CLINICAL PROTOCOL

STUDY TITLE:	A Long-Term, Open-Label Study to Evaluate the Safety of M207 (Zolmitriptan Intracutaneous Microneedle System) in the Acute Treatment of Migraine
PROTOCOL NUMBER:	CP-2017-001
PROTOCOL VERSION:	Version 3
PROTOCOL DATE:	Original: 22 June 2017 Amendment 1: 30 January 2018 Amendment 2: 06 April 2018
STUDY DRUG:	M207 (Zolmitriptan Intracutaneous Microneedle System)
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PROTOCOL SIGNATURE PAGE - PRINCIPAL INVESTIGATOR

Protocol Number: CP-2017-001

Study Title: A Long-Term, Open-Label Study to Evaluate the Safety of M207 (Zolmitriptan Intracutaneous Microneedle System) in the Acute Treatment of Migraine

Protocol Version: 3: Amendment 2

Protocol Date: 06 April 2018

I have received and read the protocol version 3 dated **06 April 2018**. I agree to undertake the protocol as defined therein, and I will work according to the principles of GCP as described in 21 CFR parts 50, 54, 56, and 312, and according to applicable local requirements. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or informed consent form must first be approved by Zosano Pharma Corporation and the Institutional Review Board/Ethics Committee, except those changes necessary to eliminate apparent immediate hazards to subjects. Failure to adhere to these stipulations may constitute a breach of United States (U.S.) Federal Regulations and may result in termination of the study.

Principal Investigator

_____ _____

Signature Date

_____

Printed Name

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

5-HT receptors	5-hydroxytryptamine receptors
AE	Adverse event
ALT	Alanine transferase (same as SGPT)
ANOVA	Analysis of variance
AP	Alkaline phosphatase
AST	Aspartate aminotransferase (same as SGOT)
AUC	Area Under the Curve
AUC_{last}	Area under the curve calculated from minute 0 to the last measurable plasma concentration
$AUC_{0\text{-}2\ hr}$	Area under the curve calculated from 0 hour to the 2 hour plasma concentration
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C	Celsius
CAD	Coronary artery disease
CDMS	Clinical data management system
CFR	Code of Federal Regulations
cm^2	Centimeter squared
C_{max}	Maximum observed plasma concentration
CPK	Creatinine phosphokinase
CRF	Case report form
CRO	Contract research organization
CTA	Clinical Trials Authorization
CTM	Clinical trial material
CVA	Cerebral vascular accident
dL	Deciliter
DMP	Data Management Plan
ECG	Electrocardiogram
F	Fahrenheit
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
HDL	High-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHS	International Headache Society
IND	Investigational New Drug
IRB	Institutional Review Board

IXRS	Interactive Voice/Web Recognition System
J	Joules
Kg	Kilogram
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last Observation Carried Forward
M207	Intracutaneous Microneedle System (M207)
Mg	Milligrams
mITT	Modified Intent-to-Treat
mL	Milliliter
MM	Medical Monitor
NDA	New drug application
NSAID	Nonsteroidal anti-inflammatory drug
PCP	Phencyclidine
PE	Physical examination
PRSPB	Patch-related superficial punctate bruising
PV	Pharmacovigilance
RDC	Remote Data Capture
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SEM	Standard error of the mean
SNRI	Serotonin-norepinephrine reuptake inhibitors
SOP	Standard operating procedures
SSRI	Selective serotonin reuptake inhibitors
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attacks
T_{max}	Time to maximum concentration
TMF	Trial master file
U/L	Units per liter
U.S.	United States
WOCBP	Women of child-bearing potential
ZP	Zosano Pharma

PROTOCOL SYNOPSIS

TITLE	A Long-Term, Open-Label Safety Study to Evaluate the Safety of M207 (Intracutaneous Microneedle System) in the Acute Treatment of Migraine
SPONSOR	Zosano Pharma Corporation
CLINICAL PHASE	Phase 3, Open-Label Safety
INDICATION	Acute migraine (with or without aura) in adults
OBJECTIVES	• The primary objective of the study is to assess the long-term safety of 3.8 mg (administered as two 1.9 mg patches) of M207 for the acute treatment of migraine • The secondary objective of the study is to evaluate the efficacy of 3.8 mg (administered as two 1.9 mg patches) of M207 for the acute treatment of migraine
TRIAL DESIGN	Open-Label, Multicenter, Safety Study
INVESTIGATIONAL TREATMENT	M207 Intracutaneous Microneedle patch system, 3.8 mg administered as two 1.9 mg patches (to be worn for 30 minutes)
BLINDING	N/A
RANDOMIZATION	N/A
STUDY POPULATION	Adults who suffer from 2-8 migraine attacks per month on average
NUMBERS OF SUBJECTS	Approximately 400 subjects will be screened to ensure up to 300 subjects are eligible to enter the two-week run-in period and approximately 250 subjects eligible for the treatment phase: • At least 150 subjects must complete the safety follow-up for six months • At least 50 subjects must complete the safety follow-up for one year
ELIGIBILITY	Inclusion Criteria: Subjects presenting with all of the following may be included in the study: 1. Able to provide written informed consent 2. Women or men 18 to 75 years of age 3. Greater than 1 year history of episodic, migraine (with or without aura) with onset prior to 50 years of age. Diagnosis must comply with International Headache Society (IHS ICHD-3beta) diagnostic criteria.

Diagnostic criteria must include a history of at least five attacks not attributed to any other disorder that include all of the following criteria:

a) Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

b) Headache has at least two of the following characteristics:

(i) unilateral location

(ii) pulsating quality

(iii) moderate or severe pain intensity

(iv) aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

c) During headache at least one of the following:

(i) nausea and/or vomiting

(ii) both photophobia and phonophobia

4. Migraine history during the 6-month period prior to initial screening must include:
   a) at least 2 migraines per month
   b) no more than 8 migraines per month
   c) no more than 15 headache days per month
5. Women of child-bearing potential must not be pregnant, must agree to avoid pregnancy during the trial, and must use an acceptable double-barrier method of birth control (examples of methods include partner using condom, female using IUD, hormonal or non-hormonal contraceptive, diaphragm with spermicide, or contraceptive sponge) for the duration of the trial.
6. No significant ECG findings, defined by:
   a) ischemic changes defined as > 1mm of down-sloping ST segment depression in at least two contiguous leads,
   b) Q-waves present in at least two contiguous leads,
   c) clinically significant intra-ventricular conduction abnormalities (left bundle branch block or Wolf-Parkinson-White syndrome), or
   d) clinically significant arrhythmias (e.g., current atrial fibrillation)
7. Able to understand and operate the electronic diary
8. Able to apply the demo study drug patches
9. In the opinion of the investigator, subject is willing to treat a minimum of 2 migraines per month with study medication and is willing to consistently perform eDiary completion for up to 12 months.

Exclusion Criteria:

Subjects presenting with any of the following **will not** be included in the study:

1. Contraindication to triptans
2. Use of any prohibited concomitant medications within 10 days of the Run-in Period (See Section 6.2.11 for list of prohibited concomitant medications prohibited for the duration of the study)
3. Use of any prescription anti-coagulant including Pradaxa (dabigatran), Coumadin (warfarin sodium), Eliquis (apixaban), and/or Xarelto (rivaroxaban) within 30 days prior to screening and throughout the duration of the study.
4. History of hemiplegic migraine or migraine with brain stem aura (formerly called basilar migraine)
5. Participation in another investigational trial during the 30 days prior to the Run-in Period or during this study
6. Diagnosis of cancer (other than non-invasive skin cancer) within the 5 years prior to the Run-in Period
7. History of unstable psychiatric illness requiring medication changes or hospitalization in the 12 months prior to the Run-in Period
8. Known allergy or sensitivity to zolmitriptan or its derivatives or formulations
9. Known allergy or sensitivity to adhesives and/or titanium
10. Planned participation in activities which cause inflammation, irritation, sunburn, lesions, and/or tattoos at the intended application site from two weeks prior to screening through the last day of study participation
11. Use of greater than 5 doses of opioid or barbiturate containing medications in the 30 days prior to screening and/or who anticipate using more than 5 doses per month of these medications at any time during the study
12. Women who are pregnant, breast-feeding or plan a pregnancy during this study
13. Clinically significant liver disease (SGPT > 150 U/L; SGOT > 130 U/L or LDH > 750 U/L)
14. History of coronary artery disease (CAD), coronary vasospasm (including Prinzmetal's angina), aortic aneurysm, peripheral vascular disease or other ischemic diseases (e.g., ischemic bowel syndrome or Raynaud’s syndrome)
15. Three or more of the following CAD risk factors identified during screening:

a) Current tobacco use
b) Hypertension (systolic BP > 140 or diastolic BP > 90) or receiving anti-hypertensive medication for treatment of hypertension
c) Hyperlipidemia – LDL > 159 mg/dL and/or HDL < 40 mg/dL (or on prescribed anti-cholesterol treatment)
d) Family history of premature coronary artery disease (CAD) (< 55 years of age in male first degree relatives or < 65 years of age in female first degree relatives)
e) Diabetes mellitus

16. History of cerebral vascular accident (CVA), transient ischemic attacks (TIA), or seizures
17. History of concurrent illness that requires hospitalization within the 30 days prior to the Run-in Period
18. Any other household member currently participating in a M207 study or relatives of site staff
19. Any reason to believe that compliance with the study requirements and completion of evaluations required for this study will not be possible
20. Any language barrier that, in the opinion of the Investigator, would preclude communication or compliance with the study requirements
21. History or current abuse or dependence on alcohol or drugs that in the opinion of the investigator would interfere with adherence to study requirements
22. Any positive urine drug screen for phencyclidine (PCP), MDMA (ecstasy), cocaine, and/or methamphetamine(s)
23. Any clinically relevant abnormal findings in the subject's medical history, physical exam, vital signs or laboratory tests that, in the opinion of the Investigator, may put the subject at risk

Eligibility Criteria for Study Treatment

To be eligible for Treatment, subjects must continue to meet all eligibility criteria for the study and the following criteria observed during the Run-in Period:

1. At least one qualifying migraine attack in the last 14 calendar days prior to Visit 3 (Day 1). The following constitutes a migraine that qualifies during the Run-in Period:
   a. Headache has at least two of the following characteristics:
      - unilateral location
      - pulsating quality

- moderate or severe pain intensity
- aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

b. During headache at least one of the following:

- nausea and/or vomiting
- both photophobia and phonophobia

2. No more than seven headache days (headache days include both qualifying migraines and/or other headache types) in the last 14 calendar days prior to Visit 3 (Day 1)
3. During the run-in period, good eDiary compliance will be confirmed by subject eDiary completion of at least 10 out of the last 14 calendar days prior to Visit 3 (Day 1)
4. Demonstrated ability to properly operate the eDiary
5. Demonstrated ability to properly apply the demo study drug patches
6. In the opinion of the investigator, subject is willing and able to treat all eDiary-confirmed migraines for up to 12 months with good eDiary completion compliance
7. Confirmation of continuing good general health, or stable non-serious disease that in the opinion of the Investigator will not place the subject at risk

CENTERS	Multicenter in the United States
STUDY DURATION	1 week screening period, two-week (+ up to 1 week) run-in period, 6 to 12 month treatment period, and a two-week safety follow-up visit
EFFICACY ASSESSMENTS	Headache symptoms at time of treatment, 30 min, 2 hour, 12 hour, 24 hour and 48 hours post patch application: • Pain severity (0 = none, 1 = mild, 2 = moderate, 3 = severe) • Most bothersome other symptom (present/absent) • Nausea (Absent/Present) • Photophobia (Absent/Present) • Phonophobia (Absent/Present) • Rescue medication use • Pain relief (present/absent) • Migraine recurrence • Migraine-ACT Questions (Assessment of Current Therapy)

SAFETY ASSESSMENTS	• Subject-reported skin assessments 30 min, 2 hours, 12 hours, 24 hours and 48 hours • Investigator skin assessment at all post-treatment visits • Adverse Events • Physical exam including height and weight • Vital signs including blood pressure • Clinical Laboratory determinations including serum chemistries and hematological parameters • 12-lead ECGs • Assessment of concomitant medications
STUDY PROCEDURES	• Screening procedures may be performed in 1 to 7 days • Run-in period for 2 (+ up to 1) weeks prior to Day 1 • Clinic visits include Screening, drug dispensation visit Day 1, Month 1, 2, 3, 6, 9, 12 (or early discontinuation) • A minimum of 2 migraine attacks treated per month with subject skin assessment recordings at 30 minutes, 2 hours, 12 hours, 24 hours and 48 hours post patch application
STATISTICAL ANALYSES	The safety population will include all subjects who received any amount of study drug (i.e., applied at least 1 patch). Adverse events will be summarized overall and by preferred term and system organ class. Adverse events will also be summarized by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized. Actual values and changes from baseline for clinical laboratory test results and vital sign measurements will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum). ECG parameters will be summarized using shift tables. The number and percentage of subjects experiencing Bruising, Erythema, and Edema and other skin assessments will be tabulated. All efficacy endpoints will be summarized using descriptive statistics. Further details regarding efficacy analyses can be found in the statistical analysis plan.

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1 INTRODUCTION

1.1 Background

According to International Headache Society (IHS) diagnostic criteria, the prevalence of migraine has been reported to be 18% of females and 6% of males within the adult population (Lipton 2002). An estimated 37 million Americans have acute migraine attacks. Less than half receive optimal medical care.

There is still an important unmet need in treating migraine despite the availability in the last 20 years of numerous triptans that bind selectively to the 5-HT_{1B} and 5-HT_{1D} receptors. Triptans offer good efficacy and tolerability and, with several alternative formulations (intranasal and SC injection), they can overcome the gastric stasis, nausea, and vomiting that commonly accompany migraine. However, currently available triptans have several shortcomings including lack of universal efficacy, inconsistency of response, numerous adverse events, slow onset of action when administered orally, high recurrence rate and potential for Medication Overuse Headache.

Zolmitriptan is a $5HT_{1B/D}$ agonist widely used for the treatment of migraine. Like other compounds in the triptan class, it has been shown to be effective and well tolerated in placebo-controlled clinical trials. Zolmitriptan is available as a conventional release tablet (2.5 mg and 5.0 mg), a "fast melt" orally disintegrating tablet (2.5 mg and 5.0 mg), and a nasal spray (2.5 mg and 5.0 mg). The last two formulations were developed to potentially provide a more convenient way to take the drug versus that of the conventional release tablet.

The bioavailability of zolmitriptan conventional release tablets has been found to be between 41 and 48%, and administration with food reduced C_{max} and AUC by 13-16% (Seaber 1998). Zolmitriptan is metabolized to N-desmethyl zolmitriptan (potent active metabolite), N-oxide zolmitriptan, and indole-acetic acid metabolites. Some of the metabolites appear to be formed from first-pass metabolism. This first pass metabolism can be impacted by drugs that affect the cytochrome p-450 system. Also, absorption is reported to be lower during an actual migraine attack.

A product that avoids first-pass metabolism, the potential for food interaction and lesser absorption during a migraine could have advantages over existing zolmitriptan formulations. Additionally, an important consideration for a non-oral formulation of zolmitriptan is the high incidence of nausea that occurs during a migraine attack. In 60-70% of migraine attacks, nausea is a significant symptom that patients experience. Therefore, a product that can be administered without using the gastrointestinal system (and is therefore not susceptible to be vomited up) could be advantageous for the patient experiencing a migraine.

1.2 Clinical Pharmacology, Efficacy, and Safety of Zolmitriptan

1.2.1 Human pharmacokinetics

A Phase 1 study (CP2015-007) compared the pharmacokinetics of the parent compound and the metabolites, and tolerability of various doses of intracutaneous zolmitriptan (M207) doses to a standard oral dose (2.5 mg) of zolmitriptan. Additionally, since onset of effect may be an important attribute of the intracutaneous system, the study included a comparison of T_{max} values with SC sumatriptan 6.0 mg. The study provided preliminary information on the potential advantages of the M207 system use for the treatment of migraine.

The study compared single administrations of 5 regimens of M207, as well as 2.5 mg of oral zolmitriptan and 6.0 mg of subcutaneous sumatriptan in a 7-way crossover design in 20 healthy volunteers.

The calculated key pharmacokinetic parameters for the zolmitriptan regimens and subcutaneous sumatriptan are shown in Table 1.

