ZOSANO PHARMA

CLINICAL PROTOCOL

STUDY TITLE:	A randomized open-label four-way crossover study to compare the pharmacokinetics, safety, and tolerability of M207 3.8 mg (administered as two 1.9 mg patches) at two different application locations (upper arm and thigh) for 30 minutes with intranasal zolmitriptan 2.5 mg and 1 hour wear time (upper arm) in healthy volunteers
PROTOCOL NUMBER:	CP-2018-002
PROTOCOL VERSION:	1.0
PROTOCOL DATE:	12 September 2018
STUDY DRUG:	M207 Intracutaneous Microneedle Patch System
SPONSOR:	Zosano Pharma Corporation 34790 Ardentech Court Fremont, CA 94555 United States
SPONSOR CONTACT:	Peter Schmidt, MD, MSc 34790 Ardentech Court Fremont, CA 94555 United States

ZOSANO PHARMA

Clinical Protocol
SPONSOR APPROVAL PAGE

Protocol CP-2018-002

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Protocol Version: 1.0

Version Date: 12 September 2018

Protocol approved by:

Hayley Lewis
Senior Vice President, Operations Regulatory **Date**

	12 Sep 18

Donald Kellerman
Vice President, Clinical Development and Medical Affairs **Date**

	12-Sep-2018

Peter Schmidt, MD
Sr. Director Medical Affairs and Medical Monitor **Date**

	12 Sep 2018

PROTOCOL SIGNATURE PAGE - PRINCIPAL INVESTIGATOR

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Protocol Date: 12 September 2018

I have received and read the protocol dated 12 September 2018. I agree to undertake the protocol as defined therein. 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 and the Institutional Review Board/Independent Ethics Committee, except those changes necessary to eliminate apparent immediate hazards to subjects. Failure to adhere to these stipulations may constitute a breach of ICH-R Guidelines and 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

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{30min}	Area under the curve from minute 0 to minute 30
AUC_t	Area under the curve from 0 hours to the last measureable concentration
AUC_{inf}	Area under the curve extrapolated to infinity
BMI	Body Mass Index
BP	Blood pressure
BSAP	Bone specific alkaline phosphate
C	Celsius
CBC	Complete blood count
C_t	Concentration at time t
CFR	Code of Federal Regulations
CM	Concomitant medication
cm^2	Centimeter squared
C_{max}	Maximum observed plasma concentrations
CPK	Creatinine phosphokinase
CRF	Case report form
dL	Deciliter
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
F	Fahrenheit
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
H	Hour
HCl	Hydrochloride
HRT	Hormone replacement therapy
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IM	Intramuscular
IRB	Institutional Review Board
IV	Intravenous

Abbreviation	Definition
J	Joules
k	Apparent elimination rate constant
kg	Kilogram
KIU	Kilo international units
µg	Microgram
L	Liter
LDH	Lactate dehydrogenase
µm	Micrometer
M207	Intracutaneous Microneedle System (M207)
mL	Milliliters
mmol	millimole(s)
NSAID	Nonsteroidal anti-inflammatory drug
PD	Pharmacodynamics
PE	Physical examination
PK	Pharmacokinetics
PPI	Proton pump inhibitors
PRSPB	Bruising
PTH	Parathyroid hormone
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
$t_{½}$	Apparent half life
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
ZP	Zosano Pharma
M207	Zosano intracutaneous microneedle system containing zolmitriptan

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PROTOCOL SYNOPSIS

TITLE	A randomized open-label four-way crossover study to compare the pharmacokinetics, safety, and tolerability of M207 3.8 mg (administered as two 1.9 mg patches) at two different application locations (upper arm and thigh) for 30 minutes with intranasal zolmitriptan 2.5 mg and 1 hour wear time (upper arm) in healthy volunteers
SPONSOR	Zosano Pharma
CLINICAL PHASE	Phase 1 – Single Center
INDICATION	Acute Treatment of Migraine
OBJECTIVES	1. To compare the pharmacokinetics, safety and tolerability of M207 3.8 mg administered to either the upper arm or thigh, particularly with respect to skin irritation (erythema, edema, bruising, bleeding) 2. To compare the pharmacokinetics, safety and tolerability of M207 3.8 mg worn for either 30 minutes or 1 hour on the upper arm 3. To compare the pharmacokinetics, safety and tolerability of M207 3.8 mg to intranasal zolmitriptan 2.5 mg
TREATMENTS	• Treatment A: M207 3.8 mg administered as two 1.9 mg patches, 30 min wear time (upper arm application) • Treatment B: M207 3.8 mg administered as two 1.9 mg patches, 30 min wear time (thigh application) • Treatment C: M207 3.8 mg administered as two 1.9 mg patches, 1 hour wear time (upper arm application) • Treatment D: Intranasal zolmitriptan 2.5mg
BLINDING	Open-label
RANDOMIZATION	Randomized to the sequence of treatments
STUDY POPULATION	Healthy volunteers (females and males)
NUMBER OF SUBJECTS	24 (12 females; 12 males)

ELIGIBILITY

Inclusion Criteria

1. Women or men 18 to 50 years of age
2. Good general health with no clinically significant abnormalities as determined by medical history, physical examination, CBC, blood chemistry, urinalysis, and ECG.
3. Negative urine drug and alcohol screens and negative serum pregnancy tests (for female subjects) at screening
4. Consent of female subjects to use a medically effective method of contraception throughout the entire study period and for 30 days after the subject completes the study. Medically effective methods of contraception that may be used by the subject include abstinence, use of diaphragm and spermicide, intrauterine device (IUD), condom and vaginal spermicide, hormonal contraceptives (subjects must be stable on hormonal contraceptives for at least the prior 3 months), surgical sterilization, and post-menopausal (≥ 2 years of amenorrhea).
5. Ability to read, understand, and provide written informed consent that they understand the purpose of the study and procedures required for the study before enrolling in the study, and willingness to comply with all study procedures and restrictions.

Exclusion Criteria

1. Evidence of significant history of hepatic, reproductive, gastrointestinal, renal, bleeding, or hematological disorders including coagulation, pulmonary, neurological, respiratory, endocrine, or cardiovascular system abnormalities (especially hypertension, peripheral vascular disease, coronary artery disease, transient ischemic attacks, or cardiac rhythm abnormalities), psychiatric disorders, acute infection, or other conditions that would interfere with study participation or with the absorption, distribution, metabolism, or excretion of drugs.
2. Presence of two or more risk factors for cardiovascular disease (family history of premature heart disease, hyperlipidemia, or hypertension)
3. Any contraindication to zolmitriptan administration including:
    - History of coronary artery disease or coronary vasospasm

- Symptomatic Wolf-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine
- Peripheral Vascular Disease
- Ischemic bowel disease
- Uncontrolled hypertension
- Any history of hepatic impairment

4. History of contact dermatitis or known dermatological disorders that would interfere with the study procedures or assessments
5. Planned participation in activities which cause inflammation, irritation, sunburn, lesions, or tattoos at the intended application sites from 2 weeks prior to screening through their last day of study participation
6. Use of any prescription anticoagulant within 1 month prior to the first dose
7. Use of prescription and over the counter medications other than the following:
   - Hormone Replacement Therapy (HRT)
   - Birth control pills, patches, injections, or implants (all hormonal contraceptives) are allowed provided the dose has been stable for at least one month prior to screening and may be continued throughout the study
   - Proton Pump Inhibitors (PPis)
   - Antihistamines
   - Intermittently used NSAIDS
   - Acetaminophen if medically necessary (not more than 2 g/day)
   - Exceptions may be allowed on a case by case basis
8. Subjects who have a known allergy or sensitivity to zolmitriptan or its derivatives or formulations
9. Known allergy or sensitivity to tapes, adhesives, or zolmitriptan
10. Regular or recent intake of prescription drugs, particularly drugs with an influence on blood pressure

	11. Use of any other investigational compound within one month of planned study drug dosing 12. On-going drug or alcohol abuse, or history of either deemed to be clinically significant by the investigator 13. Systolic BP (measured after remaining sitting for 5 minutes) greater than 140 mmHg and diastolic BP greater than 90 mmHg 14. History of nasal pathology (e.g., polyps) or abnormal nasal exam 15. Body Mass Index (BMI) greater than 35 kg/m^2 16. If, in the opinion of the investigator, the subject is not suitable for the study 17. Any positive urine drug screen result or alcohol breath test
CENTERS	Single center
STUDY DURATION	Screening is 1 day (up to 30 days prior to dosing); in-clinic duration of study participation for each subject is approximately 2 weeks total (includes 4 treatment periods), and the final end of study visit occurs on one day.
PROCEDURES & ASSESSMENTS	• Physical examination (Screening, 12 hour post drug administration and end of study/or early termination visit) • Clinical laboratory tests (Screening, and end of study/or early termination visit) • Collection of blood samples (pre-dose, 2, 5, 10, 15, 20, 30, 45, 60, 90 min, 2 hr, 4 hr, 8 hr, 12 hr and 24 hr post-dose) for pharmacokinetics determination • Patch adhesion assessment at the time of application and at 30 min and 60 min post-dose (for 60 min wear time treatment group only) • Vital signs (Screening, pre-dose and 10 min, 60 min, 2 hr, 4 hr, 12 hr post-dose, and end of study/or early termination visit) • 12-lead ECGs (Screening, pre-dose, 15 min, 60 min, 8 hr, 12 hr post-dose, and end of study/or early termination visit) • Investigator visual skin assessment of the M207 application site at 30 min (for 30 min wear time treatment group only), 60 min (for 60 min wear time treatment group only), 12 hr, 24 hour post-dose, and end of study/or early termination visit

	• Residual zolmitripan swabbing on the skin at 30 min or 60 min (depending on wear time assignment)

1 INTRODUCTION

1.1 Background

Zosano Pharma has developed a zolmitriptan intracutaneous microneedle system as a potential therapy for the acute treatment of migraine. To date, two trials have been completed, a pharmacokinetic study in healthy volunteers, and a single treatment efficacy and safety study in subjects with migraine. A long-term safety study is ongoing. In all studies, the M207 system ("patch") was applied to the upper arm for 30 minutes.

