrawal or discontinue from the clinical trial at any time without penalty or loss. Subjects will be advised at the start of the trial that they may withdraw from the trial at any time, without giving a reason. Subjects may be withdrawn by the Principal Investigator for the following reasons:

- the volunteer wishes to withdraw;
- if, in the opinion of the Investigator, it is in the best interests of the subject;
- if serious adverse reactions occur;
- inter-current illness occurs;
- there is a significant violation of the prohibitions and restrictions;
- development of an exclusion criterion.

Withdrawals due to non-attendance must be followed up to attempt to obtain the reason that the subject is 'lost to follow up'. Subjects who are lost to follow up will be encouraged to return to the site for an exit visit. Subjects withdrawn for medical reasons will be referred to a physician /dentist. Their condition will be monitored until it is resolved or clinically non-significant. All withdrawals and the reason for withdrawal will be documented. Withdrawn subjects will not be replaced.

8. Data Analysis

Mixed model repeated measures (MMRM) analysis will be used to evaluate changes over time in the BPI pain severity/intensity scale and BPI total score, PEG Scale total score and daily pain, days of use of pain medication and TMD pain-specific medication per month, JFLS-8, PHQ-4 anxiety and depression, SSS-8 Scale, and PGIC pain change within and between treatment groups. The MMRM will include factors for treatment group, time, and their interaction. Time will be repeated within subject. The MMRM will also include gender as a covariate due to stratification by gender in the randomization. The distribution of the outcomes will be examined and a transformation of the data will be used if necessary. A two-sided 5% significance level will be used for all tests without multiplicity adjustment between multiple endpoints.

8.1 Sample size calculations

A sample size of 12 subjects per group has been suggested for pilot studies to evaluate feasibility and to estimate group means and standard deviations for future study planning (Julious, 2005). Based on two-sided paired t-tests and two-sample t-tests, all conducted at a 5% significance level, this pilot study will have 80% power to detect effect sizes of 0.9 for changes over time within groups and effect sizes of 1.2 for differences between groups. To account for dropout, the study will enroll 15 subjects per group, 30 total subjects.

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10. Appendices

Appendix A – TMD Symptoms

Symptoms of TMD:
Jaw pain
Headache
Earache
Joint noise
Limited range of motion
Neck pain
Toothache
Shoulder pain
Dizziness
Changing bite
Ringing in the ear
Nausea
TemporoMandibular Joint pain
Locked shut
Locked open
Light sensitivity
Sound sensitivity
Hyper-sensitive facial skin
Hyper-sensitive oral mucosa
Sinus pain
Arm pain
Chest pain

(TMD symptoms mask, mimic and distort other diagnoses.)

Appendix B – TMD Treatments

Multiple types of Orthotic appliances
Hard acrylic
Soft vinyl
Accentuated posterior stop
Accentuated anterior stop
Boil and Bite

Multiple types of Occlusal rehabilitation
Full mouth reconstruction
Occlusal adjustment(s)
Orthodontics

Multiple types of medicinal regimen
Muscle relaxants
Over-the-counter NSAIDS
Amitriptyline
Sumatriptan

Multiple types of injections
TM joint injections – intracapsular diagnostic/therapeutic injections
Injections of anesthetic agents into the trigeminal nerve
Trigger point injections
Botulinum toxin (type A or Type B) injections

Multiple types of surgical treatments
Alloplastic joint implants
Arthrocentesis
Arthroscopic surgery
Arthrotomy or arthroplasty
Condylectomy (partial or complete)
Disc repair procedures
Diskectomy without or with replacement
Eminectomy or eminoplasty (articular surface recontouring)
Mandibular condylotomy
Nerve obliteration
Orthognathic surgery – for correction of jaw deformities could also be done as an adjunct to definitive joint treatment when related to deformities resulting in TMJ dysfunction.
Partial or total joint reconstruction
Removal of failed implants

Multiple types of Behavior Modification
ABA
Cognitive behavior therapy
Educational behavior therapy
Positive Mental Attitude

Other Miscellaneous Treatments
Acupuncture

Acupressure
Allergy Treatments
Biofeedback
Chiropractic treatments
Continuous Passive Motion (CPM) therapy
Dry needling
Low level laser
Massage Therapies
Nutrition
Physical Therapy Treatments
Pulsed radiofrequency energy – Energex
Tru-Denta combination of therapies
Ultrasonic therapy with(out) medicines

Alternative Therapies
Crystals
Magnets
Power bands
Pressure point bands
Tragus piercing

(Multiple non-predictable treatments suggest no predictable treatment for TMD has been found.)