Table 1: Key Pharmacokinetic Parameters

	Dose (mg)	C_{max} (SD) ng/mL	T_{max} Med (Range)	$AUC_{0\text{-}2hr}$ (SD) ng/mL hour	$AUC_{0\text{-}last}$ (SD) ng/mL hour	$AUC_{0\text{-}last}$ Dose	BA v Oral
A (M207)	0.48	1.8 (0.53)	20 (2-30)	2.1 (0.73)	2.8 (1.36)	5.8	67%
B (M207)	0.48 x 2	3.7 (1.05)	20 (2-30)	4.2 (0.95)	6.5 (1.97)	7.5	87%
C (M207)	1.9	6.8 (2.75)	20 (2-30)	7.4 (2.53)	12.3 (4.31)	6.5	76%
F (M207)	1.9 x 2	14.6 (4.46)	17.5 (2-30)	16.4 (5.34)	27.8 (9.93)	7.3	85%
G (M207)	3.8	22.6 (14.00)	15 (2-30)	19.3 (5.37)	31.7 (8.35)	8.3	97%
D (Oral Zolmi)	2.5	3.8 (1.51)	60 (30-240)	4.7 (2.24)	22.2 (10.79)	8.6	100%
E (SC Suma)	6.0	88.8 (27.56)	10 (5-20)	70.9 (14.15)	100.9 (23.29)	16.8	

Perhaps most relevant to the potential utility of this product for the treatment of migraine is the T_{max} for the M207 regimens, showing much more rapid absorption of the zolmitriptan from intracutaneous administration compared to oral administration.

Rapoport et al 1997 compared oral doses ranging from 1 mg to 10 mg to placebo in 1258 patients, and found that efficacy increased as a function of dose, and that all doses of

Zolmitriptan were well-tolerated, although the incidence of adverse events did increase as a function of dose.

Doses of 25 mg of oral zolmitriptan for the treatment of migraine were evaluated in two additional studies (Schoenen et al 1994 and Visser et al 1996) and in both studies this dose was well-tolerated.

Comparative Systemic Exposure: M207 vs Oral and Intranasal Zolmitriptan

Maximal plasma concentrations of zolmitriptan seen with M207 in the Phase 1 study (CP-2015-007) at the dose Zosano plans to study appear to be in the range of those seen with 2.5 mg to 10 mg oral, or 5 mg intranasal (see Table 2). Comparisons based on AUC values show that the exposure with M207 appears to be lower than with oral or intranasal zolmitriptan administration. How the different pharmacokinetic profile of M207 influences efficacy and tolerability when used for the acute treatment of migraine was evaluated in the CP-2016-001 trial.

Table 2: Comparison of exposure – M207 vs Oral and Intranasal Zolmitriptan (Phase 1 Study and Literature Comparisons)

Treatment (Study)	C_{max} (ng/ml)	$AUC_{0\text{-}last}$ (ng/ml*hr)
M207 0.96 mg (Study 2015-007)	3.73	6.5
M207 1.9 mg (Study 2015-007)	6.40	12.3
M207 2 x 1.9 mg (Study 2015-007)	14.6	27.8
Zolmitriptan 2.5 mg oral (Study 2015-007)	3.8	22.2
Zolmitriptan 5.0 mg Intranasal (Yates 2003)	6.51	42.1
Zolmitriptan 10 mg oral (Seaber 1998)	16.6(M) -20.9(F)	84.4(M)-108.6(F)

Adverse Events Reported in Phase 1 Trial

In the Phase 1 study of M207, 19 of 20 subjects reported an adverse event either related to M207 administration or SQ sumatriptan administration. Nearly all the adverse events were mild in intensity and short in duration. The most common adverse events reported are shown in Table 3. The adverse events appear to be similar to those previously reported for zolmitriptan and sumatriptan. Most of the adverse events judged to be related to study drug were also rated as mild in severity. There was a higher incidence of adverse events following the higher doses of M207 and SQ sumatriptan. The following table displays adverse events reported by 4 or more subjects (Most Common Adverse Events Table 3).

Table 3: Most Common Adverse Events

Adverse Events	Part 1					Part 2	Part 3	Total
	M207 0.48 mg	M207 0.48 mg * 2	M207 1.9 mg	Zolmi 2.5 mg (oral)	Suma 6.0 mg SC	M207 1.9 mg * 2	M207 3.8 mg	
Headache	3	2	4	0	0	4	4	17
Hot flushes	0	0	0	0	0	2	2	4
Paresthesia	0	2	3	0	6	10	8	29
Throat and jaw tightness, heaviness, ache	0	0	1	0	0	2	2	5

Vital Signs/ECGs/Labs

There were no clinically meaningful changes in ECG or laboratory parameters in any of the subjects, and mean values for ECG parameters had minimal changes in the post-dosing period. There were small mean increases in systolic and diastolic blood pressure following M207 3.8 mg and sumatriptan 6.0 mg.

The changes were in the 3-12 mm Hg range, and all M207 groups were near Baseline at 1 hour.

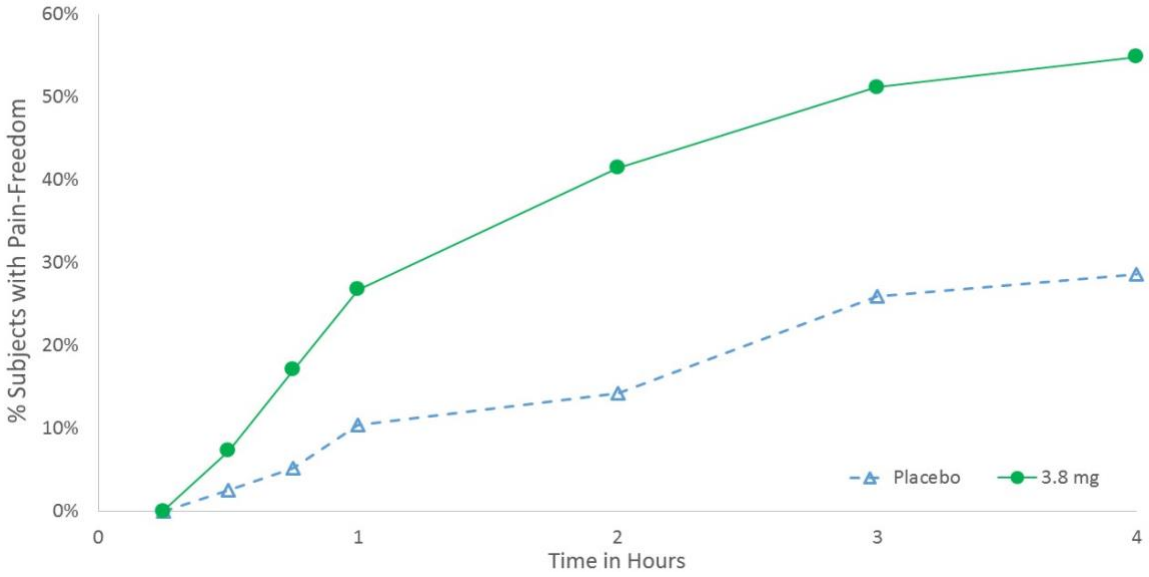
1.2.2 CP-2016-001 Clinical Efficacy and Safety Study

The CP-2016-001 efficacy and safety study evaluated the patient population, endpoints, placebo comparator, and study design typically used in trials of therapies for acute treatment of migraine, consistent with the FDA 2014 Guidance Document. This study compared three doses of M207 (1.0 mg, 1.9 mg, and 3.8 mg administered as two 1.9 mg patches) to placebo for the treatment of a single migraine attack.

Five-hundred and eighty-nine subjects were enrolled in this multi-center, double-blind, randomized, placebo-controlled study, of whom 365 were randomized. Of those randomized, 333 treated subjects were included in the safety analysis, and 321 subjects qualified for the modified intent-to-treat (mITT) population. The comparison with placebo for the 3.8 mg group was highly significant for both co-primary endpoints (pain freedom at 2 hours p = .0001 and most bothersome symptom freedom at 2 hours p = 0.0009).

The percentage of subjects with pain-freedom after treatment with M207 3.8 mg and placebo over time is shown in Figure 1.

Figure 1: Proportion of Subjects with Pain-freedom at 15, 30, 45, 60, 120, 180, and 240 min after treatment with M207 3.8 mg and placebo



1.2.2.1 Primary Efficacy Analysis

The primary efficacy analysis compared each active treatment with placebo to the co-primary endpoints of proportion of subjects who were pain free at 2 hours and the proportion of subjects who were most bothersome symptom free at 2 hours. The order of testing was pre-specified in the analysis plan with the first two tests being the highest dose (3.8 mg) vs placebo for the two co-primaries, followed by pain freedom and most bothersome symptom freedom at 2 hours (in that order) for the 1.9 mg dose vs placebo.

As shown in Table 4, the comparison with placebo for the 3.8 mg group was highly significant for both co-primary endpoints (pain freedom at 2 hours $p = 0.0001$ and most bothersome symptom freedom at 2 hours $p = 0.0009$).

For the 1.9 mg group, the comparison for pain freedom at 2 hours showed superiority as compared to placebo, but the comparison for most bothersome other symptom at 2 hours was not statistically significant. Because of the pre-defined order of testing, statistical significance for pain freedom at 2 hours cannot be claimed for the 1.0 mg group, even though the p-value was less than 0.05.

Table 4: Co-Primary Endpoints: Primary Analysis – mITT population

	Treatment Group			
	Placebo (n=77)	**1.0 mg (n=79)**	**1.9 mg (n=83)**	**3.8 mg (n=82)**
Pain Freedom at 2 hours				
N (%)	11 (14.3%)	24 (30.4%)	23 (27.7%)	34 (41.5%)
Difference from Placebo		16.1 %	13.4 %	27.2 %
P-Value		**0.0149**	**0.0351**	**0.0001**
Freedom from Most Bothersome Symptom at 2 hours				
N (%)	33 (42.9%)	45 (57.0%)	44 (53.0%)	56 (68.3%)
Difference from Placebo		14.1 %	10.2 %	25.4 %
P-Value		0.0706	0.1694	**0.0009**

1.2.2.2 Secondary Efficacy

The percentage of subjects with pain-freedom after treatment with M207 and placebo over time is shown in Figure 2. The percentage of subjects who were pain free was higher for the 3.8 mg M207 group as compared to placebo beginning at 45 minutes post-dose and continuing through 48 hours post-dose.

Figure 2: Percentage of Subjects with Pain-Freedom at 0.5, 0.75, 1, 2, 24, and 48 hours after treatment with M207 and placebo

1.2.2.3 Previous Co-Primary Endpoints in Migraine Trials for Comparison

Prior to issuance of the Guidance Document in October of 2014, the four co-primary endpoints utilized in acute treatment of migraine trials were pain relief, nausea freedom, photophobia freedom and phonophobia freedom at 2 hours. Although this trial was not powered to "win" on these endpoints, many current products are approved and labeled based on these endpoints. Therefore, we present the data for these four "old" endpoints here.

Pain relief (improvement to mild or none) from moderate or severe at the various timepoints post-dose is shown in Figure 3. The percentages are high for all treatment groups, and 80.5% at 2 hours for the M207 3.8 mg group compares very favorably with many approved products. The placebo rates are also quite high, and the therapeutic gain (active – placebo) seems in line with approved products.

Figure 3: Percentage of Subjects with Pain Relief at 0.5, 0.75, 1, 2, 24, and 48 hours after treatment with M207 and placebo

The following tables display nausea freedom, photophobia freedom, and phonophobia freedom at the various post-dose timepoints. Once again, the 3.8 mg M207 group has high percentages at 2 hours for nausea freedom and photophobia freedom and the separation from placebo is apparent. For phonophobia freedom, the separation between placebo and active was less apparent at earlier timepoints, and only at later timepoints were the differences notable.

Table 5: Nausea Freedom

Nausea Freedom (mITT)	Treatment Group			
Timepoint	**Placebo (n=77)**	**1.0 mg (n=79)**	**1.9 mg (n=83)**	**3.8 mg (n=82)**
15 Minutes	36.4%	39.2%	41.0%	32.9%
30 Minutes	59.7%	55.7%	49.4%	53.7%
45 Minutes	63.6%	58.2%	66.3%	62.2%
1 hour	63.6%	68.4%	71.1%	76.8%
2 hours	63.6%	75.9%	74.7%	81.7%
3 hours	58.4%	78.5%	74.7%	79.3%
4 hours	54.5%	78.5%	73.5%	79.3%
12 hours	45.5%	75.9%	71.1%	80.5%
24 hours	44.2%	72.2%	74.7%	79.3%
48 hours	41.6%	72.2%	72.3%	70.7%

Table 6: Phonophobia Freedom

Phonophobia Freedom (mITT)	Treatment Group			
Timepoint	**Placebo (n=77)**	**1.0 mg (n=79)**	**1.9 mg (n=83)**	**3.8 mg (n=82)**
15 Minutes	14.3%	20.3%	15.7%	25.6%
30 Minutes	35.1%	34.2%	28.9%	45.1%
45 Minutes	37.7%	44.3%	43.4%	57.3%
1 hour	46.8%	48.1%	57.8%	61.0%
2 hours	55.8%	58.2%	61.4%	69.5%
3 hours	54.4%	63.3%	71.1%	73.2%
4 hours	57.1%	69.6%	69.9%	74.4%
12 hours	44.2%	73.4%	68.7%	78.0%
24 hours	42.9%	69.6%	68.7%	76.8%
48 hours	42.9%	72.2%	68.7%	70.7%

Table 7: Photophobia Freedom

Photophobia Freedom (mITT)	Treatment Group			
Timepoint	**Placebo (n=77)**	**1.0 mg (n=79)**	**1.9 mg (n=83)**	**3.8 mg (n=82)**
15 Minutes	9.1%	11.4%	9.6%	11.0%
30 Minutes	22.1%	27.8%	24.1%	26.8%
45 Minutes	24.7%	43.0%	33.7%	41.5%
1 hour	33.8%	48.1%	44.6%	53.7%
2 hours	41.6%	60.8%	56.6%	69.5%
3 hours	44.2%	65.8%	61.4%	72.0%
4 hours	45.5%	65.8%	63.9%	74.4%
12 hours	42.9%	74.7%	66.3%	75.6%
24 hours	42.9%	72.2%	68.7%	73.2%
48 hours	40.3%	70.9%	67.5%	68.3%

1.2.2.4 Safety Results

No serious adverse events occurred in this study. Adverse events including investigator and subject-reported dermal events at the patch site were generally mild and transient. Treatment-emergent adverse events that occurred in two or more subjects summarized by System Organ Class/Preferred Term are shown in Table 8, and Investigator Dermal Adverse Events are shown in Table 9. Subject Reported Patch Application Site Reactions (redness, bruising and swelling) are shown in Figure 4, Figure 5 and Figure 6, respectively.