1.2 Investigational Products

1.2.1 M207 Intracutaneous Microneedle System

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 witih 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.

M207 systems consist of zolmitriptan coated titanium array with an adhesive backing that is applied using proprietary patch applicators. Descriptions of the 1.9 mg patches used in the study are described below.

1.2.2 Zolmitriptan Nasal Spray

Zolmitriptan nasal spray is a commercially available product (Zomig® Nasal Spray) and will be purchased for use in this study. The dose used in this study will be 2.5 mg/0.1 ml. This dose should be administered to either the right or left nostril with the subject's head tilted slightly backward.

M207 1.9 mg Patch

The M207 1.9 mg consists of a 3 cm^2 titanium array of microprojections that are nominally 340 μm in length coated with 1.9 mg of zolmitripan. The array is applied to the center of a 5 cm^2 tan adhesive patch. The patch is attached to the interior of a white to off-white polycarbonate ring co-molded with a desiccant, packaged in a cup.

2 STUDY OBJECTIVES

The study objectives are as follows:

To compare the pharmacokinetics, safety and tolerability of M207 3.8 mg administered to the upper arm to M207 3.8 mg administered to the thigh, particularly with respect to skin irritation (erythema, edema, bruising, bleeding).

To compare the pharmacokinetics, safety and tolerability of M207 3.8 mg worn for 30 minutes on the upper arm to M207 3.8 mg worn for 1 hour on the upper arm.

To compare the pharmacokinetics, safety and tolerability of M207 3.8 mg to intranasal zolmitriptan 2.5 mg.

3 ETHICAL CONSIDERATIONS

This study must be conducted in compliance with the protocol; the U.S. Code of Federal Regulations (CFR); the International Conference on Harmonisation (ICH-R) Good Clinical Practice (GCP) Guidelines; the Declaration of Helsinki (see Appendix 5); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the study.

3.1 Institutional Review

Prior to the initiation of clinical studies, the protocol, the Informed Consent Form (ICF), amendments to the protocol and ICF, advertisements and any other information for subjects will be reviewed and approved by Zosano Pharma and by the Independent Ethics Committee (IEC) of the participating study center in accordance with the CFR, the ICH-R and institutional EC policies. All protocol amendments (See Section 11.1) and changes to the consent form occurring during the study must also be IRB/IEC approved.

3.2 Informed Consent

Prior to study inception, each study participant or the legally authorized representative will be required to read, sign, and date an IRB/IEC approved ICF explaining the nature, purpose, possible risks and benefits of the study, and the duration of an individual's participation in the study. The clinical site personnel who conducted the informed consent discussion must also sign and date the consent form. Each subject or legally authorized representative will be given a copy of the ICF.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a single-center, open-label, randomized, four-way crossover study. Each subject will receive each of the four study treatments once, followed by in-clinic monitoring and extensive blood sample collection for pharmacokinetic analysis.

Dosing will occur approximately 48 hours apart, until completion of dosing in randomized order per the treatment sequence tables. Plasma samples from the dosing days will be sent to the analytical laboratory for analysis and tolerability for each of the dose levels will be summarized.

After completion of the four dosing days, subjects will be assessed one final time and dismissed from the study.

4.2 Endpoints

The endpoints of the study are:

Safety and Tolerability

- Incidence of adverse events
- Change in physical exam findings from pre-dose to 12 hours post-dose
- Changes in vital signs from pre-dose to 10 min, 60 min, 2 hour, 4 hour, and 12 hour post-dose
- Changes in ECG parameters from pre-dose to 15 min, 60 min, 8 hour, and 12 hour post-dose
- Scores from a investigator visual skin assessment for erythema, edema, bruising and bleeding at the patch application sites from pre-dose to 30 min (for 30 min wear time treatment assignments only), 60 min (for 60 min wear time treatment assignment only), 12 hour and 24 hour post-dose
- Patch adhesion score at time of application at 30 min and 60 min post-dose (for 60 min wear time treatment assignment only)

Pharmacokinetics

- C_{max} - maximum observed plasma concentrations
- T_{max} - time to maximum concentration
- $AUC_{0\text{-}last}$ - the area under the plasma concentration time profile from hour 0 to the last detectable concentration at time t will be determined by the linear trapezoidal method.
- $AUC_{0\text{-}30min}$ - the area under the plasma concentration time profile from minute 0 to minute 30 will be determined by the linear trapezoidal method.

- $AUC_{0\text{-}60min}$ - the area under the plasma concentration time profile from minute 0 to minute 60 will be determined by the linear trapezoidal method.
- $AUC_{0\text{-}120min}$ - the area under the plasma concentration time profile from minute 0 to minute 60 will be determined by the linear trapezoidal method.
- k - apparent elimination rate constant will be estimated by linear regression of the log-transformed plasma concentrations during the terminal log-linear decline phase.
- $t_{1/2}$ - apparent half-life ($t_{1/2}$) values will be calculated as 0.693/k.
- $AUC_{0\text{-}inf}$ - the AUC value extrapolated to infinity will be calculated as the sum of AUC_t, and the area extrapolated to infinity, calculated by the concentration at time t (C_t) divided by k.
- Frel - bioavailability relative to other treatment sites of application and wear times

4.3 Safety Considerations

M207 consisting two patches each 1.9 mg (3.8 mg), 30 minute upper arm application, has been studied in healthy volunteers (in clinic) and subjects with migraine (outpatient). This regimen has been generally well-tolerated, with adverse events observed (dizziness and chest tightness) of those typically reported for triptans. Adverse events reported were almost always within the first few minutes after patch application. It is anticipated that systemic exposure with forearm application will be not significantly different than that seen with upper arm application, based on our experience with glucagon. Also, since C_{max} was generally observed, on average, at around 15 minutes, wearing the patches for 1 hours will probably not be associated with higher C_{max} levels than 30 minutes and should not result in different tolerability issues.

4.4 Study Population

The study population will consist of 24 healthy volunteers (12 women and 12 men) 18 to 50 years of age in general good health.

4.4.1 Inclusion Criteria:

1. Women or men 18 to 50 years of age.
2. Good general health with no clinically significant abnormalities as determined by medical history, physical examination, CBC, blood chemistry, urinalysis, and ECG.
3. Negative urine drug and alcohol screens and negative serum pregnancy tests (for female subjects) at screening.
4. Consent of female subjects to use a medically effective method of contraception throughout the entire study period and for 30 days after the subject completes the study. Medically effective methods of contraception that may be used by the subject include abstinence, use of diaphragm and spermicide, intrauterine device (IUD), condom and vaginal spermicide, hormonal contraceptives (subjects must be stable on hormonal contraceptives for at least the prior 3 months), surgical sterilization, and post-menopausal (≥ 2 years of amenorrhea).

5. Ability to read, understand, and provide written informed consent that they understand the purpose of the study and procedures required for the study before enrolling in the study, and willingness to comply with all study procedures and restrictions.

4.4.2 Exclusion Criteria:

1. Evidence of significant history of hepatic, reproductive, gastrointestinal, renal, bleeding, or hematological disorders including coagulation, pulmonary, neurological, respiratory, endocrine, or cardiovascular system abnormalities (especially hypertension, peripheral vascular disease, coronary artery disease, transient ischemic attacks, or cardiac rhythm abnormalities), psychiatric disorders, acute infection, or other conditions that would interfere with study participation or with the absorption, distribution, metabolism, or excretion of drugs.
2. Presence of two or more risk factors for cardiovascular disease (family history of premature heart disease, hyperlipidemia, or hypertension)
3. Any contraindication to zolmitriptan administration including:
    - History of coronary artery disease or coronary vasospasm
    - Symptomatic Wolf-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders
    - History of stroke, transient ischemic attack, or hemiplegic or basilar migraine
    - Peripheral Vascular Disease
    - Ischemic bowel disease
    - Uncontrolled hypertension
    - Any history of hepatic impairment
4. History of contact dermatitis or known dermatological disorders that would interfere with the study procedures or assessments
5. Planned participation in activities which cause inflammation, irritation, sunburn, lesions, or tattoos at the intended application sites from 2 weeks prior to screening through their last day of study participation
6. Use of warfarin within 1 month prior to the first dose or heparin within 1 week prior to study drug administration
7. Use of prescription and over the counter medications other than the following:
    - Hormone Replacement Therapy (HRT)
    - Birth control pills, patches, injections, or implants (all hormonal contraceptives) are allowed provided the dose has been stable for at least one month prior to screening and may be continued throughout the study
    - Antihistamines
    - Intermittently used NSAIDS

- Acetaminophen if medically necessary (not more than 2 g/day)
- Exceptions may be allowed on a case by case basis

8. Subjects who have a known allergy or sensitivity to zolmitriptan or its derivatives or formulations
9. Known allergy or sensitivity to tapes, adhesives, or zolmitriptan
10. Regular or recent intake of prescription drugs, particularly drugs with an influence on blood pressure.
11. Use of any other investigational compound within one month of planned study drug dosing
12. On-going drug or alcohol abuse, or history of either deemed to be clinically significant by the investigator
13. Systolic BP (measured after remaining sitting for 5 minutes) greater than 140 mmHg and diastolic BP greater than 90 mmHg at screening
14. History of nasal pathology (e.g., polyps) or abnormal nasal exam
15. Body Mass Index (BMI) greater than 35 kg/m^2
16. If, in the opinion of the investigator, the subject is not suitable for the study
17. Any positive urine drug screen result or alcohol breath test

4.5 Early Termination

Participation in the study is completely voluntary and a subject can choose to withdraw from the study at any time. In addition, a subject can be withdrawn for any of the following reasons: the Principal Investigator decides that continuing the drug may be harmful, a subject is non-compliant with the protocol, a subject has a serious reaction to the treatment, or the study is stopped by the Independent Ethics Committee, US Food and Drug Administration (FDA), or Zosano Pharma.