Appendix C – Diagnostic Criteria for Temporomandibular Disorders Symptom Questionnaire

Patient name _____ Date _____

PAIN

1. Have you ever had pain in your jaw, temple, in the ear, or in front of the ear on either side? — No ☐ Yes ☐

If you answered NO, then skip to Question 5.

2. How many years or months ago did your pain in the jaw, temple, in the ear, or in front of the ear first begin? _____years _____months

3. In the last 30 days, which of the following best describes any pain in your jaw, temple, in the ear, or in front of the ear on either side?

Select ONE response.

- ☐ No pain
- ☐ Pain comes and goes
- ☐ Pain is always present

If you answered NO to Question 3, then skip to Question 5.

4. In the last 30 days, did the following activities change any pain (that is, make it better or make it worse) in your jaw, temple, in the ear, or in front of the ear on either side?

		No	Yes
A.	Chewing hard or tough food	☐	☐
B.	Opening your mouth, or moving your jaw forward or to the side	☐	☐
C.	Jaw habits such as holding teeth together, clenching/grinding teeth, or chewing gum	☐	☐
D.	Other jaw activities such as talking, kissing, or yawning	☐	☐

HEADACHE

5. In the last 30 days, have you had any headaches that included the temple areas of your head? — No ☐ Yes ☐

If you answered NO to Question 5, then skip to Question 8.

6. How many years or months ago did your temple headache first begin? _____years _____months

7. In the last 30 days, did the following activities change any headache (that is, make it better or make it worse) in your temple area on either side?

		No	Yes
A.	Chewing hard or tough food	☐	☐
B.	Opening your mouth, or moving your jaw forward or to the side	☐	☐
C.	Jaw habits such as holding teeth together, clenching/grinding, or chewing gum	☐	☐
D.	Other jaw activities such as talking, kissing, or yawning	☐	☐

JAW JOINT NOISES

		No	Yes	Office use R	L	DNK
8.	In the last 30 days, have you had any jaw joint noise(s) when you moved or used your jaw?	☐	☐	☐	☐	☐

CLOSED LOCKING OF THE JAW

9.	Have you ever had your jaw lock or catch, even for a moment, so that it would not open ALL THE WAY? **If you answered NO to Question 9 then skip to Question 13.**	☐	☐	☐	☐	☐
10.	Was your jaw lock or catch severe enough to limit your jaw opening and interfere with your ability to eat?	☐	☐	☐	☐	☐
11.	In the last 30 days, did your jaw lock so you could not open ALL THE WAY, even for a moment, and then unlock so you could open ALL THE WAY? **If you answered NO to Question 11 then skip to Question 13.**	☐	☐	☐	☐	☐
12.	Is your jaw currently locked or limited so that your jaw will not open ALL THE WAY?	☐	☐	☐	☐	☐

OPEN LOCKING OF THE JAW

13.	In the last 30 days, when you opened your mouth wide, did your jaw lock or catch even for a moment such that you could not close it from this wide open position? **If you answered NO to Question 13 then you are finished.**	☐	☐	☐	☐	☐
14.	In the last 30 days, when you jaw locked or caught wide open, did you have to do something to get it to close including resting, moving, pushing, or maneuvering it?	☐	☐	☐	☐	☐

Appendix D – Brief Pain Inventory (BPI)

BRIEF PAIN INVENTORY (BPI)

For the following questions, please answer for your facial, jaw or TMD pain:

1. Please rate your pain by circling the one number that best describes your pain at its **worst** in the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

2. Please rate your pain by circling the one number that best describes your pain at its **least** in the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

3. Please rate your pain by circling the one number that best describes your pain on the **average**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that tells how much pain you have **right now**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Circle the number that describes how, during the past week, pain has interfered with your:

5. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

6. Mood

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

7. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

8. Normal Work (includes both work outside the and housework)

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

9. Relations with other People

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

10. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

11. Enjoyment of Life

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

Appendix E – PEG (Pain, Enjoyment, General Activity) Scale and Pain Medication Assessment

PEG Pain

For the following questions, please answer for your facial, jaw or TMD pain:

1. What number best describes your pain on the <u>average</u> in the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

2. What number best describes how, in the last 24 hours, pain has interfered with your <u>general activity</u>

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

3. What number best describes how, in the last 24 hours, pain has interfered with your <u>enjoyment of life</u>

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

Pain Medication Assessment Questions

A. Did you take any medicines for pain today?
- Yes
- No

B. If YES, were any of these medicines you took today for facial, jaw or TMD pain?
- Yes
- No

Appendix F – Patient Global Impression of Change (PGIC)

Patient Global Impression of Change (PGIC)

Since the start of the study (treatment), my overall facial, jaw or TMD pain is ….