Table 8: Treatment Emergent Adverse Events Occurring in Two or More Subjects

System Organ Class/Preferred Term	Treatment Group				
	Placebo (N=83)	M207 1 mg (N=80)	M207 1.9 mg (N=87)	M207 3.8 mg (N=83)	Total (N=333)
	No. (%) Subjects	No. (%) Subjects	No. (%) Subjects	No. (%) Subjects	No. (%) Subjects
General disorders and administration site conditions	12 (14.5%)	23 (28.8%)	31 (35.6%)	38 (45.8%)	104 (31.2%)
Application site erythema	9 (10.8%)	13 (16.3%)	17 (19.5%)	22 (26.5%)	61 (18.3%)
Application site bruise	3 (3.6%)	5 (6.3%)	12 (13.8%)	12 (14.5%)	32 (9.6%)
Application site pain	1 (1.2%)	2 (2.5%)	2 (2.3%)	8 (9.6%)	13 (3.9%)
Application site haemorrhage	0 (0.0%)	3 (3.8%)	5 (5.7%)	4 (4.8%)	12 (3.6%)
Application site swelling	3 (3.6%)	1 (1.3%)	3 (3.4%)	2 (2.4%)	9 (2.7%)
Application site oedema	0 (0.0%)	1 (1.3%)	3 (3.4%)	2 (2.4%)	6 (1.8%)
Application site discolouration	1 (1.2%)	1 (1.3%)	1 (1.1%)	1 (1.2%)	4 (1.2%)
Musculoskeletal and connective tissue disorders	0 (0.0%)	1 (1.3%)	2 (2.3%)	4 (4.8%)	7 (2.1%)
Muscle tightness	0 (0.0%)	0 (0.0%)	1 (1.1%)	2 (2.4%)	3 (0.9%)
Musculoskeletal stiffness	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (1.2%)	2 (0.6%)
Myalgia	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (1.2%)	2 (0.6%)
Gastrointestinal disorders	1 (1.2%)	2 (2.5%)	2 (2.3%)	1 (1.2%)	6 (1.8%)
Nausea	0 (0.0%)	2 (2.5%)	1 (1.1%)	1 (1.2%)	4 (1.2%)
Vomiting	1 (1.2%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Investigations	1 (1.2%)	1 (1.3%)	1 (1.1%)	0 (0.0%)	3 (0.9%)
Blood creatine phosphokinase increased	1 (1.2%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	2 (0.6%)
Infections and infestations	0 (0.0%)	1 (1.3%)	1 (1.1%)	0 (0.0%)	2 (0.6%)

Table 9: Investigator Visual Dermal Adverse Events

Patch-Related Superficial Punctate Bruising (PRSPB)	N	Treatment Group			
		Placebo (N=83)	**M207 1 mg (N=80)**	**M207 1.9 mg (N=87)**	**M207 3.8 mg (N=83)**
		83	78	84	83
	None	82 (98.8%)	73 (93.6%)	72 (85.7%)	74 (89.2%)
	≤ 25% ZP patch application site has punctate bruising spots	1 (1.2%)	5 (6.4%)	9 (10.7%)	4 (4.8%)
	≥ 26% to < 50% ZP patch application site has punctate bruising spots	0 (0.0%)	0 (0.0%)	2 (2.4%)	2 (2.4%)
	> 50% ZP patch application site has punctate bruising spots	0 (0.0%)	0 (0.0%)	1 (1.2%)	3 (3.6%)
Edema	N	83	78	84	83
	None	83 (100.0%)	77 (98.7%)	81 (96.4%)	82 (98.8%)
	Slight Edema	0 (0.0%)	1 (1.3%)	3 (3.6%)	1 (1.2%)
	Moderate Edema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe Edema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Erythema	N	83	78	84	83
	None	78 (94.0%)	71 (91.0%)	71 (84.5%)	64 (77.1%)
	Mild Redness	5 (6.0%)	7 (9.0%)	10 (11.9%)	16 (19.3%)
	Well-defined Redness	0 (0.0%)	0 (0.0%)	3 (3.6%)	3 (3.6%)
	Beet Redness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Subjects' ratings of the application sites for erythema, edema, and bruising are shown in the following figures (note that the number of subjects who entered values for 4, 12, and 48 hours was smaller than at 30 minutes and 24 hours, as amendment #3 which required the addition of 4, 12, and 48 hour assessments was implemented mid-study.

Figure 4: Subject-reported Patch Application Site Reactions (Redness, Bruising, and Swelling)

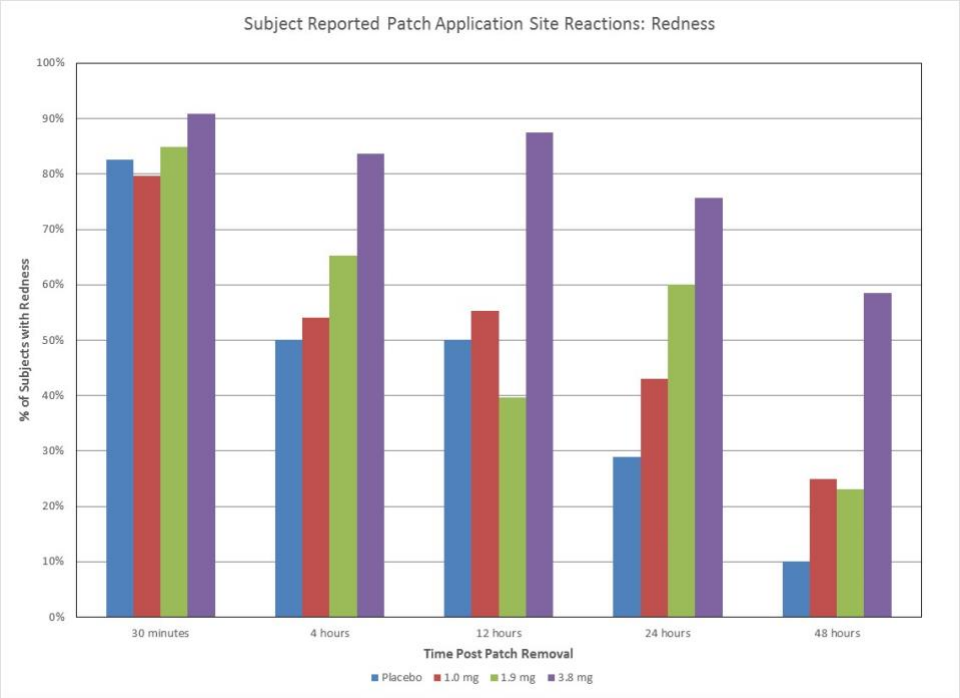


Figure 5: Subject Reported Patch Application Bruising

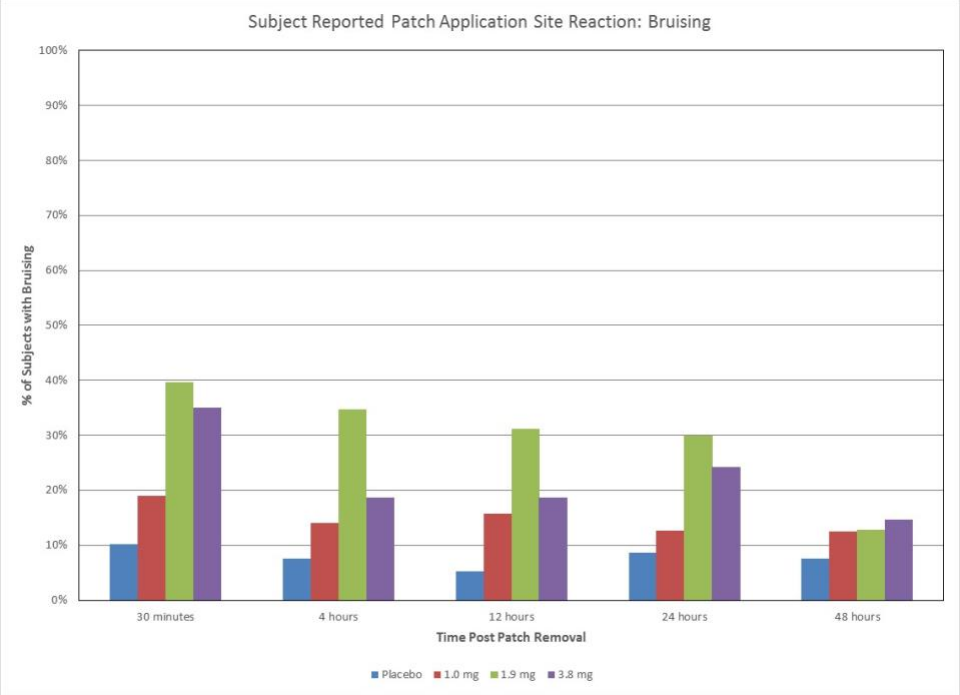
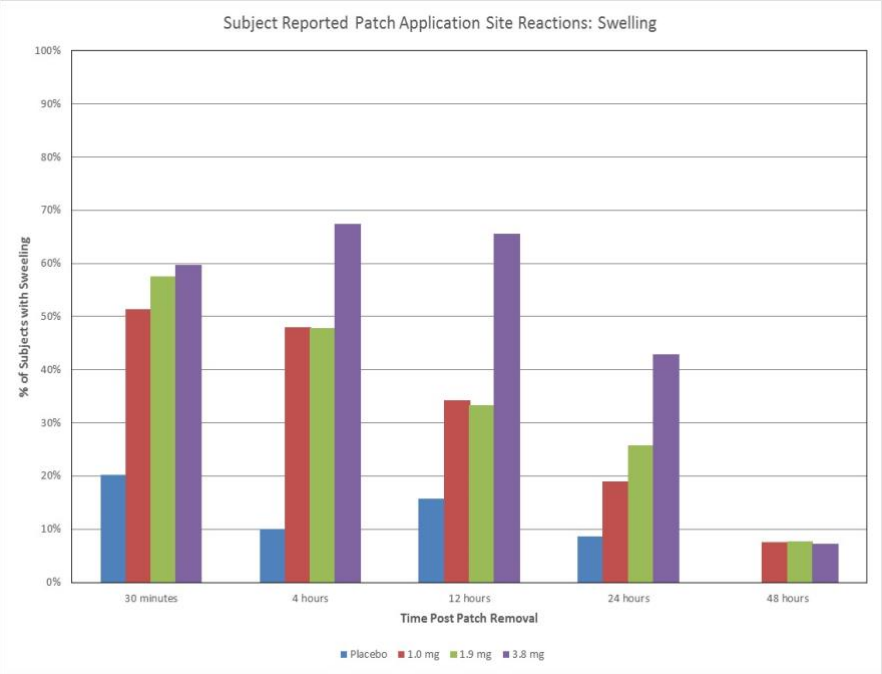


Figure 6: Subject Reported Patch Application Swelling



1.3 Study Rationale

This study is designed to evaluate the safety of repeated use of M207 2 x 1.9 mg, over the course of 6-12 months of use. The recently-completed study (CP-2016-001) showed that tolerability was acceptable when M207 was used for a single migraine treatment. It also demonstrated that subjects were able to evaluate their application site reactions in their e-diaries and most subjects reported redness at the site of application at some time points post treatment. This study will assess the effects of repeated treatment for multiple migraine attacks. Both subjects and investigators will evaluate the effects of treatment by outpatient and in-clinic assessments.

2 STUDY OBJECTIVES

This open-label study is designed to evaluate the long-term safety of repeat administration of M207 in subjects with migraine.

2.1 Primary Objective

- To assess the long-term safety of 3.8 mg (administered as two 1.9 mg patches) of M207 for the acute treatment of migraine

2.2 Secondary Objectives

- To assess the efficacy of 3.8 mg (administered as two 1.9 mg patches) of M207 for the acute treatment of migraine

3 INVESTIGATIONAL PLAN

3.1 Study Design

The study is outlined in Figure 7.

Figure 7: Study Design

SCREENING PERIOD (up to 7 days) Up to one week prior to start of Run-in period	VISIT 2 (START OF RUN-IN PERIOD) (may be combined with Visit 1) Run-in period is two weeks (plus up to 1 week) prior to Day 1 (Visit 3)	TREATMENT PERIOD Day 1 up to 12 months
Informed consent discussion and form signed; Perform screening lab work and other screening tests. ↓ If preliminary entry criteria indicate that the subject is not eligible, report the subject as a screen failure. →	If preliminary entry criteria indicate that the subject is probably eligible, complete the eDiary training, issue an eDiary, and schedule the Day 1 visit for 2 weeks later (plus up to 1 week if needed) ↓ Subject records migraine activity on the eDiary for a minimum of 14 days and up to 21 days. ↓ If the subject does not meet all the inclusion criteria and the eligibility criteria for study treatment, and/or meets one or more of the exclusion criteria, report the subject as a run-in failure. →	If the subject meets all the inclusion and none of exclusion criteria, dispense study medication to the subject at Visit 3: ↓ Subject will treat migraine attacks for up to 12 months. Subject will complete eDiary upon confirmation of each qualifying migraine and will self-administer the patches. Subject will continue to complete the eDiary at specified time points.

This is an open-label, twelve-month safety study. There will be a screening period followed by a 14-day run-in period to record migraine activity. Screening activities may be completed in a period as short as one day or may be spread out over up to one week. On the day of screening procedures, if preliminary entry criteria indicate that the subject is probably eligible, the eDiary training can be completed, the eDiary can be issued, and the subject may begin the run-in period.

If during the run-in period, additional information becomes available to exclude the subject (e.g., return of 12-lead ECG or lab results), the subject should be notified of screen failure and instructed to return any provisional eDiary device (if applicable) to the center.

The run-in period is to determine eligibility for treatment with study medication based on daily eDiary data collection, and is planned to be 2 weeks in duration but may be extended up to an additional 1 week to accommodate scheduling, and/or to confirm diary compliance and eligibility. The run-in period will be a minimum of 14 days and no more than 21 days in duration. Qualified subjects will receive study medication at Day 1 (Visit 3) for up to twelve months for the treatment of migraine headaches. Migraines will be treated with a single dose, consisting of two patches, but subjects can treat multiple migraine attacks throughout the 12 months. Using the eDiary to confirm they are experiencing a qualified migraine, subjects will self-administer the patches and continue to respond to questions in the eDiary for 48 hours post treatment administration.

3.2 Selection of Study Population

3.2.1 Number of Subjects

Approximately 400 subjects will be screened to ensure that at least 300 subjects enter the run-in period and that at least 250 subjects are enrolled into the treatment phase. Fifty subjects must complete the entire one-year treatment period and 150 subjects must complete a minimum of six months of treatment.

3.2.2 Inclusion Criteria

Subjects presenting with all of the following may be included in the study:

1. Able to provide written informed consent
2. Women or men 18 to 75 years of age
3. Greater than 1 year history of episodic, migraine (with or without aura) with onset prior to 50 years of age. Diagnosis must comply with International Headache Society (IHS ICHD-3beta) diagnostic criteria. Diagnostic criteria must include a history of at least five attacks not attributed to any other disorder that include all of the following criteria:
    a) Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
    b) Headache has at least two of the following characteristics:
        i. unilateral location
        ii. pulsating quality

iii. moderate or severe pain intensity

iv. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

c) During headache at least one of the following:

i. nausea and/or vomiting

ii. both photophobia **and** phonophobia

4. Migraine history during the 6-month period prior to the screening period must include:

a) at least 2 migraines per month

b) no more than 8 migraines per month

c) no more than 15 headache days per month

5. Women of child-bearing potential must not be pregnant, must agree to avoid pregnancy during the trial, and must use an acceptable double-barrier method of birth control (examples of methods include partner using condom, female using IUD, hormonal or non-hormonal contraceptive, diaphragm with spermicide, or contraceptive sponge) for the duration of the trial.

6. No significant ECG findings, defined by:

a) ischemic changes defined as > 1mm of down-sloping ST segment depression in at least two contiguous leads,

b) Q-waves present in at least two contiguous leads,

c) clinically significant intra-ventricular conduction abnormalities (left bundle branch block or Wolf-Parkinson-White syndrome), or

d) clinically significant arrhythmias (e.g., current atrial fibrillation)

7. Able to understand and operate the electronic diary

8. Able to apply the demo study drug patches

9. In the opinion of the investigator, subject is willing to treat a minimum of 2 migraines per month with use of study medication and is willing to consistently perform eDiary completion for up to 12 months.