In order to complete all treatments for each dose, additional subjects may be enrolled to account for subjects who withdraw or are discontinued from the study. If a subject does not complete all planned treatments, the reason and date of withdrawal from the study must be recorded in the CRF. Zosano Pharma should be notified immediately if a subject withdraws prematurely from the study.

5 STUDY TREATMENTS

5.1 Study Drug Treatments

The treatments are:

- Treatment A: M207 3.8 mg administered as two 1.9 mg patches 30 min wear time (upper arm application)
- Treatment B: M207 3.8 mg administered as two 1.9 mg patches 30 min wear time (thigh application)
- Treatment C: M207 3.8 mg administered as two 1.9 mg patches 1 hour wear time (upper arm application
- Treatment D: zolmitriptan nasal 2.5 mg (single dose)

Depending on the treatment assignment, two M207 patches will be applied to the upper arm (shoulder area) or thigh by means of a handheld reusable applicator with an application energy of 0.26 Joules. Used patches will be removed 30 or 60 minutes after application, depending on the treatment wear time assignment. The patches will be collected and frozen in storage until shipped for analysis of remaining drug.

The applicator systems and unused patches should be stored at room temperature, not to exceed 15-30°C (59-86°F). Unused patches should not be refrigerated or frozen.

5.2 Study Treatment Assignment and Schedule

The 24 subjects are planned to receive each of the four treatments (A, B, C, D) 48 hours apart. Subjects will be randomly assigned to one of 4 treatment sequences.

At the end of each dosing day, the safety data from the subjects will be evaluated. If tolerability is deemed to be acceptable by the Principal Investigator, a decision will be made to proceed to the next dosing day.

5.3 Study Treatment Accountability Procedures

All transdermal M207 Patch System components are to be used only in accordance with this protocol under the supervision of the Investigator. The Investigator will maintain detailed and verifiable records that document the receipt, storage, dispensing, and return of all M207 Patch System components provided by Zosano Pharma. These records will include a listing of which study drug supplies were dispensed for particular subjects treated in the study, by whom, when, and the specific quantities dispensed and remaining at the completion of the subject's investigational treatment. Reasons for departure from the expected dispensing and dosing regimen will also be documented. All left over used and unused study patches should be retained for drug accountability auditing to be performed by Zosano Pharma or its representatives. At the conclusion of the study, the study drug accountability records must accurately reflect the receipt and final disposition of all study drug shipped to the site.

Destruction or return of remaining used and unused drug supplies by the study site will occur only upon receipt of written authorization by Zosano Pharma or its representatives.

5.4 Prior and Concomitant Medications Allowed and prohibited During the Study

Subjects will be asked to refrain from taking either prescription or OTC medications from the time of Screening until the completion of the study, except for those discussed in this section. All concomitant medications taken during the study will be recorded on the concomitant medications case report form (CRF) with indication for use, totally daily dosage, and dates of drug administration.

Subjects must discontinue use of herbal or over-the-counter medications (with the exception of all medications listed below) for 48 hours prior to treatment days and throughout the study.

Allowed prescription and over the counter medications:

- Hormone Replacement Therapy (HRT)
- Birth control pills, patches, injections, or implants (all hormonal contraceptives) are allowed provided the dose has been stable for at least one month prior to screening and may be continued throughout the study
- Intermittently used NSAIDS
- Acetaminophen may be administered if medically necessary (not more than 2 g/day)
- Antihistamines

All other concomitant medications will be prohibited, except as specifically exempted by the Sponsor on a case-by-case basis.

Excluded prescription medications:

Regular or recent intake of prescription drugs, particularly drugs with an influence on blood pressure are excluded.

6 STUDY VISIT SCHEDULE AND ASSESSMENTS

Following review of all Screening procedures, eligible subjects will be enrolled into the dosing phase of the study. The interval between screening and first treatment may be up to 30 days. Eligible subjects will check into the clinic on the day before each treatment and are required to stay approximately 36 hours at the clinic for preparation, dosing and follow-up assessments for each dosing period. The washout period following each dose must be a minimum of 48 hours until the next dose. Subjects will be required to stay in the clinic for the entire duration of the study (unless medically necessary to leave the clinic as instructed by the principal investigator).

All procedure times listed are approximate and are provided as a guide. The PK samples should be drawn as close as possible to the specified time. Vital signs should be taken within a time frame that will allow the PK blood sample to be drawn on schedule. Actual times of procedures for each subject may vary depending on scheduling and will be recorded on the CRF.

Subjects will refrain from smoking or using tobacco products during each clinic stay. Consumption of unsweetened coffee and tea in moderate amounts will be permitted. Breakfast can be served approximately two hours post-dosing, lunch approximately 4-6 hours after dosing and dinner will be served approximately 8-10 hours after dosing.

AEs and concomitant medication usage will be assessed throughout the study from the first day of study patches application until the Final Visit (or Early Termination) procedures are completed.

6.1 Screening

All Screening procedures will be performed after obtaining informed consent and should be completed within 30 days prior to admission for the first of four sequential treatments within the study. Subjects who are not dosed within 30 days after signing the ICF must be re-assessed for eligibility. The screening procedures include:

6.1.1 Screening Visit (Day -30 to -1)

Subjects who are considered to be good candidates for the study will be seen in the clinic and have the following procedures performed:

- Obtain informed consent
- Obtain a medical history and demographics
- Record concomitant medications
- Perform a physical examination
- Measure Vital signs (inclusive of temperature)
- Measure height
- Measure body weight and calculate BMI
- Confirm eligibility

- Collect blood and urine samples for clinical laboratory tests
- Perform serum pregnancy test (for all females)
- Collect blood for serology (HIV, Hepatitis B, Hepatitis C)
- Perform urine drug and alcohol (breath) testing
- Record a 12-lead ECG

Medical history, physical examination, ECG and laboratory findings are to be reviewed, and eligibility determined. The sponsor must approve any exception to the inclusion or exclusion criteria before planned admission for dosing.

A subject number will be assigned when the subject signs the informed consent. Only subject number, initials and date of birth will identify subjects to the Sponsor. In the event that a subject who has signed the informed consent but did not receive a dose of study medication experiences an SAE, the following information will be captured: demographic data (initials, age, and race), all other Screening assessments that have been completed, AE(s), and concomitant medication(s).

6.2 Admission/baseline (Day Before Each Dose)

If subjects continue to meet all entry criteria the day prior to each dosing, the subject will stay in the clinic overnight. The following procedures will be performed the day prior to each dosing:

- Record concomitant medications
- Perform urine drug and alcohol (breath) testing
- Urine pregnancy test (all women)
- Collect temperature
- Confirm eligibility

Standardized meals and beverages will be served the evening prior to dosing and will be provided by the clinical site. Subjects should complete their dinner by 10 p.m. Subsequently, subjects will fast overnight and receive only clear liquids after 10 p.m.

6.3 Study Dosing Days

General Considerations

Subjects will fast during the night preceding dosing and until 2 hours after dosing. Water is allowed ad libitum, as well as tea and coffee in moderate amounts.

The following morning (between 0630 and 0930) they will receive that day's scheduled treatment (A, B, C or D). Breakfast should be withheld until two hours post-dosing.

On all study treatment days, an intravenous cannula may be inserted to aid blood sampling. The cannula may be replaced as needed on subsequent study days at the discretion of the Investigator.

All AEs, including any skin irritations and sensations as well as concomitant medication usage will be documented.

When multiple assessments are required at the same time point, they will be conducted in the order as specified in the footnotes of the schedule of events. All procedures should be performed relative to "Time 0" (patch application) when a time is listed.

6.3.1 Dosing Visit (all Periods) – All Treatments

The following procedures will be performed on each of the four dosing days. The actual procedures will be identical at each of the dosing days, only the study drug administered on each of the treatment days will vary.