1. Much better
2. Moderately better
3. A little better
4. No change
5. A little worse
6. Moderately worse
7. Much worse

Appendix G – Jaw Function Limitation Scale (JFLS-8)

Jaw Functional Limitation Scale - 8

For each of the items below, please indicate the level of limitation **during the last month.** If the activity has been completely avoided because it is too difficult, then circle '10'. If you avoid an activity for reasons other than pain or difficulty, leave the item blank.

	No Limitation										**Severe Limitation**
1. Chew tough food	0	1	2	3	4	5	6	7	8	9	10
2. Chew chicken (e.g., prepared in oven)	0	1	2	3	4	5	6	7	8	9	10
3. Eat soft food requiring no chewing (e.g., mashed potatoes, apple sauce, pudding, pureed food)	0	1	2	3	4	5	6	7	8	9	10
4. Open wide enough to drink from a cup	0	1	2	3	4	5	6	7	8	9	10
5. Swallow	0	1	2	3	4	5	6	7	8	9	10
6. Yawn	0	1	2	3	4	5	6	7	8	9	10
7. Talk	0	1	2	3	4	5	6	7	8	9	10
8. Smile	0	1	2	3	4	5	6	7	8	9	10

Appendix H – Depressive and anxiety symptoms (PHQ-4)

PHQ-4: Depression (PHQ-2) and Anxiety (GAD-2)

Over the <u>last 2 weeks</u>, how often have you been bothered by any of the following problems? *Use a check (✓) to indicate your answer for each item*	**Not at all** **(0)**	**Several days** **(1)**	**More than half the days** **(2)**	**Nearly every day** **(3)**
1. Feeling nervous anxiety or on edge	☐	☐	☐	☐
2. Not being able to stop or control worrying	☐	☐	☐	☐
3. Little interest or pleasure in doing things	☐	☐	☐	☐
4. Feeling down, depressed, or hopeless	☐	☐	☐	☐

Appendix I – Somatic symptom severity as measured by the SSS-8

Somatic Symptom Scale (SSS-8)

During the <u>past 7 days</u>, how much have you been bothered by any of the following problems?

	Not at all	A little bit	Some what	Quite a bit	Very much
1. Stomach or bowel problems	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Back pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Pain in your arms, legs, or joints	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Headaches	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Chest pain or shortness of breath	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Dizziness	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Feeling tired or having low energy	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Trouble sleeping	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

11. Table 1

ISS – Timeframes for Submission of Safety Data to Amgen

For Interventional studies with Amgen IMP[a]:

Safety Data	Timeframe for submission to Amgen	Send to
Suspected Unexpected Serious Adverse Reaction (SUSARs)	At time of regulatory submission	Amgen Safety
Pregnancy/Lactation exposure and any associated reports/outcomes (i.e. unexpected pregnancy, pregnancy of partner, spontaneous abortion, congenital anomaly etc.)	Within 1 business day of Sponsor awareness, for reports meeting serious criteria Not to exceed 15 calendar days of Sponsor awareness, for non-serious reports	Amgen Safety

[a] Specific requirements are to be outlined in the Research Agreement.

For all study types – aggregate reports[a](as applicable):

Safety Data	Timeframe for submission to Amgen	Send to
Listing for Safety data reconciliation[b]	Once per year and at the end of the study	NASCR Manager
Annual Safety Report (eg, EU Clinical Trial Directive DSUR and US IND Annual Report)	Annually	NASCR Manager
Other aggregate analyses (any report containing Safety data generated during the course of the study)	At the time of Sponsor submission to any body governing research conduct (eg. RA, IRB etc.)	NASCR Manager
Final (End of Study Report, including): • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	At the time of Sponsor submission to any body governing research conduct (eg. RA, IRB etc.) but no later than 1 calendar year of study completion	NASCR Manager

[a] Specific requirements are to be outlined in the Research Agreement.

[b] Listing for reconciliation should include all ICSRs submitted to Amgen Safety per contract (i.e. for studies in Table 1 listing should include ADRs, SADRs, Other Safety Findings, USADEs, SADEs and non-serious ADEs ; for studies in Table 2 listing should contain SUSARs, pregnancy and lactation exposure (and any associated reports/outcomes), USADEs, SADEs and non-serious ADEs; studies in table 3 do not require reconciliation).