3.2.3 Exclusion Criteria

Subjects presenting with any of the following **will not** be included in the study:

1. Contraindication to triptans
2. Use of any prohibited concomitant medications within 10 days of the Run-in Period (See Section 6.2.11 for list of prohibited concomitant medications prohibited for the duration of the study)
3. Use of any prescription anti-coagulant including Pradaxa (dabigatran), Coumadin (warfarin sodium), Eliquis (apixaban), and/or Xarelto (rivaroxaban) within 30 days prior to screening and throughout the duration of the study.
4. History of hemiplegic migraine or migraine with brain stem aura (formerly called basilar migraine)
5. Participation in another investigational trial during the 30 days prior to the Run-in Period or during this study
6. Diagnosis of cancer (other than non-invasive skin cancer) within the 5 years prior to the Run-in Period
7. History of unstable psychiatric illness requiring medication changes or hospitalization in the 12 months prior to the Run-in Period
8. Known allergy or sensitivity to zolmitriptan or its derivatives or formulations
9. Known allergy or sensitivity to adhesives and/or titanium
10. Planned participation in activities which cause inflammation, irritation, sunburn, lesions, and/or tattoos at the intended application site from two weeks prior to screening through the last day of study participation
11. Use of greater than 5 doses of opioid or barbiturate containing medications in the preceding 30 days prior to screening and/or who anticipate using more than 5 doses per month of these medications at any time during the study
12. Women who are pregnant, breast-feeding or plan a pregnancy during this study
13. Clinically significant liver disease (SGPT > 150 U/L; SGOT > 130 U/L or LDH > 750 U/L)
14. History of coronary artery disease (CAD), coronary vasospasm (including Prinzmetal's angina), aortic aneurysm, peripheral vascular disease or other ischemic diseases (e.g., ischemic bowel syndrome or Raynaud’s syndrome)
15. Three or more of the following CAD risk factors identified during screening:

- Current tobacco use
- Hypertension (systolic BP > 140 or diastolic BP > 90) or receiving anti-hypertensive medication for treatment of hypertension
- Hyperlipidemia – LDL > 159 mg/dL and/or HDL < 40 mg/dL (or on prescribed anti-cholesterol treatment)
- Family history of premature coronary artery disease (CAD) (< 55 years of age in male first degree relatives or < 65 years of age in female first degree relatives)
- Diabetes mellitus

16. History of cerebral vascular accident (CVA), transient ischemic attacks (TIA), or seizures
17. History of concurrent illness that requires hospitalization within the 30 days prior to the Run-in Period
18. Any other household member currently participating in a M207 study or relatives of site staff
19. Any reason to believe that compliance with the study requirements and completion of evaluations required for this study will not be possible
20. Any language barrier that, in the opinion of the Investigator, would preclude communication or compliance with the study requirements
21. History or current abuse or dependence on alcohol or drugs that in the opinion of the investigator would interfere with adherence to study requirements
22. Any positive urine drug screen for phencyclidine (PCP), MDMA (ecstasy), cocaine, and/or methamphetamine(s)
23. Any clinically relevant abnormal findings in the subject's medical history, physical exam, vital signs or laboratory tests that, in the opinion of the Investigator, may put the subject at risk

3.2.4 Eligibility Criteria for Study Treatment

To be eligible for Treatment, subjects must continue to meet all eligibility criteria for the study and the following criteria observed during the Run-in Period:

1. At least one qualifying migraine attack in the last 14 calendar days prior to Visit 3 (Day1). The following constitutes a migraine that qualifies during the Run-in Period:

   a) Headache has at least two of the following characteristics:

   - unilateral location
   - pulsating quality
   - moderate or severe pain intensity
   - aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

   b) During headache at least one of the following:

   - nausea and/or vomiting
   - both photophobia and phonophobia

2. No more than seven headache days (headache days include both qualifying migraines and/or other headache types) in the last 14 calendar days prior to Visit 3 (Day 1)

3. During the run-in period, good eDiary compliance will be confirmed by subject completion of at least 10 out of the 14 calendar days prior to Visit 3 (Day 1)

4. Demonstrated ability to properly operate the eDiary

5. Demonstrated ability to properly apply the demo study drug patches

6. In the opinion of the investigator, subject is willing and able to treat all eDiary-confirmed migraines for up to 12 months with good eDiary completion compliance

7. Confirmation of continuing good general health, or stable non-serious disease that in the opinion of the Investigator will not place the subject at risk

3.2.5 Prior and Concomitant Medications Allowed During the Study

Medications that are considered necessary for the subject's welfare and are not specifically prohibited (Section 6.2.11), may be given at the discretion of the investigator. All medication(s) taken within 30 days prior to the screening visit and throughout the study must be recorded in the appropriate source document and in the case report form (CRF). Over the counter medications, topical skin ointments and/or creams, prescription medications, herbal supplements and/or vitamins will be recorded as concomitant medications.

Migraine prophylaxis medications are allowed if subjects have been on a stable dose for at least 30 days prior to screening and with no changes during the study.

Medications with ergot or another triptan or vasoconstrictor drugs are prohibited on the day of a confirmed migraine prior to M207 application and for 24-hours post-administration of M207.

Aspirin, acetaminophen, NSAIDS and other PRN or daily medications indicated specifically for migraine symptoms are prohibited on the day of a confirmed migraine prior to M207 application and during the two hours following M207 application.

Following M207 application, subjects will enter into the eDiary whether they took any medications (other than M207) for migraine symptoms prior to M207 application (on the day of application) or during the 48 hours post M207 application.

3.2.6 Early Termination

3.2.6.1 Withdrawal of Subjects

Subjects may be withdrawn from treatment or from the study for the following reasons:

- Subject did not experience at least 6 qualifying migraines within 12 weeks after patch and applicator dispensation (Visit 3);
- At their own request or at the request of their legally authorized representative;
- If, in the investigator's opinion, continuation of treatment would be detrimental to the subject's well-being;
- If the subject experiences any AE believed to be possibly or probably related to study drug and severe enough to warrant withdrawal of treatment;
- If the subject starts and continues to use a prohibited drug, as listed in Section 6.2.11;
- If the subject is non-compliant with the study drug, eDiary completion, or any other requirement of this protocol; or
- If a subject becomes pregnant anytime during the study.

Subjects who early terminate from the study after applying study medication, will return for an early termination visit and a two-week safety follow-up visit if they applied any patches. For all subjects who are withdrawn from study drug or from the study, the reason must be recorded on the appropriate source document and on the appropriate CRF. The subject must be followed up to establish whether the reason was an AE, and, if so, this must be reported in accordance with the procedures in Section 8.3. Subjects with ongoing systemic and skin AEs at study termination will be followed until all significant changes have resolved or become medically stable.

To the extent possible, all examinations scheduled and all data normally collected at completion of the study (the final study visit) must be performed on all subjects who receive study drug but do not complete the study according to protocol. These assessments must be done at the time of the subject's early termination visit.

The investigator must make at least three documented attempts (phone, email, etc.) to contact subjects lost to follow-up up until the time of database lock. This includes one certified letter sent to the subject's primary place of residence. A copy must be maintained in the source documentation.

3.2.6.2 Replacement of Subjects

Subjects who discontinue after starting treatment but before six months will be replaced to ensure adequate enrollment, i.e., 150 subjects in the study who complete six months and 50 subjects who complete a year.

3.2.6.3 Premature Discontinuation of the Trial

The Sponsor has the right to terminate this study at any time. Reasons for termination of the study may include, but are not limited to, the following:

- The Health Authority or IRB/EC terminates the study;
- The incidence or severity of AEs in this or other studies indicates a potential hazard to subjects;
- Subject enrollment is unsatisfactory;
- The trial is not conducted in accordance with the procedures defined in the approved protocol (i.e., protocol deviations, failure to ensure the quality of the data collected);
- New information on the study drug warrants study termination;
- The discretion of the Sponsor

The IRB/Ethics Committee(s) and Health Authorities should be informed about a premature discontinuation of the trial.

4 STUDY TREATMENTS

4.1 Identity of Investigational Products

4.1.1 M207

The M207 patches will be manufactured by Zosano Pharma in Fremont, CA (see Investigator's Brochure for more information).

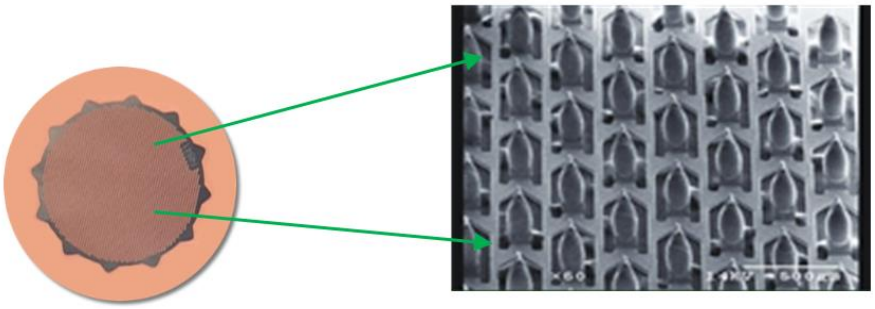
4.1.2 Product Description and Patch Application

The Zosano M207 Intracutaneous Microneedle System is a novel drug delivery technology which consists of a disposable titanium patch centered on an adhesive backing with microneedles that are dry-coated with the drug product formulation, and a reusable handheld applicator that ensures that the patch is applied with a defined application speed and energy to the site of administration.

The M207 Intracutaneous Microneedle System is a proprietary disposable patch and a reusable applicator. The zolmitriptan-coated titanium microneedle array (3 cm^2 array) is attached to a 5 cm^2 adhesive patch (Figure 8). A magnified image of the zolmitriptan-coated microneedles is shown in Figure 8. The patch system is composed of several parts. The patch is mounted inside a polycarbonate plastic ring with a co-molded desiccant (Figure 9).

The M207 drug product used in CP-2017-001 is packaged in a nitrogen purged foil pouch or cup (see Figure 10). The reusable applicator is shown in Figure 9 and Figure 10 with a lock-out function to avoid accidental firing. The applicator provides a spring-driven piston to apply the patch with consistent impact energy of 0.26 Joules. The user presses the handheld reusable applicator onto the patch ring assembly for attachment, then the applicator is un-locked by twisting the cap. The user applies the patch by pressing the applicator/patch ring assembly onto the skin site and holding it to the arm for 3 seconds (Figure 10).

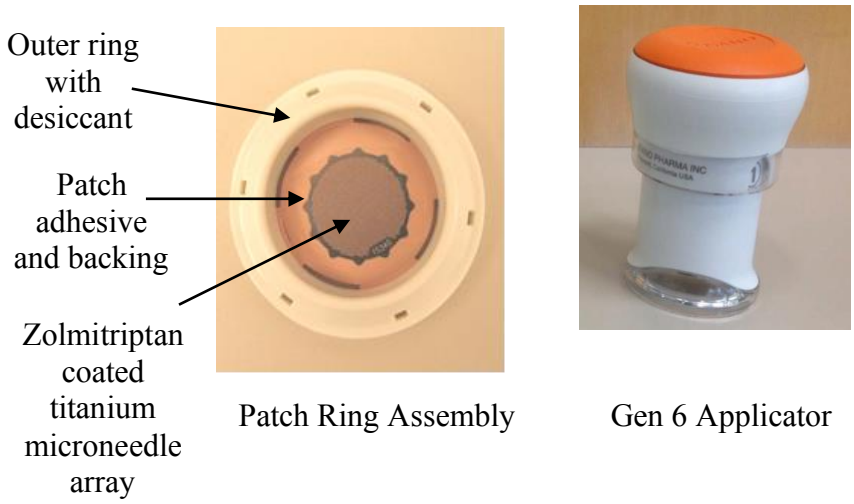
Figure 8: 5 cm^2 Patch with Zolmitriptan Coated Titanium Microneedle Array



M207 Intracutaneous Patch with Titanium Array

Magnified section – M207 Intracutaneous Patch with Titanium Array

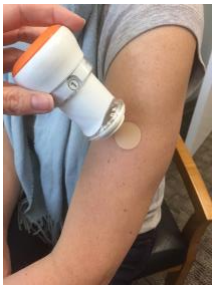
Figure 9: Handheld Gen 6 Patch Ring Assembly and Applicator

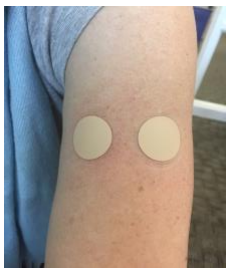


Patch Ring Assembly

Gen 6 Applicator

Figure 10: *M207 Patch Application

 	Open the foil pouches or cups (depending on the kit dispensed).
 	Snap one patch-ring assembly onto the applicator.
	Twist applicator cap clockwise from Position 1 to Position 2 to unlock for patch application.
	Press applicator downward to apply patch to upper arm. Press down firmly against the skin until you hear a click then hold for 3 seconds. Patches are left on for 30 minutes.

 	Remove the outer ring in order to load and apply the second patch.
	Repeat all of the above steps to apply second patch next to the first patch.

*See subject training video and instructions for use for exact instructions on how to apply the patches

4.2 Dispensing Clinical Trial Material (CTM) Kits

All subjects in the study will receive open label M207, 3.8 mg to administer as two 1.9 mg patches to treat each qualified migraine during the study.

There are two types of M207 kits for each subject, starter kits and refill kits, clearly labeled and visually distinguishable. Each M207 CTM kit includes either 4 (starter kit) or 8 (refill kit) individual foil pouches or cups. Each pouch or cup contains one patch. The starter kit dispensed on day 1 contains the applicator. Refill kits will be dispensed as needed throughout the study. A replacement applicator will be issued at approximately six months, and or/as needed if a previously dispensed applicator is defective or lost.

Zosano may employ an electronic system for supply management of clinical trial material (CTM) kits. The CTM system, if employed, is for drug supply management purposes only. There is no drug randomization as drug assignment is open-label.

At each medication dispensation visit, after it has been established that a subject continues to qualify for the study, study staff will document the total number of patches dispensed to each subject and unopened (unused) patches returned at each visit in the eCRF and drug accountability records.

4.3 Packaging, Labeling, and Receipt of Supplies

In this study, M207 drug product patches will be open-label.

The M207 patches are individually packaged in foil pouches or cups. There are two types of M207 kits for each subject, starter kits and refill kits, which are clearly labeled and visually distinguishable. Each starter kit contains an applicator and 4 individual foil pouches or cups, and each refill kit contains 8 individual foil pouches or cups. Each pouch or cup contains one patch. The kit labels contain at minimum the manufacturer's name, CTM kit number, storage conditions, and a statement indicating that the study drug is for investigational use only.

The pharmacist or designee will inventory and acknowledge receipt of all shipments of study drug.

Optional Instructions for Use (IFU) Survey

Each starter kit of cup-packaged products include a card inviting subjects to participate in an optional online survey inclusive of questions about their experience with the IFU for the cup-packaged product. The invitation card provides the link to the survey website and states that the survey is voluntary and optional. The card also states that if the online survey is completed, the subject will receive a small stipend. The survey consists of approximately 5 questions to collect information about the clarity of the IFU instructions for application of 2 cup-packaged patches to achieve a full dose.

4.4 Study Drug Stability, Storage, and Retention

M207 patches are stable at 15-30°C. The M207 patches and handheld applicators, packaged in individual subject kits, should be stored at a controlled room temperature (15-30°C). All CTM must be kept in a locked and temperature controlled area with access restricted to designated study personnel.

4.5 Study Drug Kit Administration, Dispensation, Accountability, and Return

The study drug will be dispensed only to qualified subjects included in this study in accordance with the eligibility criteria specified in the study protocol.

Throughout the study, upon eDiary confirmation of each migraine qualifying for treatment, subjects will self-administer the study drug. Study personnel will train subjects on how to apply the patches with the M207 applicator.

The study physician or designee will record the CTM kit numbers dispensed to each subject on the drug accountability record. The designated site monitor will periodically check the supplies of CTM to ensure accountability of used applicators and unused kits. If necessary, subjects may return for unscheduled visits for dispensation of additional drug kits. Subjects should be

instructed to bring all unused patches to every clinic visit. Returned patches may be re-dispensed for use to the same subject; however, all patches must be accounted for on the drug accountability log as returned and re-dispensed. The number of patches dispensed at each visit, date dispensed, the number of patches used, and the number of returned unused patches at each visit will be documented. Any discrepancies between the 'actual' number of patches returned versus the 'expected' number to be returned will be explained. If a subject did not apply both patches to treat a migraine, the site must document the reason in the subject's source record.

Final study drug accountability will be completed after the last subject visit. All drug accountability records will be filed in the site file and TMF as appropriate.

At the end of the study, all unused study drug kits and used and unused applicators will be inventoried and returned as per the sponsor's instructions.

4.6 System Performance

An applicator associated with field observations of atypical appearance or system performance should be returned directly to Zosano Pharma. Return instructions for defective applicators with malfunctions are provided in the M207 Site User Manual. A description of the field observation should accompany the shipment. Only problem applicators will be returned to Zosano Pharma.

4.7 Medication Compliance

The investigator will emphasize the importance of correctly self-administering the study medication each time a qualifying migraine is confirmed through the eDiary. Subjects will be instructed to bring the following items to the clinic visit:

- eDiary
- M207 applicator
- Any unused M207 patches

Subjects may discard used patches. The subject will record information regarding each study drug administration in the eDiary.

5 SAFETY AND EFFICACY ASSESSMENTS

5.1 Safety

Safety assessments will be initiated after the informed consent form (ICF) has been signed and will conclude when the post-study procedures are completed (or early discontinuation).

Safety will be assessed through the following:

- Physical exam including height (at screening and final visit only) and weight
- Vital signs including blood pressure
- Clinical laboratory determinations including serum chemistries and hematological parameters
- 12-lead ECGs
- Assessment of concomitant medications
- All treatment-emergent systemic and skin AEs (TEAEs)
- Subject reported Skin Assessment
- Investigator Skin assessment

5.2 Efficacy

- Pain freedom
- Most bothersome other symptom freedom
- Pain relief
- Nausea freedom
- Photophobia freedom
- Phonophobia freedom
- Rescue medication use
- Migraine recurrence
- Subject satisfaction with treatment as assessed by the Migraine-ACT

6 STUDY PROCEDURES AND SCHEDULE

6.1 Study Schedule

A schedule of study procedures is presented in Table 10.