6.3.1.1 Pre-Dose - Before treatment Administration on the Day of Dosing

- Record concomitant medications
- Confirm eligibility
- Measure vital signs
- Record a 12-Lead ECG
- Investigator visual skin and nasal assessment (visual inspection)
- Determine that subject is stable and in good health and appropriate for dosing
- Collect blood for a PK sample within 15 minutes prior to administering study drug

6.3.1.2 Treatment Administration (t = 0)

- Apply patches or administer intranasal zolmitriptan (see Appendix 1 for instructions on patch administration)
- Begin recording all AEs, whether observed by investigator, reported by the subject, observed in laboratory findings, or discovered by other means, on the AE CRF through the End of Study (or Early Termination) final visit. All adverse events must be followed to resolution.
- Record patch adhesion score

6.3.1.3 2 Minutes after Treatment Administration

- Collect blood for a PK sample
- Record concomitant medications

6.3.1.4 5 Minutes after Treatment Administration

- Collect blood for a PK sample
- Record concomitant medications

6.3.1.5 10 Minutes after Treatment Administration

- Collect blood for a PK sample
- Measure vital signs
- Record concomitant medications

6.3.1.6 15 Minutes after Treatment Administration

- Collect blood for a PK sample
- Record a 12-Lead ECG
- Record concomitant medications

6.3.1.7 20 Minutes after Treatment Administration

- Collect blood for a PK Sample
- Record concomitant medications

6.3.1.8 30 Minutes after Treatment Administration

- Collect blood for a PK sample
- Record concomitant medications and adverse events
- Record patch adhesion score
- Remove patches and perform the following procedures in the order listed below (for 30 minute wear time treatment assignment only):

- Investigator visual skin assessment of the patch application sites
- Retain and package patches for freezing. Refer to full instructions in Appendix 3.
- Application site swabbing. Refer to full instructions in Appendix 3.

6.3.1.9 45 Minutes after Treatment Administration

- Collect blood for a PK sample
- Record concomitant medications

6.3.1.10 60 Minutes after Treatment Administration

- Collect blood for a PK sample
- Measure vital signs
- Record a 12-lead ECG
- Record concomitant medications and adverse events
- Record patch adhesion score (60 minute wear time assignment only)
- Remove patches and perform the following procedures in the order listed below (for 60 min wear time assignment only):
  - Investigator visual skin assessment of the application sites
  - Retain and package patches for freezing. Refer to full instructions in Appendix 3.
  - Application site swabbing. Refer to full instructions in Appendix 3.

6.3.1.11 90 Minutes after Treatment Administration

- Collect blood for a PK sample
- Record concomitant medications

6.3.1.12 Two Hours after Treatment Administration

- Collect blood for a PK sample
- Measure vital signs
- Record concomitant medications

6.3.1.13 Four Hours after Treatment Administration

- Collect blood for a PK sample
- Measure vital Signs
- Record concomitant medications

6.3.1.14 Eight Hours after Treatment Administration

- Collect blood for a PK Sample

- Record a 12-Lead ECG
- Record concomitant medications

6.3.1.15 Twelve Hours after Treatment Administration

- Collect blood for a PK Sample
- Measure vital Signs
- Record a 12-Lead ECG
- Determine if subject is stable for the next dosing period
- Investigator visual skin assessment of the application sites
- Perform a physical examination
- Record concomitant medications and adverse events

6.3.1.16 Twenty Four Hours after Treatment Administration

- Collect blood for a PK Sample
- Record concomitant medications and adverse events
- Investigator visual skin assessment of the application sites

6.3.1.17 Zolmitriptan PK Sample Handling

Details related to zolmitriptan PK sample collection and shipment is provided in Appendix 2.

6.4 End of Study Visit/or Early Termination

- Within 48 hours after completion of all protocol required procedures on the last dosing day, subjects will complete an End of Study Visit. At that time, the following assessments will be performed:
- Record all AEs, whether observed by investigator, reported by the subject, observed in laboratory findings, or discovered by other means, on the AE CRF through the end of study final visit.
- Record a 12-Lead ECG
- Record any new concomitant medications and adverse events
- Measure vital signs (inclusive of temperature)
- Perform a physical examination
- Measure body weight
- Investigator visual skin assessment of the application sites
- Collect blood and urine for laboratory tests and serum pregnancy test (for all females)
- Dismiss subject from the study

6.5 Post Study Phone Call - Follow-up on Adverse Events

Subjects must be called within 5-10 days following the day of discharge to follow-up on resolution of all ongoing AEs.

6.6 Early Termination

Subjects who terminate early will complete the assessments normally scheduled for the End of Study Visit (see above).

7 STUDY PROCEDURES

7.1 General Confinement Restrictions

Alcohol is prohibited 24 hours before study drug administration until discharge from the clinic.

Subject will not engage in any activity that may cause inflammation, irritation, sunburn, lesions or tattoos at the intended application sites from 2 weeks prior to Screening through their last day of study participation. Subject will not engage in strenuous activity at any time during their stay at the clinical unit. Subjects will be required to stay in the clinic for the entire duration of the study (unless medically necessary to leave the clinic as instructed by the principal investigator).

7.2 Collection, Processing and Assay of Samples

Blood sampling will be performed at several close time points throughout the study therefore the study center may utilize an IV cannula. After blood sampling, the cannula will be flushed with saline.

Each of the plasma samples collected for pharmacokinetic analysis will be separated into two containers. One of the samples will be sent to the analytical laboratory for analysis and one sample will be maintained at the investigative site. The plasma sample retained at the site may be used for further analysis (additional metabolites, etc.) at some future timepoint.

Subjects who complete all four treatments will have a blood draw volume of approximately 395 mL for the entire duration of the study (See Table below).

Blood Volume Requirements (mL)

Purpose	Expected Number	Sample Amount (in mL)	Total Amount (in mL)
Clinical laboratory tests (blood chemistry)	2	8.5	17.0
Hematology and Serum Pregnancy	2	4.0	8.0
PK	60 (15 samples per period x 4 periods)	4.0	240.0
	60 (discard volume with cannula flush)	2.0	120.0
Serology (screen only)	1	10.0	10.0
		GRAND TOTAL	**395 mL**

7.3 Assessment Details

7.3.1 Clinical Laboratory Tests

Standard clinical laboratory tests (serum pregnancy for all women, CBC, hematology, and urinalysis) will be performed at Screening and End of Study (or early termination) and urine pregnancy testing for all women at each Admission/baseline visit.

A blood sample at screening will be taken to perform serological tests for HIV, Hepatitis B and Hepatitis C.

CBC will include the following: Hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, platelets, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

Blood hematology will include the following: Urea, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), lactate dehydrogenase (LDH), sodium, phosphate, potassium, chloride, creatinine phosphokinase (CPK), globulin, cholesterol, creatinine, serum calcium, total bilirubin, triglyceride, cholesterol (HDL and LDL), gamma glutamyl transpeptidase (GGT) and uric acid.

Urinalysis will include the following: bilirubin, blood, glucose, ketones, leuokocyte esterase, nitrite, pH, protein, specific gravity, and urobilinogen. Microscopic examination will be conducted if protein, leukocyte esterase, nitrite and/or blood are detected.

Urine drug screen and alcohol (breath) testing will be performed at screening and each Admission/baseline visit. Urine drug screen will test for amphetamine, barbituates, cocaine, cannabinoids, phencyclidine (PCP), opioids, and methamphetamines.

Samples will be analyzed by a local laboratory. After reviewing the laboratory reports and evaluating the results, the Investigator must review, sign/date the laboratory report.

7.3.2 Vital Signs

Vital signs include heart rate, pulse, respiratory rate, as well as systolic and diastolic arterial pressure. Vital signs will be recorded after subjects have been in the seated resting position for 2 minutes. Temperature will be taken at Screening, admission/baseline, and at end of study visit/or early termination only.

7.3.3 Electrocardiograms

A standard 12-lead ECG will be performed by a qualified individual at the site. General morphology and intervals [Heart rate, QRS, PR interval, QRS, QTn, QTcf], of interest will be assessed with each tracing. The principal or sub-investigator must review the tracing and assess it for any clinically significant abnormality. Any clinically significant abnormality noted at the time of screening on the ECG will be recorded in the appropriate source document and may result in the exclusion of the subject from the study.

7.3.4 Investigator Visual Skin Assessments of the Application Sites

Each M207 patch site (where a patch has been removed) will be observed for the following skin assessments pre-dose and immediately after removal of the patches from the subject's skin (and before swabbing) at 30 min (for 30 min wear time treatment groups only), 60 min, 12 hr, 24 hr and at the End of Study/or Early Termination visit.

7.3.4.1 Erythema

The erythema evaluations will be performed using the following scale:

- 0 = None
- 1 = Mild redness
- 2 = Moderate colored redness
- 3 = Beet colored redness

7.3.4.2 Edema

The edema evaluations will be performed using the following scale:

- 0 = None
- 1 = Slight edema
- 2 = Moderate edema
- 3 = Severe edema

7.3.4.3 Bruising

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

- 0 = None
- 1 = ≤ 25% application site has bruising spots
- 2 = ≥ 26 to ≤ 50% application site has bruising spots
- 3 = > 50% application site has bruising spots

7.3.4.4 Bleeding

Bleeding will be assessed using the following scale:

- 0 = None
- 1 = Pink color on skin
- 2 = Visible blood drop
- 3 = Active bleeding

7.3.5 Residual Drug on Used M207 Patches

The used patches should be placed in the proper cryovial tube provided by Zosano and immediately placed on dry ice or frozen at approximately -80°C (plus or minus 10°C) and kept frozen until shipment to the bioanalytical lab. Used patches may be assayed for residual zolmitriptan if considered relevant after review of the pharmacokinetic results. Instructions for removing and storing the patches are provided in Appendix 3.

7.3.6 Residual Drug on Skin after M207 Patch Removal

At the time patches are removed (for all patch treatment groups), the M207 patch skin sites will be swabbed to collect any residual drug that may be on the skin surface where a transdermal M207 patch has been applied. The process consists of using 3 swabs to capture the drug residual for each patch site. The procedure is described in Appendix 3.

7.3.7 Patch Adhesion Assessment

For each assessment, investigators should use a 5-point numerical scale in which each score corresponds to a specified range of adhered surface area of each patch, as follows:

0 = ≥ 90% adhered (essentially no lift off the skin)

1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin)

2 = ≥ 50% to < 75% adhered (less than half of the patch lifting off the skin)

3 = > 0% to < 50% adhered (not detached, but more than half of the patch lifting off the skin without falling off)

4 = 0% adhered (patch detached; completely off the skin)

7.3.8 Recording Adverse Events

Adverse events are collected from the time of of first patch application until the end of the study. A detailed discussion regarding the collection and reporting of adverse events is provided in Section 8.

8 ADVERSE EVENTS

All skin and systemic AEs, regardless of treatment group or suspected causal relationship to the investigational products, will be reported as described in the following sections.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification of the Sponsor. For all skin and AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. The Investigator is required to assess causality. For skin and systemic AEs with a causal relationship to the investigational product, follow-up by the Investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Zosano Pharma concurs with that assessment.

Reporting Period

Collection of skin and systemic AEs will be initiated from the time of treatment application and will conclude when the end of study procedures for the fouth treatment are completed (or Early Termination). The Investigator will also report to the Sponsor all SAEs that come to his/her attention after the study termination within 30 days of the last dose of study drug.

Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to the investigational product is suspected.

8.1 Adverse Event Definitions

An AE is any untoward medical event that occurs in a clinical investigation, where a subject is administered a product or medical device, without regard to causal relationship between the event and the treatment. An AE can be any unfavorable and unintended sign or symptom, including clinically significant laboratory values and test results, concomitant illness, accident, or worsening of an existing medical condition.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory or other means, will be collected and recorded on the Adverse Event CRF using the signs, symptoms or diagnosis associated with them and followed until resolution or, in the Investigator's opinion, a stable condition is reached, or until the patient is lost to follow up.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

In the event of a clinically important AE, a serum sample may be collected as soon as possible after the occurrence of the event for drug assay or for additional laboratory tests. The Investigator will ensure that the serum sample is properly labeled and stored. The Investigator and other study personnel responsible for the care of the patient will institute any supplementary investigations of significant AEs based on the clinical judgment of the likely causative factor(s). This may include seeking further opinion of a specialist in the field of the AE.

Any abnormal lab tests starting from the day of study patch application 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 a change in study dosing or 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 Documentation and Reporting of Adverse Events By the Investigator

All adverse events (AEs) occurring after the application of the first dose through the End of study visit/or early termination, will be reported on the AE CRF pages. Based on the medical judgement of the investigator, all non-serious systemic and skin AEs will be followed until 30 days after the final end of study visit. All non-resolved, non-serious systemic and skin AEs beyond such date will be recorded as 'ongoing' without further follow up.

However, an AE form will not be filled out for subjects who sign the ICF but fail the entry criteria (Screening failures) during the Screening process and experience a non-serious AE.

Application site reactions will be reported on a dedicated assessment form for the visual skin assessment of the application sites. The regular AE form does not have to be completed for such events unless the events are not covered by the questions on the visual skin assessment form or are reported outside their time window. However, all such events will be included in the analyses of adverse event incidence.

Each AE, including skin AEs, 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 (See Section 8.4). It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. Systemic and skin AEs should be reported using concise medical terminology on the CRF pages as well as on the form for collection of SAE information.

In addition to recording the signs, symptoms or diagnosis associated with them to describe the adverse event, the following will also be assessed and recorded:

8.2.1 Duration

Record the start date and time of the event, and, if applicable, the end date and time. If the event is still ongoing at the final or early termination visit or after the end of follow-up, this should also be recorded.

8.2.2 Severity Ratings

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

- Mild - event may be noticeable to patient; does not influence daily activities; usually does not require intervention.
- Moderate - event may be of sufficient severity to make patient uncomfortable; performance of daily activities may be influenced; intervention may be needed.
- Severe - event may cause severe discomfort; usually interferes with daily activities; patient may not be able to continue in the study; treatment or other intervention usually needed.

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 patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.2.3 Relationship to Study Drug

The Investigator's assessment of causality must be provided for all systemic and skin AEs (serious and non-serious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility 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. 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 may be suggestive. An alternative explanation is less likely, e.g., concomitant drug(s), concurrent disease(s).

Possibly Related: An AE that may or may not be due to 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 disease(s).

Not Related: An AE that is judged to be clearly due only to extraneous causes (disease, environment, etc.). The cause must be noted on the AE CRF page.

8.3 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;
- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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

Life-threatening SAE: Any AE that places the patient, 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 trials associated with hospitalization or prolongation of hospitalization is 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., patient 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 patient.

Pregnancies, though not expected in this subject population, are to be reported as SAEs. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications and their relation to the study treatment.

Unexpected Adverse Events

An unexpected AE is any AE, the specificity or severity of which is not consistent with the current Investigator brochure; or if an Investigator 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. "Unexpected," as used in this definition, refers to an AE that has not been previously observed (i.e., is not included in the Investigator brochure) rather than an event that is not anticipated based on the pharmacological properties of the pharmaceutical product.

8.4 Reporting Requirements For Serious Adverse Events

ALL SERIOUS ADVERSE EVENTS, REGARDLESS OF CAUSE(S) OR RELATIONSHIP TO STUDY DRUG MUST BE REPORTED IMMEDIATELY TO THE SPONSOR BY TELEPHONE AND FAX.

8.4.1 Sponsor SAE Contact Information

Pete Schmidt, MD, MSc
Phone/fax: 510-745-1251

If an SAE occurs, the Sponsor 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 Sponsor 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.

The Investigator must complete the SAE Report Form and send it along with other relevant source documents to the medical monitor within 24 hours. For all SAEs, the Investigator is obligated to pursue and provide information to the medical monitor in accordance with the timeframes for reporting specified above. The Investigator (or a physician on the investigational staff) must provide relationship to study drug as soon as possible and sign the SAE forms. 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 CM administered in association with the SAE will be documented on the 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.

8.4.2 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 patient is lost to follow up. Based on the medical judgment of the Investigator, all non-serious systemic and skin AEs will be followed until 30 days after the last visit. All non-resolved, non-serious systemic and topical AEs beyond such date will be recorded as "ongoing" without further follow up.

9 DATA MANAGEMENT

9.1 Data Collection

Designated investigator staff must enter the information required by the protocol into the study CRF, whether paper or electronic on an ongoing basis. The completed CRF pages will be reviewed against source documents by the monitor at each monitoring visit. If any data, signatures, or forms are missing or incorrect, the Investigator will be informed and corrections made. If paper CRF is used, they will be collected from the study site after monitoring visits and data queries are completed and the investigator has reviewed and signed off on each subject's CRF certifying that the data are complete and accurate. Electronic CRF require the same procedures for timely completion, transmittal, monitoring, query resolution and Investigator review as paper CRF and will meet all GCP/ICH-R requirements, including 21 CFR, Part 11 regarding electronic records and signatures.

9.2 Database Management and Quality Control

Study auditing, data entry, verification and validation of the database, and subsequent analysis will be performed by any or all of the sponsor's Clinical Research and Development, Clinical Pharmacology, Statistics, and Regulatory Compliance Departments or the sponsor's representatives for these functions according to current GCP requirements. In addition, computerized data entries will be checked against paper CRF if used. If electronic CRFs are used, the system will meet all GCP/ICH-R requirements for database integrity, including 21 CFR, Part 11.

10 STATISTICAL METHODS AND DATA ANALYSIS

10.1 Sample Size Considerations

No formal sample size calculation was performed. In previous studies of Zosano Pharma transdermal products in healthy volunteers, a sample size of 24 was sufficient to provide directional information on tolerability, as well as adequate information on pharmacokinetics, and comparative pharmacokinetics for various regimens.

10.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively.

10.3 Analysis Population and Handling of Drop-Outs

All subjects who receive any amount of study drug will be included in the safety analyses (Safety Population). The PK population will include all subjects who receive any amount of study drug and for whom the PK profile can be adequately characterized. Drop-outs within a 24-hour period are not anticipated; however should they occur prior to 2 hours after patch application then additional eligible subjects may be enrolled.

10.4 Zolmitriptan Pharmacokinetics

Plasma zolmitriptan and n-desmethyl zolmitriptan concentrations as a function of time following M207 patch administration will be plotted by treatment. The following pharmacokinetic parameters will be calculated for each treatment and subject with samples analyzed using each assay.

- C_{max} - maximum observed plasma concentrations
- T_{max} - time to maximum concentration
- $AUC_{0\text{-}t}$ - the area under the plasma concentration time profile from hour 0 to the last detectable concentration at time t will be determined by the linear trapezoidal method.
- $AUC_{0\text{-}30min}$ - the area under the plasma concentration time profile from minute 0 to minute 30 will be determined by the linear trapezoidal method.
- $AUC_{0\text{-}60min}$ - the area under the plasma concentration time profile from minute 0 to minute 60 will be determined by the linear trapezoidal method.
- $AUC_{0\text{-}120min}$ - the area under the plasma concentration time profile from minute 0 to minute 60 will be determined by the linear trapezoidal method
- k - apparent elimination rate constant will be estimated by linear regression of the log-transformed plasma concentrations during the terminal log-linear decline phase.
- $t_{1/2}$ - apparent half-life ($t_{1/2}$) values will be calculated as 0.693/k.
- $AUC_{0\text{-}inf}$ - the AUC value extrapolated to infinity will be calculated as the sum of AUC_t, and the area extrapolated to infinity, calculated by the concentration at time t (C_t) divided by k.