Table 10: Schedule of Study Procedures

Procedure	VISIT 1[1] Screening	VISIT 2[1] Start of Run-In	VISIT 3	VISIT 4, 5, 6	VISIT 7	VISIT 8	VISIT 9 Final visit or ET	VISIT 10 Two Week Post Study Visit
	Up to 1 week prior to Run-in	Week -2 (up to -3)	Day 1 (dispense patches)	Month 1, 2, 3	Month 6	Month 9	Month 12	Two Week Safety visit
Day/Visit Windows				Day 28, 56, 84 ± 7 days	Day 168 ± 7 days	Day 252 ± 7 days	Day 336 ± 7 days	14 (+ up to 14) days following final visit or ET
Week				Week 4, 8, 12	Week 24	Week 36	Week 48	Week 50 - 52
Informed Consent	X							
Inclusion/Exclusion/ Eligibility Criteria	X	X	X					
Med History/ Migraine History	X							
Fitzpatrick Skin Scale (subject completed)	X							
Demographics	X							
Physical Exam[3]	X		X		X		X	
Weight/Height (Height only at screen and final visit or ET) [4]	X		X	X		X	X	
Vital Signs[5]	X	X	X	X	X	X	X	X
Lab Chem/Hematology (fasting)	X[6]						X	
Serum or Urine Pregnancy (only for WOCBP)	X - Serum		X - Urine	X - Urine	X - Urine	X - Urine	X - Urine	
Drug Abuse Testing	X				X		X	
12-lead ECG	X				X		X	
Train Subject on How to Apply Patches (using demo patches)		X	X					

Procedure	VISIT 1[1] Screening	VISIT 2[1] Start of Run-In	VISIT 3	VISIT 4, 5, 6	VISIT 7	VISIT 8	VISIT 9 Final visit or ET	VISIT 10 Two Week Post Study Visit
	Up to 1 week prior to Run-in	Week -2 (up to -3)	Day 1 (dispense patches)	Month 1, 2, 3	Month 6	Month 9	Month 12	Two Week Safety visit
Train/dispense eDiary		X	X					
Dispense Study Medication			X	X	X	X		
Study Drug Self-Administration			→	→	→	→	→	
Subject eDiary Reported Skin Assessments			→	→	→	→	→	
Migraine-ACT (subject completed)				X	X	X	X	
Investigator Skin Assessments				X	X	X	X	X
Monthly phone contacts to subject[7]					→	→	→	
Collect Unused Patch(es)/Perform Drug Accountability[8]				X	X	X	X	
Collect and Review eDiary data			X	X	X	X	X	
Record Adverse Events	X	X	X	X	X	X	X	X
Record Concomitant Medications	X	X	X	X	X	X	X	X

[1] Visit 1 and Visit 2 may be combined into one visit. On the day of screening procedures, if preliminary entry criteria indicate that the subject is probably eligible, the eDiary can be issued and the subject may begin the run-in period. If during the run-in period, additional information becomes available to exclude the subject (e.g., return of 12-lead ECG or lab results), the subject should be notified of screen failure and instructed to return any provisional eDiary device (if applicable) to the center.

[3] Physical exam to include (but not limited to) HEENT, Dermatologic, Neurological, General Appearance, Lymph Nodes, Cardiovascular, Respiratory, Gastrointestinal, and Musculoskeletal

[4] Weight at each visit; both height and weight to be collected at screening and final visit only (or early termination visit)

[5] Vital signs include temperature, respiratory rate (RR), blood pressure (BP), and heart rate (HR)

[6] Clinically significant abnormal values may be repeated to confirm eligibility

[7] Phone contacts monthly at months 4, 5, 7, 8, 10, and 11 to remind subjects to treat at least two migraine attacks per month and to assess for adverse events and concomitant medication use

[8] Subjects may return for an unscheduled visit to pick up additional study medication as needed.

All study visits and procedures will be performed according to the Schedule of Study Procedures as listed in Table 10. Subject visits should be scheduled as soon as possible within the specified windows.

Subjects must be fasting (i.e., nothing by mouth for at least 4 hours; drinking water during the 4-hour fast before clinical laboratory assessments is permitted) for all laboratory collections.

6.1.1 Screening (Visit 1): Up to 1 Week Prior to Start of the Run-in Period

In order to determine if a subject meets entry criteria, the following activities and evaluations will be performed during screening. Screening activities may be completed over a period as short as one day or spread out over up to one week. On the day of screening procedures, if preliminary entry criteria indicate that the subject is probably eligible, the eDiary training can be completed, the eDiary can be issued, and the subject may begin the run-in period; i.e., Visits 1 and 2 may be combined. If during the run-in period, additional information becomes available to exclude the subject (e.g., return of 12-lead ECG or lab results), the subject should be notified of screen failure and instructed to return any provisional eDiary device (if applicable) to the center.

The following procedures are to be performed during screening:

- Provide informed consent discussion; collect signed ICF (must be done prior to commencing screening assessments)
- Assess subject eligibility based on inclusion/exclusion criteria
- Record demographics
- Subject will be instructed to complete the Fitzpatrick Skin Scale questionnaire (See Appendix 1)
- Record medical history including migraine history, allergies, and current drug and alcohol use
- Perform PE, including height and weight
- Record vital signs: temperature, respiratory rate (RR), blood pressure (BP), and heart rate (HR)
- Collect blood (4-hr fasting) for clinical laboratory measurements including clinical chemistries and hematology
- Collect blood for serum pregnancy for all women of child-bearing potential (WOCBP)
- Urine drug screen

- Perform 12-lead electrocardiogram (ECG)
- Record concomitant medications taken within 30 days prior to Screening
- Register in the case report form any subject who becomes a screen failure

6.1.2 Run-in Period: 2 Weeks [up to +1 week] Prior to Dispensation of Study Medication through Day 1

The Run-in period can begin on the day screening activities are completed, and should be 14 days in duration prior to Visit 3. However, the run-in period may be extended up to an additional 1 week, to a maximum total of 21 days, to accommodate scheduling and/or to confirm compliance and presence of migraine. The Day 1 visit (Visit 3) should be scheduled as soon as possible after 2 weeks of run-in within the specified window, to determine if a subject still meets entry criteria, including the occurrence of at least one qualifying migraine attack per a 14-day period. The following activities and evaluations will be performed during the Run-in period:

6.1.2.1 First Day of Run-in (Visit 2): Week -2 (up to week -3)

- Record vital signs: temperature, respiratory rate (RR), blood pressure (BP), and heart rate (HR)
- Record concomitant medications
- Record adverse events
- Train the subject on how to apply the patches (using demo patches) and the use of the eDiary
- Record that the subject understands how to apply the patch and can administer a demo patch
- Dispense eDiary
    - Subject declares most bothersome symptom **other than pain** (nausea [with or without vomiting], photophobia, or phonophobia—**that is most bothersome most of the time with their migraines)** and it is entered in the eDiary

6.1.2.2 Daily through Run-in Period (2 weeks [+ up to 1 additional week])

- Subject records daily headache activity in eDiary. If the subject did not experience a headache in the past 24 hours, the eDiary will require the subject to answer whether he/she experienced excessive yawning, mood changes, or excessive fatigue (tiredness).
- Subjects must have at least one qualifying migraine in the last 14 calendar days prior to visit 3 (day 1) in the run-in period to meet eligibility for treatment (see Section 3.2.4 for Eligibility Criteria for Study Treatment)

6.1.3 Day 1 (Visit 3, Dispense Study Medication)

- Perform brief physical exam, including weight
- Record vital signs: temperature, respiratory rate (RR), blood pressure (BP), and heart rate (HR)
- Review run-in eDiary data for subject compliance and eligibility for treatment
- Confirm subject is willing to treat all eDiary-confirmed migraine attacks with study medication, and is willing to consistently perform eDiary completion for up to 12 months
- Record concomitant medications, including medication(s) taken to treat migraine attacks
- Urine pregnancy test for all WOCBP
- Record Adverse events
- Train the subject on how to apply the patch to the upper arm with the applicator and have the subject practice applying the demo patches to his/her arm 2-3 times (more is allowable, if necessary)
- Record that the subject can apply patch(es) with the applicator unaided
- Instruct the subject to apply the patches on the same upper arm for each application
- Reconfirm subject's eligibility based on inclusion/exclusion criteria
- Dispense CTM kit and the applicator
- Provide instructions for scheduling the next visit in one month

- Remind the subject that ergot, another triptan and/or vasoconstrictor drugs are prohibited on the day of patch application prior to applying and within 24-hours post-administration of the patch
- Provide any follow-up eDiary training necessary and re-dispense the eDiary
- Dispense the Subject Skin Grading Card (Appendix 4) and instruct the subject to refer to this card when grading their skin reaction(s)/symptom(s) in the eDiary.

6.1.4 Treatment Phase: Up to 12 Months

Visit 3 will be considered the "Day 1" visit for data capture purposes. Subjects will be instructed to complete the eDiary at the time of each suspected migraine attack. Once the eDiary confirms that the migraine qualifies for treatment, the subject will follow the steps provided to self-administer the study drug. If necessary, subjects may return for unscheduled visits for dispensation of additional drug kits.

The following constitutes a migraine that qualifies for treatment with study drug:

- No medication has already been taken to treat the migraine symptoms on the day of the suspected attack before applying M207.
- Presence of at least two of the following characteristics:
  - Unilateral location
  - Pulsating quality
  - Moderate or severe pain intensity
  - Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
- During headache, at least one of the following:
  - Nausea and/or vomiting
  - BOTH photophobia AND phonophobia

The following procedures are to be started at Day 1 after receiving study medication:

- Using the eDiary, the subject will record the following to confirm the headache meets the qualifications for a migraine:
    - Migraine symptoms and pain assessment
- Once the qualifying migraine has been confirmed, subject self-administers the study drug patches. Patches cannot be applied to a previous application site unless the site is free of redness, swelling, and/or bruising. In addition, patches must not be applied to any area where the skin appears tattooed, sunburned, broken and/or irritated.
- Each set of two patches must be applied next to one another (or one above the other), on the same arm. If any skin appears broken or irritated, subsequent doses will be applied a few inches away from the previously applied patches on the same arm (or both patches on the other arm) to avoid applying in an irritated area.
- Qualifying migraine attacks cannot be treated any earlier than 48 hours after the time of patches application for a previously treated migraine attack.
- Subject will continue to record the following in the eDiary at specified time points as follows:
    - Migraine symptoms and pain assessment at the time of treatment, 30 minutes, 2 hour, 12 hours, 24 hours, and 48 hours post patch application
    - Subject reported skin assessment for bleeding at 30 minutes only
    - Subject reported skin assessment for bruising, swelling, and/or redness (at 30 minutes, 2 hours, 12 hours, 24 hours and 48 hours post patch administration time points only)
    - Subject reported skin pain and skin itching at 48 hours post patch administration
- Dispense the Subject Skin Grading Card (Appendix 4) with the eDiary and instruct the subject to refer to this card when grading their skin reaction(s)/symptom(s) in the eDiary. The Grading Card will include a subject reminder to contact the study physician if he/she experiences any serious or severe skin reaction(s) at any time point or for worsening or non-resolving reactions at approximately 3 days post patches application (at 72 hours). In addition, the eDiary will remind the subject to call the study physician if he/she experiences any skin reaction(s) and/or symptom(s) at the patch application site which worsens rather than improves over approximately a five-day period. If the subject

contacts the study physician at any time point for worsening or non-resolving reactions, the subject must be seen for an unscheduled visit. The skin reaction(s)/symptom(s) will be assessed, recorded as an adverse event in the eCRF and followed to resolution.

6.1.5 Month 1 (Visit 4), Month 2 (Visit 5), Month 3 (Visit 6), Month 6 (Visit 7)

Visits must be scheduled to occur on (or within ±7 days) of the protocol specified study day, ie, on study days 28 (Month 1), 56 (Month 2), 84 (Month 3), and 168 (Month 6). The following procedures will be performed at each visit:

- Administer the Migraine Assessment of Current Therapy (Migraine-ACT) which is completed by the subject
- Collect any unused patches, perform accountability, and dispense patches with applicator
- Perform physical exam, (Month 6 only) (height does not need to be recorded)
- Record vital signs: temperature, respiratory rate (RR), blood pressure (BP), and heart rate (HR)
- Collect urine for urine pregnancy test for all WOCBP
- Collect urine for drug abuse testing (Month 6 only)
- Perform 12-lead electrocardiogram (ECG) (Month 6 only)
- Ensure subject is dispensed the Subject Skin Grading Card (to be used with eDiary entries).
- Collect and review subject's eDiary data with the subject for the following:
    - Subject compliance with study drug treatment and subject responses in eDiary
- Perform Investigator Skin Assessment (presence of blisters, scaly or flakey skin, erosions or open sores, scarring, hyperpigmentation, bruising, redness, and/or swelling) of upper arm where patches have been applied
- Any cutaneous signs or symptoms found on the investigator skin assessment will be recorded as an adverse event on the eCRF and followed to resolution.
- Record concomitant medications
- Record adverse events. In addition, any skin reaction(s) entered into the eDiary by the subject must also be recorded as an adverse event in the eCRF and followed to resolution.

6.1.6 Month 9 (Visit 8) and Month 12 End of Study Final Visit (Visit 9/or Early Termination)

The Month 9 and 12 visits are to be scheduled on (or within ± 7 days) of the protocol specified study day, i.e., on study days 252 (Month 9) and 336 (Month 12). The following procedures will be performed. If a subject terminates early from the study at any time after applying M207, an Early Termination visit must be scheduled to occur within 7-14 days after the subject's last patch application.

- Administer the Migraine Assessment of Current Therapy (Migraine-ACT) to be completed by the subject
- Collect the applicator, any unused patches, and perform accountability
- Dispense M207 patches (Month 9 only)
- Perform physical exam, including weight and height (Month 12 final visit/or early termination only)
- Record vital signs: temperature, respiratory rate (RR), blood pressure (BP), and heart rate (HR)
- Collect blood (4-hr fasting) for clinical laboratory measurements including clinical chemistries and hematology (Month 12 final visit/or early termination only)
- Collect urine for urine pregnancy test for all WOCBP
- Perform 12-lead electrocardiogram (ECG) (Month 12 final visit/or early termination only)
- Ensure subject is dispensed a Subject Skin Grading Card (at Month 9 only)
- Collect and review subject's eDiary data with the subject for the following:
    - Subject compliance with study drug treatment and subject responses in eDiary
- Perform Investigator Skin Assessment (presence of blisters, scaly or flakey skin, erosions or open sores, scarring, hyperpigmentation, bruising, redness, and/or swelling) of upper arm where patches have been applied
- Any cutaneous signs or symptoms found on the investigator skin assessment will be recorded as an adverse event on the eCRF and followed to resolution.
- Record concomitant medications

- Record adverse events. In addition, any skin reaction(s) entered into the eDiary by the subject must also be recorded as an adverse event in the eCRF and followed to resolution.

6.1.7 Monthly Phone Contacts at Months 4, 5, 7, 8, 10, and 11 (± 7 days)

Contact subject each month to assess for adverse events, collect and record concomitant medications and remind subject to continue to treat a minimum of 2 qualifying migraine attacks per month.

6.1.8 Two Week Post Study Safety Visit (Visit 10)

This visit will occur 14-28 days after the End of Study Final Visit (or Early Termination visit). The following procedures will be performed:

- Record vital signs: temperature, respiratory rate (RR), blood pressure (BP), and heart rate (HR)
- Perform Investigator Skin Assessment (presence of blisters, scaly or flakey skin, erosions or open sores, scarring, hyperpigmentation, bruising, redness, and/or swelling) of upper arm(s) where patches have been applied
- Any cutaneous signs or symptoms found on the investigator skin assessment will be recorded as an adverse event on the eCRF and followed to resolution.
- Record concomitant medications

Record adverse events

6.2 Study Procedures

6.2.1 Informed Consent

Each study participant (or legally authorized representative) will be required to read, sign, and date the current institutional review board/independent ethics committee (IRB/IEC) approved version of the ICF. The consent process should also be documented in the study site's source documents. Informed consent must be obtained prior to performing any study-specific procedures. Both the participant and the study staff member who participated in the consent discussion with the participant must sign and date the ICF. Each study participant will be given a copy of the ICF. All participants will have an opportunity to ask questions before signing the ICF, and the study staff member who obtains consent will probe the subject to ascertain understanding of the elements of consent.

6.2.2 Inclusion/Exclusion Criteria

All inclusion criteria and eligibility criteria for subject treatment, and none of the exclusion criteria must be satisfied prior to assignment of a CTM kit to the subject and the start of study drug dosing.

6.2.3 Medical History and Demographics

Demographic information and a medical history, including history of menopausal status, will be obtained during screening. The medical history should include all current conditions, allergies, including recent illnesses and relevant past medical history. Subjects will be asked about current use of illicit drugs or alcohol. Information will also be obtained on the subject's history of migraine therapy. The Fitzpatrick Skin Type Questionnaire scale (Appendix 1) will also be administered at screening to document the subject's skin type.