- Frel - bioavailability relative to other treatment sites of application and wear times

PK parameters (C_{max}, T_{max}, and AUCs) for M207 and intranasal zolmitriptan will be compared. Descriptive statistics (arithmetic and geometric means, standard deviation [SD], coefficient of varions [CV(%)], minimum [Min], maximum [Max], and median) of the plasma concentrations versus time will be presented. Calculation of T_{max} will start from the time of study drug administration. Further details on the analysis of PK parameters can be found in the statistical analsyis plan.

10.5 Analyses of Safety Data

Verbatim AEs will be mapped to preferred term and body-organ system using MedDRA™. The number and percentage of subjects reporting AEs will be summarized by AE preferred term and AE body-organ system. Adverse events will be summarized by severity and relationship to study drug.

Scores of the investigator skin assessments of the application sites at 30 min (30 min wear time assignment only), 60 min (1 hr), 12 hours and 24 hours post-dose will be summarized by treatment group using frequency tables.

Descriptive summaries of actual values and changes from pre-dose to 10 min, 60 min (1 hr), 120 min, 240 min (4 hr), and 720 minutes (12 hr) post-dose will be calculated for vital signs including heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure and presented by treatment group.

Descriptive summaries of actual values and changes from pre-dose by treatment group will also be provided for the quantitative ECG parameters of rhythm, heart rate, PR interval, QRS interval, QT, QTcF, (Fridericia's) corrections for heart rate.

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

10.6 Analyses of Adhesion

Adhesion scores will be summarized by time point and treatment group using frequency tables. Mean adhesion scored by time point and treatment group will also be provided. Further details on the analysis of adhesion scores will be provided in the SAP.

10.7 Analyses of Residual Drug

Analyses may be performed to quantify the amount of drug remaining on the M207 patch system and the amount of drug recovered from the skin of the subject following removal of each of the patches. In that case, a description of the disposition of the remaining drug will be presented. The results from analysis of residual zolmitriptan on the skin and the residual zolmitriptan on the used patches will provide a basis for the calculation of the total amount of drug delivered from each treatment.

11 ADMINISTRATIVE PROCEDURES

11.1 Changes to the Protocol

Any change or addition to the protocol requires a written protocol amendment initiated and approved by the sponsor, Zosano Pharma and the IRB/IEC and any applicable regulatory authority.

Amendments of an administrative nature do not require formal protocol amendments or approval by the IRB/IEC, but the IRB/IEC must be informed in writing of such administrative changes. Examples include changes in the staff used to monitor the trial, editorial corrections and clarifications.

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

The Investigator must promptly report to the IRB/IEC all changes in the research activity and all unanticipated problems involving risk to human patients 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 regulatory authorities (serious, unexpected SAEs possibly or probably related to study drug). Concurrently, the Investigator must send documentation to the Sponsor of such IRB/IEC notification. The Investigator must not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human patient.

11.3 Withdrawal and Study Termination

Subjects will be informed that they are free to withdraw from the study at any time. The Investigator, the Investigator in consultation with the Medical Monitor, or the Medical Monitor may exercise his/her medical judgment to terminate a participant's participation in the study due to clinically significant changes in any clinical or laboratory parameter (See Section 4.3).

Zosano Pharma reserves the right to terminate the study at any time. All data normally collected at completion of the study must be collected either at the time of the subject's early termination, or on or before the scheduled study close out. Subjects with ongoing AEs at termination will be followed until all significant changes have resolved or become medically stable.

11.4 Monitoring

The clinical site will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspections by providing direct access to source data/documentation.

The sponsor's representatives will monitor the study at all stages of study conduct from inception to completion in accordance with current GCPs/ICH-R and a study monitoring plan. This monitoring will be in the form of site visits and other communication and will include review of original source documents and CRF. 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 required certifications, IRB/IEC notifications and approvals, equipment, recruiting, record-keeping, protocol adherence, data collection, adverse event reporting and other factors.

11.5 Retention of Documents

The Investigator will retain all study documents for at least two years after the approval date for marketing the product or until 2 years after the investigational use of the study drug is discontinued. The Investigator must obtain written permission from Zosano Pharma before destroying any study documents.

11.6 Publicaton Policy

All information concerning Zosano Pharma operations, patent applications, formulas, manufacturing processes, and basic scientific data provided by Zosano Pharma to the investigator and not previously publishes, are considered confidential and remain the sole property of Zosano Pharma.

It is understood by the investigator that Zosano Pharma will use the information obtained in this clinical study in connection with M207, and therefore may disclose this information as required to other Zosano investigators, appropriate international regulatory agencies, or others. In agreeing to participate in this study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to Zosano Pharma. Zosano Pharma requires that permission to publish details of this study must be obtained in writing by Zosano as further detailed in the Clinical Study Agreement signed by the investigator and/or institution.

11.7 Auditing Procedures

Zosano Pharma or their agents and contractors may conduct audits of clinical research activities in accordance with applicable Standard Operating Procedures. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If an inspection is requested by a regulatory authority, the investigator must inform Zosano Pharma immediately that this request has been made.

12 REFERENCES

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13 SCHEDULE OF ASSESSMENTS

Assessment*	**Screening Visit****	**Admission/ baseline**	**Dosing Visit*****																**End of Study/Early Termination**
	Screening	**Day Prior to Each Dose**	**Pre-dose**	**0 mn**	**2 mn**	**5 mn**	**10 mn**	**15 mn**	**20 mn**	**30 mn**	**45 mn**	**60 mn**	**90 mn**	**2 hr**	**4 hr**	**8 hr**	**12 hr**	**24 hr**	**Within 48 hours after completion of all procedures on final dosing day**
Informed consent	X																		
Medical history/ demographics	X																		
Concomitant medications	←																		→
Physical exam	X																X		X
Serum pregnancy test	X																		X
Urine dipstick pregnancy test		X																	
Height	X																		
Weight	X																		X
Confirm eligibility	X	X	X																
Clinical laboratory tests (CBC, hematology, UA)	X																		X
Serology	X																		
Urine Drug & Alcohol (breath) Testing	X	X																	
Collect PK samples			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study drug administration				X															
Patch Adhesion Scale$^{\infty}$				X						X$^{\infty}$		X$^{\infty}$							
Vital signs	X		X				X					X		X	X		X		X
ECG	X		X					X				X				X	X		X

Assessment*	**Screening Visit****	**Admission/ baseline**	**Dosing Visit*****															**End of Study/Early Termination**
	Screening	**Day Prior to Each Dose**	**Pre-dose**	**0 mn**	**2 mn**	**5 mn**	**10 mn**	**15 mn**	**20 mn**	**30 mn**	**45 mn**	**60 mn**	**90 mn**	**2 hr**	**4 hr**	**8 hr**	**12 hr**	**24 hr**	**Within 48 hours after completion of all procedures on final dosing day**
Remove and retain (freeze) patches (at 30 min or 60 min depending on assignment)										X		X							
Investigator skin assessment of the application sites•			X							X•		X•					X	X	X
Swabbing****										X		X							
Record Adverse events					→														→

* When multiple procedures are scheduled for the same time point, PK samples will be taken at the protocol assigned time point within plus or minus 1 minute of the specified time points for the first hour and within plus or minus 5 minutes of the specified time points after one hour. The other measurements (i.e., vital signs, ECG, skin assessments) will be taken before or after the protocol-specified time point within an interval of plus or minus 5 minutes.

** Screening Visit – Up to 30 days prior to first admission/baseline visit.

*** The washout period following each dose must be a minimum of 48 hours until the next dose is administered.

∞ Patch Adhesion Scale – Only the 60 min wear time treatment assignment will have the scale completed at both 30 and 60 min.

• Investigator skin assessment – The 30 min assessment is only applicable to the 30 min wear time treatment assignments and the 60 min skin assessment is only applicable to the 60 min wear time group.

**** Swabbing of both patch sites will occur when patches are removed at either 30 or 60 min depending on the wear time treatment assignment.

APPENDIX 1: M207 PATCH ADMINISTRATION

TABLE OF CONTENTS

I. INTRODUCTION

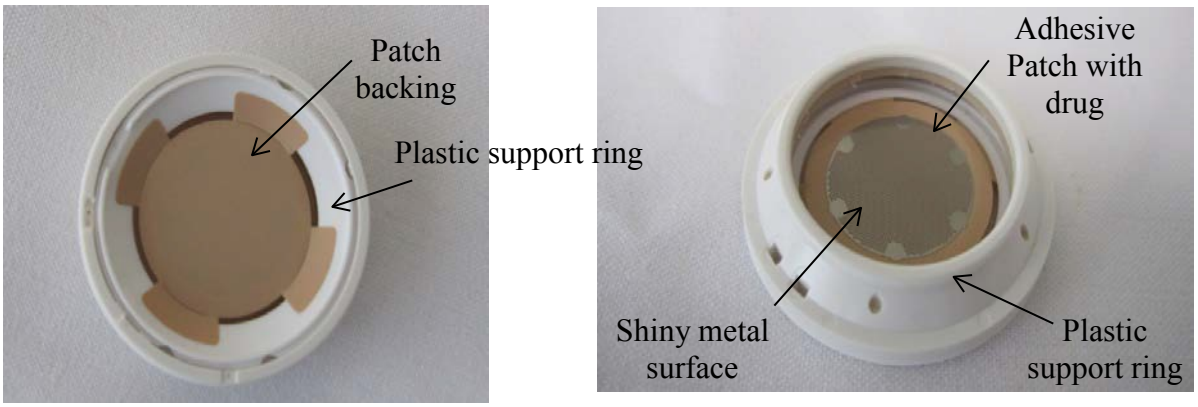
The M07 patches and a specially designed applicator are made by Zosano Pharma. This User's Guide provides instructions for the clinical staff on how to apply patches to subjects. The patches look like round adhesive Band-Aids and have study drug on tiny metal points on one side. Patches are applied to the subject's skin using a spring-loaded applicator specially designed for these patches. Each patch is used only once. The applicator can be reused.