6.2.4 Randomization

Not applicable.

6.2.5 Migraine Assessment of Current Therapy (Migraine-ACT)

See Appendix 2 for the Migraine Assessment of Current Therapy (Migraine-ACT). This subject completed questionnaire will be administered at each clinic visit starting at Month 1.

6.2.6 Physical Examination

A physical exam will include, but is not limited to, HEENT, dermatologic, brief neurological, general appearance, lymph nodes, cardiovascular, respiratory, gastrointestinal, and musculoskeletal examinations.

6.2.7 Height and Weight

Subjects will have height measured only at the screening and the final visit (or early termination visit). Weight will be collected at screening, Day 1, Month 1, 2, 3, 6, Month 9 and Month 12, the final visit (or early termination visit). The subject must not wear shoes during the height measurement.

The subject should wear light clothing and no shoes during weight measurements. Subjects should be weighed on the same clinic scale during this study.

6.2.8 Vital Signs

All subjects will have vital signs (temperature, RR, BP, and HR) measured at screening and all subsequent visits.

Whenever possible, vital sign measurements will be taken before any blood samples are taken.

6.2.9 Clinical Laboratory Tests

Subjects must be fasting (i.e., nothing by mouth for at least 4 hours before the visit; drinking water during the 4-hour fast before clinical laboratory assessments is permitted). All samples (except urine pregnancy tests) will be processed by a central laboratory. The following parameters will be assessed:

Table 11: Clinical Laboratory Tests

Serum Chemistry	Hematology	Additional Tests
▪ Glucose ▪ Aspartate aminotransferase (AST) ▪ Alanine aminotransferase (ALT) ▪ Alkaline phosphatase (AP) ▪ Lactate dehydrogenase (LDH) ▪ Sodium ▪ Phosphorus ▪ Potassium ▪ Chloride ▪ Creatine phosphokinase (CPK) ▪ Globulin ▪ Cholesterol (HDL and LDL) ▪ Creatinine ▪ Blood urea nitrogen (BUN) ▪ Prothrombin (PT) and INR (International Normalized Ratio) ▪ Serum calcium ▪ Total bilirubin ▪ Triglyceride ▪ Gamma glutamyl transpeptidase	▪ Hematocrit ▪ Hemoglobin ▪ Red Blood Cell Count ▪ White Blood Cell Count with Differential ▪ Platelet Count ▪ Mean corpuscular volume ▪ Mean corpuscular hemoglobin ▪ Mean corpuscular hemoglobin concentration	▪ Serum (at screen visit only) and Urine Pregnancy (WOCBP only)[1] ▪ [2] Urine drug screens will test for: amphetamines, barbiturates, cocaine, cannabinoids, opioids, phencyclidine (PCP), and methamphetamines

Serum Chemistry	Hematology	Additional Tests
(GGT) ▪ Serum glutamic pyruvic transaminase (SGPT) ▪ Serum glutamic oxaloacetic transaminase (SGOT) ▪ Uric acid		

1 If positive at any visit during the study, confirm by serum pregnancy test.

2 Positive drug screen for phencyclidine (PCP), MDMA (ecstasy), cocaine, and/or methamphetamine(s) is exclusionary. Eligibility of subjects who test positive for cannabinoids is up to the discretion of the investigator.

Clinically significant abnormal values at screening may be repeated to confirm eligibility.

The central laboratory will provide a laboratory manual and appropriate supplies (containers and labels). Laboratory values that are out of range will be identified and may be repeated at the investigator's discretion with sponsor approval. The investigator will determine if any out-of-range laboratory values that emerge during treatment are clinically significant and if so, record these on the appropriate source document and on the AE CRF page if applicable. All clinically significant out-of-range laboratory values will be followed until they return to normal, or become medically stable.

6.2.10 Twelve-Lead Electrocardiogram

The ECGs will be sent to a central ECG laboratory for interpretation. ECG equipment and an ECG manual will be provided by the central ECG lab.

Any clinically significant abnormality noted by the central reader on the screening ECG will be recorded on the appropriate source document and will result in exclusion of the subject from this study. The investigator may refer the subject for further evaluation and will continue to follow the subject's condition until the changes have resolved or the subject is medically stable.

6.2.11 Concomitant and Prohibited Medications

Concomitant medications, taken within 30 days of screening and throughout the study, include over the counter medications, topical skin ointments and/or creams, prescription medications, herbal supplements, and/or vitamins. These medications will be recorded on the appropriate source document and on the appropriate CRF at all visits including screening, run-in, and end of study (or early discontinuation) through the duration of the study.

Migraine prophylaxis medications are allowed if subjects have been on a stable dose for at least 30 days prior to screening and with no changes during the study.

Medications with ergot or another Triptan or vasoconstrictor drugs are prohibited on the day of the confirmed migraine prior to M207 application and for 24-hours post-administration of M207.

Aspirin, acetaminophen, NSAIDS, and other PRN or daily medications taken specifically for migraine symptoms are prohibited on the day of a confirmed migraine prior to M207 application and during the two hours following patch application.

On the day of M207 application, subjects will enter into the eDiary whether they took any medications (other than M207) for migraine symptoms prior to M207 application and/or during the 48 hours post M207 application.

Table 12 lists all prohibited concomitant medications taken within 10 days prior to the Run-in Period and for the duration of this study.

Table 12: Prohibited Concomitant Medications

Drug Type	Medication
Monoamine oxidase inhibitors	Selegiline Tranylcypromine Isocarboxazid phenelzine
Selective serotonin reuptake inhibitors (SSRIs)	Paroxetine Fluoxetine Sertraline Citalopram Escitalopram Fluvoxamine
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Duloxetine Venlafaxine Desvenlafaxine Milnacipran Levomilnacipran
All Prescription Anticoagulants	Pradaxa Coumadin Eliquis Xarelto

6.2.12 Assessment of Adverse Events

AEs are collected from the time of signing the informed consent form and throughout the study duration. New systemic and skin AEs will be recorded on the appropriate source document and CRF.

6.2.13 Subject Reported and Investigator Reported Skin Assessments

Subject reported bruising, bleeding (at 30 minutes only), erythema, edema, skin itching and skin pain are collected through the eDiary and will also be recorded as adverse events in the eCRF. The subject is also provided a Subject Skin Grading Card to help him/her assess whether they have any skin reaction(s) and how to grade any reaction(s) (see Appendix 4). If the subject contacts the investigator at any time point for worsening or non-resolving reactions, the subject must be seen for an unscheduled visit. The skin reaction(s)/symptom(s) will be assessed, recorded as adverse events in the eCRF and followed to resolution.

In addition, investigator skin assessments in Section 6.2.13.1 will be completed at each in-clinic visit during the treatment period. Any findings related to the upper arm(s) where the patches were applied will be recorded as an adverse event in the eCRF and followed until the signs/ symptoms resolve.

6.2.13.1 Investigator Skin Assessments

The following skin assessment will be made by the investigator at each in clinic visit starting at month 1. The entire surface area of the outer upper arm from the upper shoulder to the elbow will be assessed for the following skin signs or symptoms. For further instructions, photographs and descriptors are in Appendix 5 (Investigator Assessments - Skin Signs or Symptoms and Photographs) and Appendix 6 (Investigator Assessments – Rating for Bruising, Erythema, Swelling and Photographs).

Skin signs or symptoms	**Indicate arm assessed: Subject's Left and/or Right (circle)**
Blisters or pustules?	Present: Yes or No If Yes, describe:
Scaly or flakey skin?	Present: Yes or No If Yes, describe:
Erosions or open sores?	Present: Yes or No If Yes, describe:

Skin signs or symptoms	Indicate arm assessed: Subject's Left and/or Right (circle)
Scarring?	Present: Yes or No If Yes, describe:
Hyperpigmentation or Hypopigmentation?	Present: Yes or No If Yes, describe:

6.2.13.2 Bruising

The Bruising assessment will be performed by the investigator at each in clinic visit starting at Month 1.

Bruising assessments (visual rating) will be performed using the following ratings:

Symptom	Rating (circle)
M207 application sites have bruising spots?	0 (clear) = None 1 (mild) = ≤ 25% Present in the upper arm region of all M207 applications 2 (moderate) = ≥ 26 to ≤ 50% Present in the upper arm region of all M207 applications 3 (severe) = > 50% Present in the upper arm region of all M207 applications

6.2.13.3 Other Skin Assessments – Erythema and Edema

Erythema and Edema will be assessed by the investigator at each in clinic visit starting at Month 1.

The following ratings will be used to describe the amount of erythema and edema indicative of irritation:

Symptom	Rating (circle)
Skin Erythema	0 (clear) = None 1 (mild) = ≤ 25% Present in the upper arm region of all M207 applications 2 (moderate) = ≥ 26 to ≤ 50% Present in the upper arm region of all M207 applications 3 (severe) = > 50% Present in the upper arm region of all M207 applications

Symptom	Rating (circle)
Skin Edema	0 (clear) = None 1 (mild) = ≤ 25% Present in the upper arm region of all M207 applications 2 (moderate) = ≥ 26 to ≤ 50% Present in the upper arm region of all M207 applications 3 (severe) = > 50% Present in the upper arm region of all M207 applications

Adverse Events of Special Interest: Any site reactions requiring further evaluation or care (e.g., by a dermatologist), as well as those resulting in scarring are considered adverse events of special interest. If these reactions are detected, the de-identified photograph of the patch application site and contralateral arm (containing the date of photograph, visit number and subject number) must be transmitted to the sponsor within 24 hours of the clinic visit for further dermatological evaluation.

7 STATISTICS

A complete description of the statistical analyses to be performed will be provided in a statistical analysis plan (SAP), which will be finalized prior to database lock.

7.1 Analysis Variables

7.1.1 Safety Endpoints

- Changes from baseline in physical examination findings at Months 6 and 12
- Changes from baseline in vital signs at Months 1, 2, 3, 6, 9, 12, and at the 2-week post-study visit
- Changes from baseline in clinical laboratory parameters at Month 12
- Changes from baseline and/or shifts in 12-lead ECG parameters at Months 6 and 12
- Frequency of concomitant medications
- Incidence of treatment-emergent systemic and skin AEs (TEAEs)
- Frequencies of type of redness, severity of swelling, amount of bruising, and amount of bleeding (30 minutes only) at the application site as reported by the subject at 30 minutes, 2 hour, 12 hour, 24 hour, and 48 hours post-dose
- Frequencies of amount of skin itching and severity of pain at the application site as reported by the subject at 48 hours post-dose
- Frequencies of amount of bruising, erythema, and edema at the application site as assessed by the Investigator at Months 1, 2, 3, 6, 9, 12, and at the 2-week post-study visit
- Proportion of subjects with presence of skin signs and symptoms as assessed by the Investigator at Months 1, 2, 3, 6, 9, 12, and at the 2-week post-study visit

7.1.2 Efficacy Endpoints

- Proportion of subjects with pain freedom at 30 minutes, 2 hours, 12 hours, 24 hours, and 48 hour post-dose
- Proportion of subjects with most bothersome other symptom freedom at 30 minutes, 2 hours, 12 hours, 24 hours, and 48 hours post-dose

- Proportion of subjects with pain relief at 30 minutes, 2 hours, 12 hours, 24 hours and 48 hours post-dose
- Proportion of subjects with nausea freedom at 30 minutes, 2 hours, 12 hours, 24 hours and 48 hours post-dose
- Proportion of subjects with photophobia freedom at 30 minutes, 2 hours, 12 hours, 24 hours and 48 hours post-dose
- Proportion of subjects with phonophobia freedom at 30 minutes, 2 hours, 12 hours, 24 hours and 48 hours post-dose
- Proportions of subjects using rescue medication within 2 hours post-dose
- Proportion of subjects with migraine recurrence at 24 and 48 hours post-dose
- Proportion of subjects with sustained pain freedom from 2 to 24 hours post-dose and from 2 to 48 hours post-dose
- Frequency of responses on the migraine ACT

7.2 Populations for Analysis

The Safety Population will include all subjects who receive any amount of study drug (applied at least one patch). The mITT (modified intent-to-treat) population will include all subjects who receive any amount of study drug to treat a qualifying migraine, and who have efficacy data.

7.3 Statistical Methods

7.3.1 Baseline Characteristics

Demographic and baseline characteristic variables such as age, gender, race/ethnicity, height, and weight will be summarized using descriptive statistics. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation [SD], minimum, and maximum).

7.3.2 Safety Analyses

Safety will be assessed by the monitoring and recording of AEs, clinical laboratory tests, vital signs, physical examination findings, ECG parameters, and Investigator and subject reported skin assessments.

All safety analyses will be based on the Safety Population. Adverse events will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) dictionary (using the latest version) and will be summarized overall and by preferred term and system organ class. Adverse events will also be summarized by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized.

Actual values and changes from baseline for assessments of clinical laboratory test results, ECG parameters, and vital sign measurements will be summarized at each visit using descriptive statistics (n, mean, SD, median, minimum, and maximum) or shift tables as appropriate. The number and percentage of subjects experiencing Bruising, Erythema, Edema and other skin assessments will also be summarized.

All data gathered will be listed by patient and parameter, separate listings of all abnormal laboratory findings will be provided, and clinically significant abnormalities will be recorded as AEs.

7.3.3 Efficacy Analyses

All efficacy analyses will be based on the mITT Population. The proportion of subjects experiencing pain freedom, most bothersome other symptom freedom, pain relief, nausea freedom, photophobia freedom, phonophobia freedom, those using rescue medication, those with sustained pain freedom, and those with migraine recurrence will be summarized using descriptive statistics. Frequencies and percentages will be provided for all subject responses on the ACT. Further details regarding efficacy analyses can be found in the statistical analysis plan.

8 ADVERSE EVENTS

All systemic and cutaneous AEs, regardless of suspected causal relationship to the investigational products, will be reported as described in the following sections. Subject reported bruising, bleeding, erythema, edema, skin itching and skin pain are collected through the eDiary and will also be recorded as adverse events in the eCRF and followed to resolution.

For all systemic and cutaneous AEs, the investigator must obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (see Section 8.2.1.1) requiring immediate notification (within 24 hours) to the Medical Monitor (MM) and Pharmacovigilance Group (PV) by completing a SAE Report Form. Sufficient information should also be obtained by the investigator to determine the causality of the AE, since he/she is required to assess causality. For systemic and cutaneous AEs with a causal relationship to the investigational product, including **all** application site reactions, investigator is required to follow-up until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.

Pregnancy: In the event that a pregnancy occurs, it will not be considered an AE but requires notification within 24 hours of investigator awareness to the Medical Monitor and Pharmacovigilance Group by completing a Pregnancy Report Form. The investigator will follow the pregnancy and report the outcome. The subject will be discontinued from the study if she becomes pregnant anytime during the study.

8.1 Reporting Period

Collection of systemic and cutaneous AEs will be initiated after the ICF has been signed and will conclude when the post-study procedures are completed (or Early Discontinuation). The investigator will also report to the Medical Monitor and Pharmacovigilance any SAEs that come to his/her attention that occur within 30 days after study drug administration.

8.2 Adverse Event Definitions

8.2.1 Adverse Events (Adverse Experiences)

Collection of systemic and cutaneous AEs will be initiated after the ICF has been signed and conclude when the post-study procedures are completed (or Early Discontinuation). This includes the time between screening and the first patch application.

An AE is any untoward medical event that occurs in a clinical investigation, where a subject is administered a medicinal (investigational) product or medical device, and which does not necessarily have a causal relationship between the event and the treatment. An AE can be any

unfavorable and unintended sign or symptom, including clinically significant abnormal laboratory result, concomitant illness, or worsening of an existing medical condition.

A Treatment Emergent Adverse Event (TEAE) is an event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state.

Abnormal laboratory tests that are clinically significant, as determined by the investigator, should be reported as AEs if:

- the test result is associated with accompanying symptoms;
- the test result requires additional diagnostic testing or medical/surgical intervention;
- the test result leads to discontinuation from the study, significant additional concomitant drug treatment, or other therapy;
- the test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.2.1.1 Serious Adverse Event Definitions

A **serious** adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization (Emergency department outpatient visits for an event not fulfilling any of the other definitions of SAE given do not qualify as hospitalization. If an emergency department visit leads to inpatient hospitalization, it would qualify as an SAE.);
- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect.
- Other important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such

medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Definition of disability: A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening SAE: Any AE that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death).

Hospitalization: AEs reported from clinical studies resulting in hospitalization or prolongation of hospitalization are considered serious. Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency department admissions; or
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly PE); or
- Pre-planned treatments or surgical procedures that have been noted in the baseline documentation for the entire protocol and/or for the individual subject.

8.2.1.2 Unexpected Adverse Event

An unexpected AE is any AE the nature or severity of which is not consistent with the applicable product information (e.g., current investigator's brochure); or if an investigator's brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

8.2.1.3 Severity Ratings

The investigator will evaluate the severity of each AE using the following definitions:

Mild - event may be noticeable to subject; does not influence daily activities; usually does not require intervention.

Moderate - event may be of sufficient severity to make a subject uncomfortable; performance of daily activities may be influenced; intervention may be needed.

Severe - event may cause severe discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or other intervention usually needed.

Life-Threatening – Event that, in the view of the investigator, places the subject at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death).

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above. Additionally, an SAE of abdominal pain in an elderly patient that results in hospitalization to rule out diverticulitis may be mild, whereas severe abdominal pain (that interferes with most daily activities) in a younger, stoic patient may not result in hospitalization, and thus be a severe non-serious AE.

8.2.1.4 Relationship to Study Drug

The investigator's assessment of causality must be provided for all systemic and topical AEs (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility or likelihood that the investigational product caused or contributed to an AE. If the investigator's final determination of causality is unknown and the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. Thus, it is

imperative that all initial SAE reports include an assessment of causality. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

After careful medical consideration, the investigator will evaluate the relationship of each AE to study drug applying the following definitions:

Probably Related

An AE that is likely due to the use of the study drug. The relationship in time is suggestive. An alternative explanation is unlikely, e.g., concomitant drug(s), concurrent illness(es).

Possibly Related

An AE that might be caused by the use of the study drug. The relationship in time is reasonable; therefore, a causal relationship cannot be excluded. An alternative explanation is inconclusive, e.g., concomitant drug(s), concurrent illness(es), but unlikely.

Not Related

An AE that is judged to be clearly due only to extraneous causes (disease or illness, environment, etc.).

The cause must be noted on the appropriate source document and on the AE CRF page.

8.3 Documentation and Reporting of Adverse Events by Investigator

Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

All AEs, both expected and unexpected, occurring during this clinical trial must be recorded on the AE page of the eCRF. AEs will be described in precise medical terms, along with the date and time of onset and the date and time of resolution, action taken and outcome. In order to avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words. Whenever possible, the Investigator should group together into a single term signs and symptoms which constitute a single diagnosis. Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the investigational drug. The severity of the AE and its relationship to the test product will be

assessed by the Investigator. When reporting SAEs, the AE form of the eCRF and the SAE form must be completed in a consistent manner. For example, the same AE term should be used on both forms.

8.3.1 Reporting Requirements for Serious Adverse Events

ALL **SERIOUS** ADVERSE EVENTS, REGARDLESS OF CAUSE(S) OR RELATIONSHIP TO STUDY DRUG, MUST BE REPORTED **IMMEDIATELY** TO PHARMACOVIGILANCE GROUP (PV) AND MEDICAL MONITOR (MM) BY TELEPHONE (24/7 Safety Line), FAX, OR EMAIL (Contact info are provided in Section 8.5).

All SAE reporting will adhere to 21 CFR 312.32 for IND safety reporting, applicable FDA and ICH-GCP regulations.

If an SAE occurs, PV and MM are to be notified within 24 hours of awareness of the event by the investigator. In particular, if the SAE is fatal or life-threatening, notification to PV and MM must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports. An initial assessment of causality must be included in all SAE reports.

To report an SAE, the investigator must complete the SAE Report Form, and to report a pregnancy, the investigator must complete the Pregnancy Report Form. Occurrence of any SAE/pregnancy must be reported immediately (within 1 working day) once the investigative site has knowledge of the event. The investigator must also provide any relevant information regarding the SAE and respond to requests for follow-up in a timely manner. All SAEs will also be reported on the AE CRF page and concomitant medications administered in association with the SAE will be documented on the appropriate CRF.

If an SAE occurs and comes to the attention of the investigator after study termination within 30 days of the last dose of study drug(s), it must be reported immediately to the sponsor in the same way as the SAEs occurring during the study.

8.3.1.1 Investigator Reporting Responsibilities to the Independent Ethics Committee and Other Agencies

The investigator must promptly report to the IRB/IEC or independent ethics committees (IEC) all changes in the research activity and all unanticipated problems involving risk to human subjects or others. This includes all SAEs that have occurred at the study site and all study-related SAEs that have resulted in an expedited safety report to the FDA (serious, unexpected SAEs possibly or probably related to study drug). The investigator must send all IRB/IEC documentation (including notifications and acknowledgements) to the sponsor or its

designee. The investigator must not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

8.3.2 Reporting Requirements for Non-Serious Adverse Event

Non-serious systemic and skin AEs experienced after the randomization phase of the study will be reported on the AE CRF pages, which will be submitted to the sponsor or its designee.

8.4 Follow up of Adverse Events

All SAEs must be followed up until resolution or, in the investigator's opinion, a stable condition is reached, or until the subject is lost to follow up. All follow up reports should be made by completing the SAE Report Form and by utilizing the same reporting procedures as the initial report.

Based on the medical judgment of the investigator, all non-serious systemic and skin AEs will be followed until 14 days after the final two week safety follow-up visit. All non-resolved, non-serious systemic and skin AEs beyond such date will be recorded as "ongoing" without further follow up.

8.5 Contacts for Serious Adverse Events and Medical Monitoring

In case of an SAE or any medical-related issues, the investigator will contact the medical monitor at any time.

Medical Monitor: Pete Schmidt, MD
Tel: 510-745-1251

For SAE Reporting, the investigator will send the SAE Report Form to the PV Group (24/7 Safety Line) by one of the following:

- Fax: 1-877-464-7787 (US toll-free)
- Scanned and emailed: INCDrugSafety@INCResearch.com

9 EMERGENCY PROCEDURES

9.1 Emergency Contact

In emergency situations, the investigator should contact the medical monitor by telephone at the numbers listed on the title page of the protocol. If an SAE occurs, the PV Group is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the SAE is fatal or life-threatening, notification to the PV Group and the sponsor must be made immediately, irrespective of the extent of available AE information.

9.2 Unblinding Procedures

Not applicable. There is no blinding of treatment assignment in this study.

9.3 Emergency Treatment

During and following a subject's participation in the study, the investigator/institution should ensure that adequate medical care is provided to a subject for any systemic or topical AEs, including clinically significant laboratory values, related to the study. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

10.1 Study Monitoring

The study will be monitored by the Sponsor and/or Sponsor's representatives at all stages of study conduct from inception to completion in accordance with current GCPs. This monitoring will be in the form of site visits and other communication and will include review of original source documents and eCRFs. The Sponsor's monitor or representative will notify the Principal Investigator prior to conducting any investigational site visit. The frequency of these visits will depend upon the progress of the study, and will include monitoring to assess facilities and equipment, recruiting, record-keeping, protocol adherence, data collection, AE reporting and other factors.

10.2 Audits and Inspections

The clinical site will be subject to audit and inspection by the Sponsor or designee during or at the end of the study as appropriate.

The Investigator will permit representatives of Zosano's monitoring team or FDA/local health authority auditors to inspect facilities and records relevant to this study.

10.3 Institutional Review Board (IRB)/Independent Committee

This protocol will be submitted to an appropriate central or local IRB/IEC and its written unconditional approval obtained and submitted to Zosano or its designee before arrival of the first subject.

Zosano will supply relevant data for Investigators to submit to the IRB/IEC for the protocol's review and approval. Written verification of IRB/IEC unconditional approval of the protocol and the subject Informed Consent Form (ICF) will be transmitted to Zosano or its designee prior to granting access to the eCRF to study sites. This approval must refer to the study by exact protocol title and number, identify documents reviewed and state the date of approval.

The Investigator must promptly report to the IRB/IEC all changes in the research activity and all unanticipated problems involving risk to human subjects or others. This includes all SAEs that have resulted in an expedited safety report to the FDA (serious, unexpected AEs possibly related to study drug). Concurrently, the Investigator must send the study Sponsor documentation of such IRB/IEC notification and acknowledgement(s). The Investigator must not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

10.4 Participant Recruitment

If an Investigator chooses to advertise for subjects, whether in professional or consumer publications, radio, or television, all advertising must be approved by Zosano and the IRB/IEC prior to initiation.

11 QUALITY CONTROL AND QUALITY ASSURANCE

The clinical site will be monitored routinely to ensure GCP compliance. The eCRF will be verified against the source document and any queries concerning the eCRF will be generated and resolved/reconciled to assure data integrity, and to assure clean data before study close out. The clinical site may be audited by the Sponsor or Sponsor designee for quality control and quality assurance purposes. The clinical site may also be audited by the regulatory agency.

12 ETHICS

12.1 Ethics Review

The IRB/IEC will review and approve the study protocol, the ICF and other relevant substantive data before the study is initiated. A copy of the IRB/IEC approval letter for the protocol and the consent form/subject information sheet which specifically identifies the protocol name and the Zosano protocol number, must be sent to Zosano (or designee) prior to initiating the study. Subsequently, the Investigator is responsible for keeping the IRB/IEC advised of the progress of the study as deemed appropriate but, in any case, at least once a year during the course of the study and for keeping the IRB/IEC informed of any significant adverse reactions.

12.1.1 Ethical Conduct of the Study

This study will be conducted in strict compliance with GCP, IRB/IEC and other relevant regulatory requirements. The Investigator must ensure that each subject's anonymity is maintained as described within this protocol. On the eCRFs or other documents submitted to Zosano or its designee, subjects must be identified only by their initials and a subject number. Documents that are not for submission to Zosano and/or its designee (i.e., signed ICFs) should be kept in strict confidence by the Investigator, in compliance with Federal regulations and ICH GCP Guidelines. The Investigator and institution must permit authorized representatives of Zosano or its designee, or the regulatory agencies and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are needed for the evaluation of the study. The Investigator is obligated to inform the subject in the ICF that his/her study-related records will be reviewed by the above named representatives.

12.2 Written Informed Consent

Prior to study inception, each study participant (or legally authorized representative) will be required to read, sign and date an IRB/IEC-approved ICF that explains the nature, purpose, possible risks and benefits, and the duration of the study. The study staff member who participated in the consent discussion with the participant must also sign and date the ICF. Each participant will be given a copy of the ICF.

The Investigator or designee shall give either the subject or the subject's legally authorized representative adequate opportunity to read the ICF before it is signed and dated.

The ICF must contain the subject's dated signature or the signed and dated signature of the subject's legally authorized representative (if applicable). In addition, the dated signature of the person who conducted the informed consent discussion will also be documented on the consent

form. Each subject's signed ICF must be kept on file by the Investigator and be available for possible inspection by regulatory authorities, and/or the study Sponsor or the regulatory compliance monitor, or the IRB/IEC. All subjects will be informed of the nature of the program, its possible hazards, and their rights to withdraw at any time from the study without prejudice and without jeopardy to the subject's future medical care at the center. Documentation of the informed consent and subject information discussion must appear in the subject's medical record. HIPAA authorization must also be provided (if applicable).

A copy of the IRB/IEC-approved ICF must be sent to Zosano or designee.

Each subject must agree to cooperate in all aspects of the study and must give informed written acknowledgment (ICF) to the Investigator for participation.

Signed acknowledgments (ICF) must remain in the subject's file and be available for verification by monitors at any time.

12.3 Disclosure of Data

Individual subject medical information obtained as a result of this study is considered confidential, and disclosure to third parties other than those noted below is prohibited. Subject confidentiality will be further assured by utilizing subject identification code numbers to correspond to treatment data in the computer files.

However, such medical information may be given to the subject's personal physician, or to other appropriate medical personnel responsible for the subject's welfare.

In addition, data generated as a result of this study are to be available for inspection upon request by FDA or local health authority auditors, the Sponsor's monitors, or by the IRB/IEC. Therefore, absolute confidentiality cannot be guaranteed.

13 DATA HANDLING AND RECORDKEEPING

13.1 Inspection of Records

All study-related documents and records are subject to inspection and audit by the Sponsor (or designee), and by the FDA, IRB/IEC or other relevant regulatory bodies. The Statement of Investigator Form FDA 1572 and/or appropriate local health authority documents authorize the FDA or local health authority to inspect the data where the clinical trial was conducted.

The Investigator/institution guarantees access to source documents by the study Sponsor or its designee, the FDA, other regulatory bodies and the IRB/IEC. It is important that the Investigator and other study personnel are available during the monitoring visits, and that sufficient time is devoted to the process. If the FDA or local health authority should schedule an inspection, Zosano's Clinical Operations and Regulatory Affairs departments should be advised prior to the time this inspection is to occur.

13.2 Case Report Forms

All clinical study data will be collected by the Investigator and staff, recorded on source documents and captured electronically in the proprietary subject e-source application, if appropriate. Clinical data includes the following: demographics, history, physical examination, vital signs, clinical laboratory test results, safety ECGs, adverse event queries, adverse events, and concomitant medication queries.

The data will be directly recorded on or transcribed to the study-specific eCRF. The clinical investigator(s) will assume responsibility (by electronically signing the eCRF) for ensuring the completeness and accuracy of all clinical documents.

Staff at each investigator site will perform data entry into the eCRF. Study subjects will perform data entry in response to questions on the eDiary. The Remote Data Capture (RDC) database that has been validated for this protocol will automatically generate data discrepancy notices within the system that will be identified to the clinic for resolution. A list of all data quality checks utilized in the validation of the data will be provided in the Data Management Plan (DMP). Query resolution will take place within the system and an audit trail will be attached to any data changes that will identify the user who is making the change and time that this change has occurred. The eCRF will be monitored against source documents by the Sponsor's representative and any subsequent data discrepancies identified will be captured within the CDMS.

The eCRF development and database validation programs will be documented in the Data Management Plan (DMP) and will be tested before the database is released for data entry. The

validation of the data once entered into the eCRF/database will occur dynamically or nightly dependent upon the type of edit check required. Any data discrepancies identified as a result of this validation routine will be documented.

13.3 Retention of Records

The Investigator must maintain adequate records for the study including completed eCRFs, medical records, laboratory reports, signed ICFs, drug disposition records, adverse event reports, information regarding subjects who discontinued, all correspondence with the IRB/IEC and the Sponsor (or designee) and other pertinent data.

All records are to be retained by the Investigator as required by applicable law or regulation.

To avoid any possible errors, the Investigator must contact Zosano (or designee) prior to the destruction of any study records. The Investigator will also notify Zosano (or designee) in the event of accidental loss or destruction of any study records.

14 REFERENCES

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APPENDIX 1 – Fitzpatrick Skin Type Chart (Subject Completed)

Add up the score for each of the questions. At the end, there is a scale providing a range for each of the skin-type categories.

Genetic Disposition

Score	0	1	2	3	4
What is the colour of your eyes?	Light blue, Grey, Green	Blue, Grey or Green	Blue	Dark Brown	Brownish Black
What is the natural colour of your hair?	Sandy Red	Blond	Chestnut/Dark Blond	Dark Brown	Black
What is the colour of your skin (non exposed areas)?	Reddish	Very Pale	Pale with Beige tint	Light Brown	Dark Brown
Do you have freckles on unexposed areas?	Many	Several	Few	Incidental	none

Total score for Genetic Disposition: _____

Reaction to Sun Exposure

Score	0	1	2	3	4
What happens when you stay in the sun too long?	Painful redness, blistering, peeling	Blistering followed by peeling	Burns sometimes followed by peeling	Rare burns	Never had burns
To What degree do you turn brown?	Hardly or not at all	Light colour tan	Reasonable tan	Tan very easy	Turn dark brown quickly
Do you turn brown within several hours after sun exposure?	Never	Seldom	Sometimes	Often	Always
How does your face react to the sun?	Very sensitive	Sensitive	Normal	Very resistant	Never had a problem

Total score for Reaction to Sun Exposure: _____

Tanning Habits

Score	0	1	2	3	4
When did you last expose your body to sun (or artificial sunlamp/tanning cream)?	More than 3 months ago	2-3 months ago	1-2 months ago	Less than a month ago	Less than 2 weeks ago
Did you expose the area to be treated to the sun?	Never	Hardly ever	Sometimes	Often	Always

Total score for Tanning Habits: _____

Add up the total scores for each of the three sections for your Skin Type Score.