II. GENERAL DESCRIPTION

The M207 intracutaneous microneedle system has two parts: a patch attached to a plastic supporting ring, and an applicator.

1. **The Patch:** The patch comes attached to a plastic supporting ring that allows you to attach it to the applicator. When you apply the patch to the skin, the patch stays on the skin and the plastic ring stays on the applicator and is later thrown away.

Top **Bottom**



There is study drug on the shiny metal on the sticky side of the patch. You can touch the supporting plastic ring, ***but do not touch the sticky side of the adhesive patch or the shiny metal piece with your fingers***. Touching this may damage the patch.

2. The Applicators

Applicator 0.26J

Use the applicator to apply the patch for treatments A-C to the skin. Hold the applicator in your hand to apply the patch. The patch cannot be applied without the applicator. The ring and patch attach to the bottom of the applicator. The applicator cap is twisted to unlock the applicator. When the applicator is pressed against the skin, a plunger pushes the patch out of the support ring and applies it to the skin.

3. Storage of Supplies (patches and applicators):

Room temperature storage: Store the patches in their cups at room temperature. Store the applicator at room temperature in its box between uses.

III. PRECAUTIONS AND OTHER NOTES

Lotions, Ointments, or Powders: Ensure no lotions, ointments, or powders have been applied to the patch application sites immediately before or after applying the patch.

Wash Hands: Always wash your hands before applying a patch.

IV. INSTRUCTIONS FOR USE

1. Before You Apply the Patch

- Check the skin at the upper arm or thigh to be sure that it is not irritated from rash, inflammation, redness, or other skin problems such as cuts or open wounds. In addition, the application area must be free of tatoos, scars, birthmarks, and/or any skin abnormalities.
- Clean the the skin area (upper arm or thigh) where the patches will be applied with an alcohol wipe. Only wipe with alcohol prior to the first patch application for each dose.

2. Opening the Cup Containing the Patch and Plastic Ring

Patch and Ring in Package

- Each patch is individually sealed in its own protective outer cup.
- DO NOT USE the patch if its cup has a hole in it, has already been torn open, or is otherwise damaged.

- With the tab pointing towards you, to open the cup, lay the cup flat with printed side up. Using the notches provided, slowly peel back the top layer of the cup to open with "This side up" facing up. If the cup is difficult to open, you can use scissors to cut along the dotted line.

- Leave the patch on the bottom side of the cup. You can touch the white plastic patch ring with your fingers. However, do not touch the patch or shiny metal surface of the patch with your fingers. This may damage or contaminate the patch. If you accidentally touch the shiny metal surface with your finger, return the patch to the original cup, write the date on the cup, and start over with a new patch.

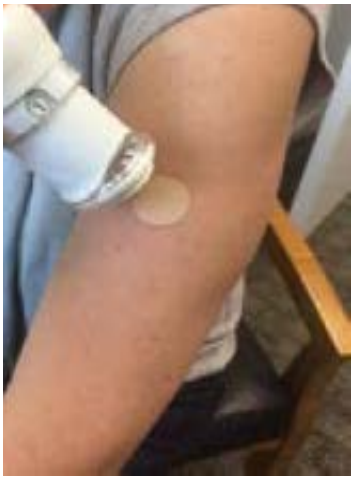
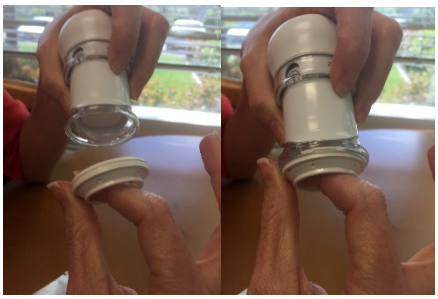
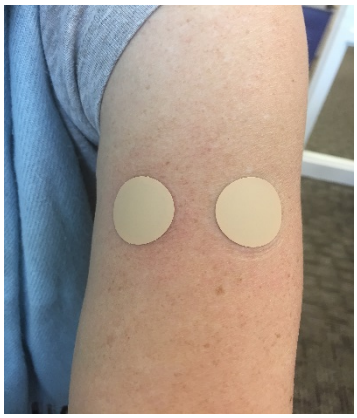
3. Attaching the Patch Ring to the Applicator, and Applying the Patch to the Skin (see Figure 1)

1. Prepare the patch and applicator
   - o Open the applicator box and remove the applicator from its box
   - o Ensure the applicator is set to '1'. The applicator is ready to attach a patch when in the number '1' position. If the number '2' is showing in the window, change it to '1' by depressing the applicator onto your palm or other soft surface until it activates.
   - o Ensure the patch is sitting shiny metal side down. If not, gently pick up the patch ring assembly by touching only the plastic support ring and flip it over. The shiny metal side should now be face down.
2. Attach the patch and ring to the applicator by placing the applicator directly on top of the patch ring and push down gently until the patch clicks into place. You will likely hear or feel a "click." The patch is now attached to the applicator.
3. Holding the bottom half of the applicator with one hand, unlock the applicator by twisting the top half of the applicator clockwise until it clicks into the "2" position.

   The patch and applicator are now ready for application.
4. Ensure the number shows '2' in the window, indicating the applicator is unlocked. If not, go back to step 4 to change it from '1' to '2'.
5. Place the applicator on the skin and push the applicator against the skin.
6. When you have pushed against the skin hard enough, you will hear the plunger push the patch from the ring onto the skin. Continue to hold the applicator down against the skin for 3 seconds. The patch is now applied and the medicine is now being delivered through the patch. You may now remove the applicator. You will see the patch sticking to the skin. The empty plastic ring will still be attached to the applicator.
7. If edges of the patch are lifted or curled, lightly press down WITH THE FLAT OF YOUR PALM to make the patch stick to the skin better.
8. DO NOT USE YOUR FINGERTIPS to press the edges of the patch because your fingertips may push one side down but pull the other side loose.
9. With your forefinger and thumb, remove the ring from the bottom of the applicator by pulling it out. You may discard the ring in the rubbish bin.
10. Leave the patches on the subject's skin for the duration assigned in accordance with the protocol treatment assignment (30 minutes or 60 minutes).

Figure 1: M207 Patch Application

 	**1. Snap patch-ring assembly onto applicator**
	**2. Twist applicator cap clockwise from Position 1 to Position 2 to unlock for patch application**

	**3. Place applicator against cleaned area and press applicator downward to apply patch to skin until you hear a click then HOLD for 3 seconds. Patch is applied. Ring assembly remains attached to the applicator**
	**4. Remove the outer ring in order to load and apply the second patch.**
	**5. Repeat all of the above steps to apply second patch next to the first patch**

4. After Applying the Patch

Leave the patches on the subject's skin for the duration assigned in accordance with the protocol.

Before applying the second patch, remove the used plastic support ring from the applicator and discard it. Use your finger to pull the used patch ring off the applicator. Throw away the patch ring.

5. Removing the Patch

After the appropriate assigned time of patch application, peel the edge of the patch back and remove the patches from the subject's skin as you would remove a Band-Aid. Refer to Appendix 3 for handling and processing of used patches, storage, and return instructions.

APPENDIX 2: ZOLMITRIPTAN PK SAMPLE HANDLING

1. Plasma Zolmitriptan Sample Collection

Approximately 4 ml of blood will be collected into a labeled K2 EDTA blood collection tubes at each pharmacokinetic time point as specified in the the schedule of events. The actual date and time of blood collection will be recorded for each subject.

The blood samples will be maintained in a chilled ice bath prior to centrifuging. The samples will be centrifuged for 10 minutes at 4°C at 2000 x g and the aliquots will be placed in the freezer within 60 minutes of sample collection. The plasma supernatant will be transferred to polypropylene tubes and labeled identically to the original sample container. Two aliquots will be prepared. Plasma will be aliquoted into a separate LDPE containers labeled (at minimum) with the study number, subject's identification number, date and time of collection, and analyte (zolmitriptan). Aliquot 1 will contain 1 mL of plasma, and Aliquot 2 will contain the rest of the plasma (approximately 1 mL). After processing, the tubes will be sealed and the plasma will be frozen in an upright position (to avoid frozen plasma in the caps) and stored in a -80 °C (+/- 10 °C) freezer in an upright position until shipped for analysis. The plasma samples will be shipped to the bioanalytical laboratory on dry ice.

Each sample will be labeled or barcoded (at minimum) with the study number, subject identification number, actual date and time of collection, analyte (zolmitripan).

2. Plasma Zolmitriptan Sample Shipment

Securely pack the frozen samples in Styrofoam freezer boxes with sufficient dry ice to ensure the samples remain frozen for at least 72 hours. Samples will be transported to the bioanalytical facility in at least two separate shipments, with each set of aliquots in separate shipments. Once the bioanalytical laboratory confirms receipt of the first shipment, the second set of aliquots may be sent upon approval by Zosano. The shipping container will include TempTale temperature monitoring device provided by World Courier.

APPENDIX 3: HANDLING AND PROCESSING OF USED PATCHES AND SKIN SWABS

Delivery performance of M207 patches is determined by drug residual analysis. The amounts of zolmitriptan left on the microneedle array and skin surface after each application are compared against the original coated amount on the array, allowing total amount delivered or delivery efficiency to be determined by mass balance. This Appendix 3 provides detailed procedures for used patch removal and subsequent swabbing of the treated skin surface. The collected used patches and skin swabs (in swab buffer) will be shipped to the site where plasma samples are analyzed.