Skin Type Score - Fitzpatrick Skin Type

0-7	I
8-16	II
17-24	III
25-30	IV
over 30	V -VI

TYPE 1: Highly sensitive, always burns, never tans. Example: Red hair with freckles
TYPE 2: Very sun sensitive, burns easily, tans minimally. Example: Fair skinned, fair haired Caucasians
TYPE 3: Sun sensitive skin, sometimes burns, slowly tans to light brown. Example: Darker Caucasians.
TYPE 4: Minimally sun sensitive, burns minimally, always tans to moderate brown. Example: Mediterranian type Caucasians, some Hispanics.
TYPE 5: Sun insensitive skin, rarely burns, tans well. Example: Some Hispanics, some Blacks
TYPE 6: Sun insensitive, never burns, deeply pigmented. Example: Darker Blacks.

APPENDIX 2 – The Migraine Assessment of Current Therapy (Migraine-ACT)

Subject Questions related to their M207 study medication:

When you take your treatment: Does your migraine medication work consistently, in the majority of your attacks? Yes or No.

When you take your treatment: Does the headache pain disappear within 2 hours? Yes or No.

When you take your treatment: Are you able to function normally within 2 hours? Yes or No.

When you take your treatment: Are you comfortable enough with your medication to be able to plan your daily activities? Yes or No.

APPENDIX 3 – eDiary Questions

Most Bothersome Symptom (To be completed when site is setting up the eDiary for the subject)

- Ask the subject what his/her most bothersome symptom is. This is the symptom other than pain that is most bothersome most of the time with their migraine. (Sick to their stomach, sensitive to light, sensitive to sound/noise)

Run-in Period Diary, Nightly Questions (Start the evening of Visit 2)

- Did you have a headache in the past 24 hours? (Yes, No)
- *If No is answered for bullet one question*
    - Did you experience excessive yawning today? (Yes, No)
    - Did you experience mood changes today? (Yes, No)
    - Did you experience excessive fatigue (tiredness) today? (Yes, No)
- *If yes, please answer the following questions based on your headache symptoms in the last 24 hours:*
    - How bad was your headache pain at its worst? (Mild, Moderate, Severe)
    - Was the headache pain on only one side of your head? (Yes, No)
    - Was the headache pulsating (throbbing)? (Yes, No)
    - Did activity make your headache get worse? (Yes, No)
    - Were you nauseated (sick to your stomach)? (Yes, No)
    - Did you vomit (throw up)? (Yes, No)
    - Did light bother you? (Yes, No)
    - Did sound or noise bother you? (Yes, No)
    - Did you take any medication to treat your headache? (Yes, No)

Migraine Treatment Diary (Starts at Day 1 when subject feels he/she is experiencing a migraine attack)

Please fill in your diary when you feel you are experiencing a migraine attack

- Are you currently experiencing a migraine attack? (Yes, No)
- How bad is your headache pain? (Mild, Moderate, Severe)
- Is the headache pain on only one side of your head? (Yes, No)
- Is the headache pulsating (throbbing)? (Yes, No)
- Does activity make your headache pain get worse? (Yes, No)
- Are you nauseated (sick to your stomach)? (Yes, No)
- Did you vomit (throw up)? (Yes, No)
- Does light bother you? (Yes, No)
- Does sound or noise bother you? (Yes, No)
- Have you taken any medication to treat your headache? (Yes, No)
- Were you experiencing an aura (e.g., flickering light, flashes, or spots) at the start of headache? (Yes, No)
- What day and time did your headache start? (Today, Yesterday) Choose time
- Did you wake up with this headache? (Yes, No)
- eDiary confirms whether this is a qualified migraine and instructs subject to apply the patches:
- *If a non-qualifying migraine:*
    - The following text shows - DO NOT APPLY THE PATCHES. YOU **HAVE NOT** REPORTED a qualifying migraine. Please save your answers and return to the diary next time you think you are experiencing a migraine attack.
- *If a qualifying migraine:*
    - The following text shows - You have reported a qualifying Migraine. Please apply the patches now. **After applying the patches**, press next to answer the remaining questions.
- Where were the study drug patches applied? (Both to left arm, Both to right arm, Other)
    - If Other is checked for above question – the following text shows - You have applied the patches incorrectly. Both patches must be applied. What was the

reason for not applying both? (Applied one patch to left arm, Applied one patch to right arm, Technical problem with applicator and/or patch, None were applied)

Questions at the 30-minute diary post patch application

Please remove the patches from your upper arm, fold in half, and discard

- How bad is your headache pain? (None, Mild, Moderate, Severe)
- Are you nauseated (sick to your stomach)? (Yes, No)
- Did you vomit (throw up)? (Yes, No)
- Does light bother you? (Yes, No)
- Does sound or noise bother you? (Yes, No)
- Since applying the patches, did you take any medication to treat your migraine other than the patches you applied?
- After removing the patches, how much redness do you see on the skin? (None, Mild redness, Moderate colored redness, Beet colored redness)
- After removing the patches, how much swelling do you see? (None, Slight swelling, Moderate swelling, Severe swelling)
- After removing the patches, how much bruising of the skin do you see? (None, Less than a quarter of the application site has bruising spots, About one-half of the application site has bruising spots, More than one-half of the application site has bruising spots)
- After removing the patches, how much bleeding do you see? (None, pink color on skin, visible blood drop, active bleeding)

Post patch application: 2, 12, 24, 48 hours post patch application

- How bad is your headache pain? (None, Mild, Moderate, Severe)
- Are you nauseated (sick to your stomach)? (Yes, No)
- Did you vomit (throw up)? (Yes, No)
- Does light bother you? (Yes, No)
- Does sound or noise bother you? (Yes, No)
- Since applying the patches, did you take any medication to treat your migraine other than the patches you applied? (Yes, No)
- At the patch application sites, how much redness on the skin do you see now? (None, Mild redness, Moderate colored redness, Beet colored redness)
- At the patch application sites, how much swelling on the skin do you see now? (None, Slight swelling, Moderate swelling, Severe swelling)
- At the patch application sites, how much bruising of the skin do you see now? (None, Less than a quarter of the application site has bruising spots, about one-half of the application site has bruising spots, more than one half of the application site has bruising spots)

Post patch application: Additional questions at 48 hour only

- Do you have any skin itching at the application sites? (None, Mild itching, Moderate itching, Sever itching)
- Do you have any skin pain at the application sites? (None, Mild pain, Moderate pain, Severe pain)

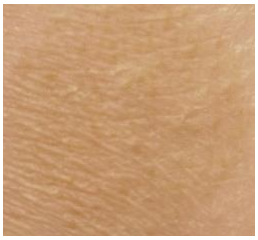
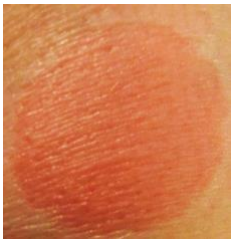
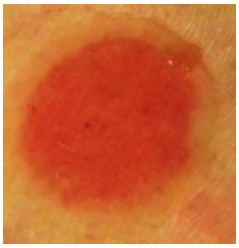
Post patch application: 48 hour notification

- The following text shows – If you are experiencing any skin reaction which worsens rather than improves in the next 5 days, please contact your study physician

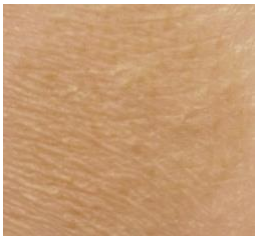
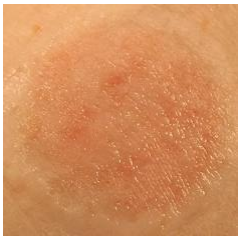
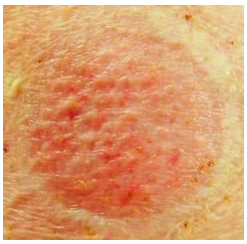
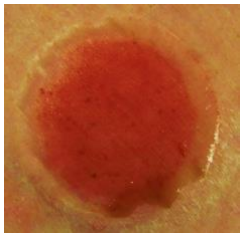
APPENDIX 4 – Subject Skin Grading Card

- Subject Instructions:
  - Use the images and text descriptions to best grade any skin effects you may be seeing.
  - Select the options in your eDiary that best correspond to what you are seeing. The eDiary options are listed above the photographs for your reference.
  - Please contact your research site if you experience what you consider to be a serious or severe skin reaction at any time
  - Please contact your research site for worsening or non-resolving skin effects present at 72-hours (3 days) after applying the patches
  - When you return to the clinic, you will be expected to tell your study physician how long the skin effects lasted.

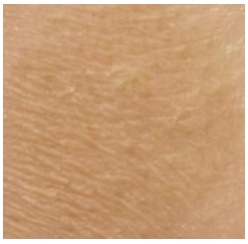
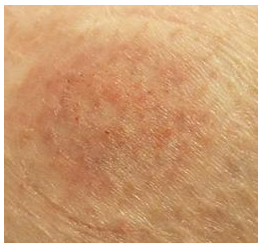
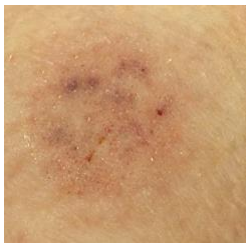
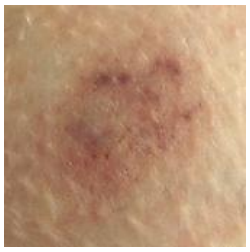
Redness

None	Mild redness	Moderate colored redness	Beet colored redness
			
	Faintly detectible, very light color	Dull red, clearly distinguishable	Deep, dark red

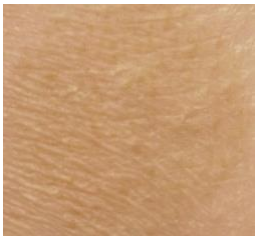
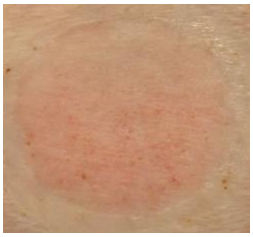
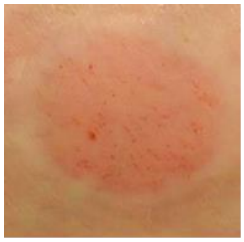
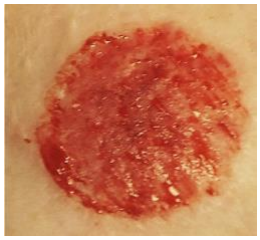
Swelling

None	Slight swelling	Moderate swelling	Severe swelling
			
	Barely perceptible elevation of skin	Clearly perceptible elevation of skin limited to the application site	Significant elevation of skin, extending beyond the application site

Bruising

None	Less than a quarter of the application site has bruising spots	About one-half of the application site has bruising spots	More than one-half of the application site has bruising spots
			

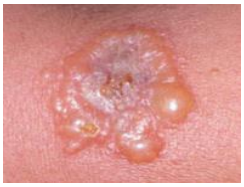
Bleeding

None	Pink color on skin	Visible blood drop	Active bleeding
			

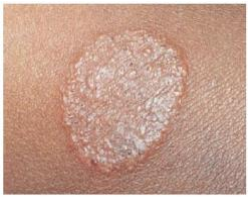
APPENDIX 5 – Investigator Assessments - Skin Signs or Symptoms and Photographs

As stated in Section 6.2.13.1 Investigator Skin Assessments will be made by the investigator at each in clinic visit starting at month 1. The entire surface area of the upper arm where patches have been applied will be assessed for the following signs or symptoms. Below are photographs depicting what these skin signs and symptoms may look like and how to describe them. Any findings will be recorded as an adverse event and followed to resolution.

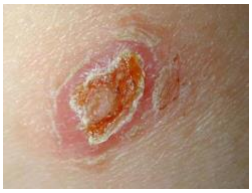
Blisters or pustules: If present, describe the number size and location



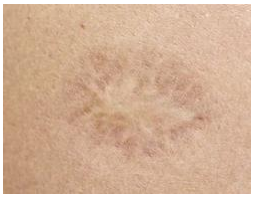
Scaly or flakey skin: If present, describe the color of scale (white, yellow, hemorrhagic), thickness of scale (fine or thick), amount (minimal/trace to over more than half of the lesion)



Erosions or open sores: If present, describe the size and whether there is any crusting

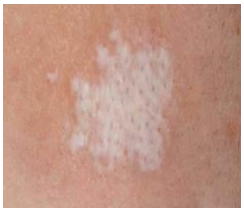


Scarring: If present, desribe size, color (erythematous, hypopigmented, hyperpigmented), thickness, shape (whether limited to area of application or extends beyond)



Hyperpigmentation or Hypopigmenation: If present, desribe color (tan, brown, black, blue, gray, white), size (for example greater or less than 1 cm), and distribution (limited to application sites or beyond application sites)


Hyperpigmentation


Hypopigmentation

APPENDIX 6 – Investigator Assessment Photography Rating for Bruising, Erythema, Edema and

The Bruising, Erythema, and Edema assessment will be performed by the investigator at each in clinic visit starting at Month 1 and performed using the following ratings. When determining the percentage of application sites affected for a given sign, the investigator should consider the entire outer arm from the top of the shoulder to the elbow as the denominator. Any findings with ratings of 1 (mild), 2 (moderate), or 3 (severe) must be recorded as an adverse event in the eCRF and followed to resolution. The investigator will use the definitions of AE Severity Ratings for Mild, Moderate, Severe, Life-Threatening (Section 8.2.1.3) to assess the Severity of the AE.

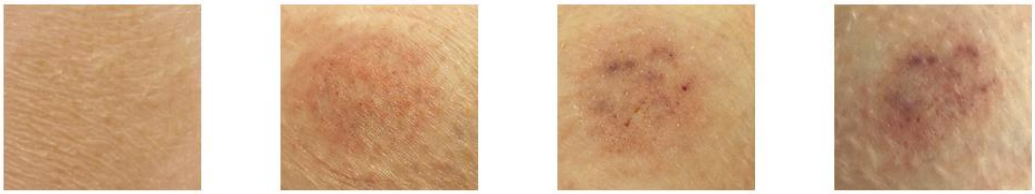
Symptom	Rating (circle)
M207 application sites have bruising spots?	0 (clear) = None 1 (mild) = ≤ 25% Present in the upper arm region of all M207 applications 2 (moderate) = ≥ 26 to ≤ 50% Present in the upper arm region of all M207 applications 3 (severe) = > 50% Present in the upper arm region of all M207 applications

Symptom	Rating (circle)
Skin Erythema	0 (clear) = None 1 (mild) = ≤ 25% Present in the upper arm region of all M207 applications 2 (moderate) = ≥ 26 to ≤ 50% Present in the upper arm region of all M207 applications 3 (severe) = > 50% Present in the upper arm region of all M207 applications

Symptom	Rating (circle)
Skin Edema	0 (clear) = None 1 (mild) = ≤ 25% Present in the upper arm region of all M207 applications 2 (moderate) = ≥ 26 to ≤ 50% Present in the upper arm region of all M207 applications 3 (severe) = > 50% Present in the upper arm region of all M207 applications

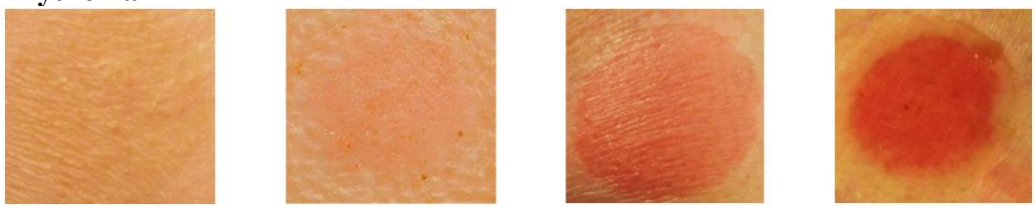
The photographs below for bruising, erythema, and edema are examples for the investigator as to what these skin reaction(s) in the upper arm region may look like. The investigator will use the definitions of AE Severity Ratings for Mild, Moderate, Severe, Life-Threatening (Section 8.2.1.3) to assess the Severity of the AE.

Bruising



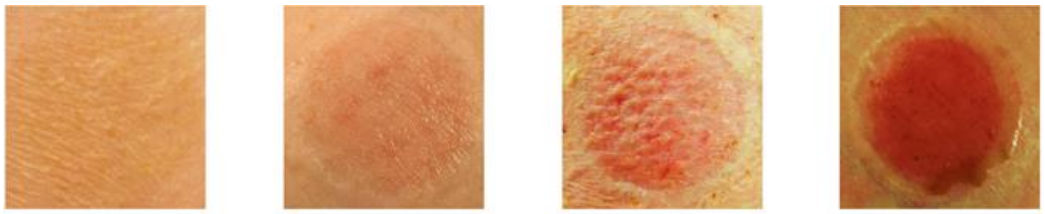
None (Clear) Mild Moderate Severe

Erythema



None (Clear) Mild Moderate Severe

Edema



None (Clear) Mild Moderate Severe