MATERIALS:

A. Content of Used Patches and Skin Swabbing Kits

Figure 1 outlines the materials provided by Zosano to perform the used patch collection and skin swabbing procedures. The materials for both procedures will be combined into one kit (for each dosing period) and designated as the Used Patch/Skin Swab Kit. Each kit contains materials (Table 1) to collect from one dosed patient: 2 used patches and two skin swabbing for each patch.

Figure 1. Content of Used Patch/Skin Swab Kits (Item 1-8) from Zosano:

1) Orange-cap cryovial with 1-mL swab buffer*

2) 2 swab buffer vials, each with 1 dry swab

3) 2 pairs of forceps

4) 2 used patch collection vials

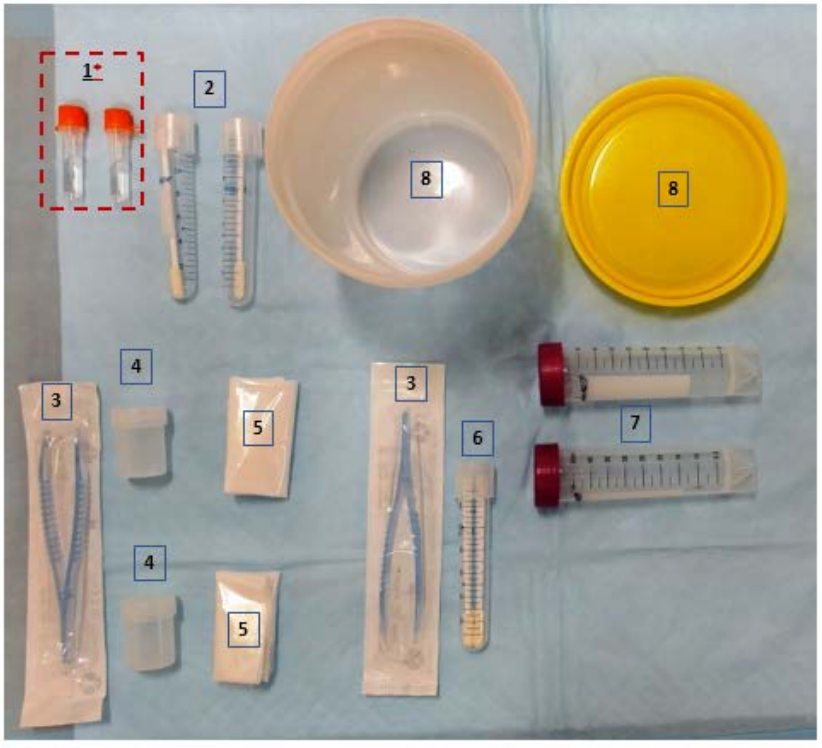
5) 2 Ziploc bags for used patch vials (Item #4)

6) 1 vial with 4 dry swabs

7) 2 purple-top 50-mL tubes

8) 1 white tub with 1 yellow lid to contain Items # 1-7

**Refer to Appendix 3 Section B1 for details*



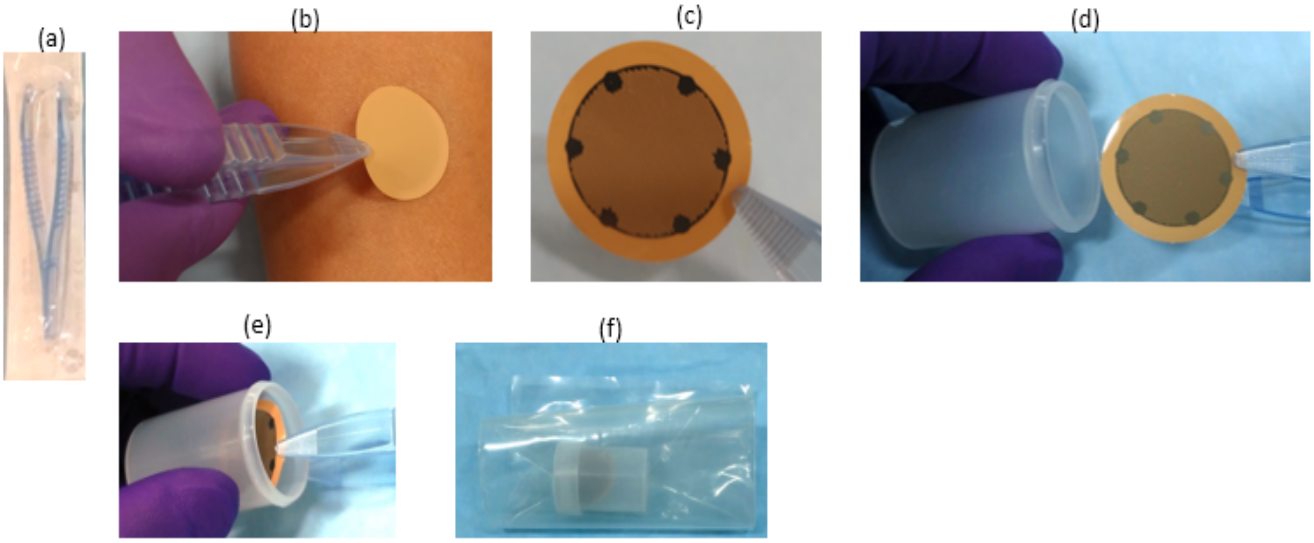
PROCEDURE:

USED PATCH REMOVAL PROCEDURE FROM SKIN AND PROCESSING

Refer to Figure 1 (above) for material identification and Figure 2 (below) for used patch removal procedure. Note the following procedural highlights:

1. Do not touch or contaminate the patch-treated skin sites after patch removal.
2. Since each patient has two patches applied, remove one patch at a time and note the skin area where the patch was removed for subsequent skin swabbing in Section B.
3. Try to perform used patch removal and skin swabbing, for the first and second patches, within 5 minutes of the removal of the first used patch.

Figure 2. Used Patch Removal Procedure



1) Used forceps to lift and remove patch off the skin (a-b)
2) Make sure that tip of forceps does not touch the metal array perimeter (c)
3) Place used patch into vial and cap vial (d-e); check labeling of vial prior to placing into Ziploc bag.
4) Place capped vial with used patch in Ziploc bag.
5) Place Ziploc bags in dry ice or -80°C freezer for storage.

A minimum of 80 kits will be provided by Zosano and of the 80, 8 (10%) kits are allotted for backups and 72 are allotted for 24 subjects with 3 treatments. Once the used patch collection and skin swabbing are completed for all subjects, there should be in total 144 used patch vials and 144 swab buffer vials to be processed and shipped to Syneos Health.

Table 1. Tally/Labeling of Materials Included in each Used Patch/Skin Swab Kit

Item #	Description	Quantity	Labeling
1*	Orange-cap cryovial with 1-mL swab buffer	2	#1 to 144 (sequentially) with "1-mL Swab Buffer"
2**	Swab buffer vial with 1 dry swab	2	**For Items # 2 and 4 include at least the following: - Subject ID - Patch location (upper arm or thigh and number or side (e.g., 1 and 2, or left and right) - Sample collection date and time - Protocol number
3	Sterile forceps, individually packaged	2	
4**	Used patch collection vial	2	
5	Ziploc bag for Item 4	2	
6	Vial with 4 dry swabs	1	
7	Purple-top 50-mL tube	2	
8**	White tub with yellow lid to contain Items 1-7	1	
*This orange-cap cryovial containing buffer will be stored in refrigeration at approximately 0-4°C and removed several hours before swabbing.			

Labeling: *Item #1 will be numbered from 1 to 144 by Zosano. **Items # 2, 4 and 8 will need to be labeled prior to use with a minimum of the following: Subject ID, patches location (upper arm or thigh), and numbering or position (e.g., site 1 or 2 or left/right), sample collection date and time, and protocol number.

B. Skin Swabbing After Each Used Patch Removal

Refer to Figure 1 for material identification and Figure 3 for skin swabbing procedure.

For each separate patch, the patch-treated skin surface is swabbed using three polyurethane swabs: 1 wetted and 2 dry. The first swab is soaked in 1.0-mL of 0.05% Tween 20 (in phosphate buffer saline). The 0.05% Tween 20 in phosphate buffer saline is also referred to as "swab buffer" and shown in Figure 1, Item 1. The wetted swab is applied over the skin site by rolling the swab with slight pressure in several directions (e.g., left to right and up and down) and around the periphery of the treatment site. Two additional swabs, dry, are applied sequentially over the wetted skin site using the same rolling motions to absorb all residual buffer. Make sure to absorb all residual buffer on the skin since this is the medium used to capture the residual zolmitriptan from the skin. Once used, all three swabs are placed in the swab buffer vial and sent Syneos Health for zolmitriptan analysis.

Note the following procedural highlights:

1) Cryovials with swab buffer: 1-mL of the swab buffer aliquot is contained in each orange-cap cryovial (Item #1) and 144 will be sent from Zosano and should be stored at 0-4°C prior to use. Two cryovials (containing buffer) are allotted for each of the two used patches and should be removed from refrigeration and placed with Kit several hours before swabbing. At least 1 hour before swabbing, pour the content of one cryovial into one swab buffer vial with dry swab (Item # 2) and repeat for the other set. Place both swab buffer vials into the Kit tub to keep them slightly upright as shown.

2) Start skin swabbing procedure immediately after patch removal.

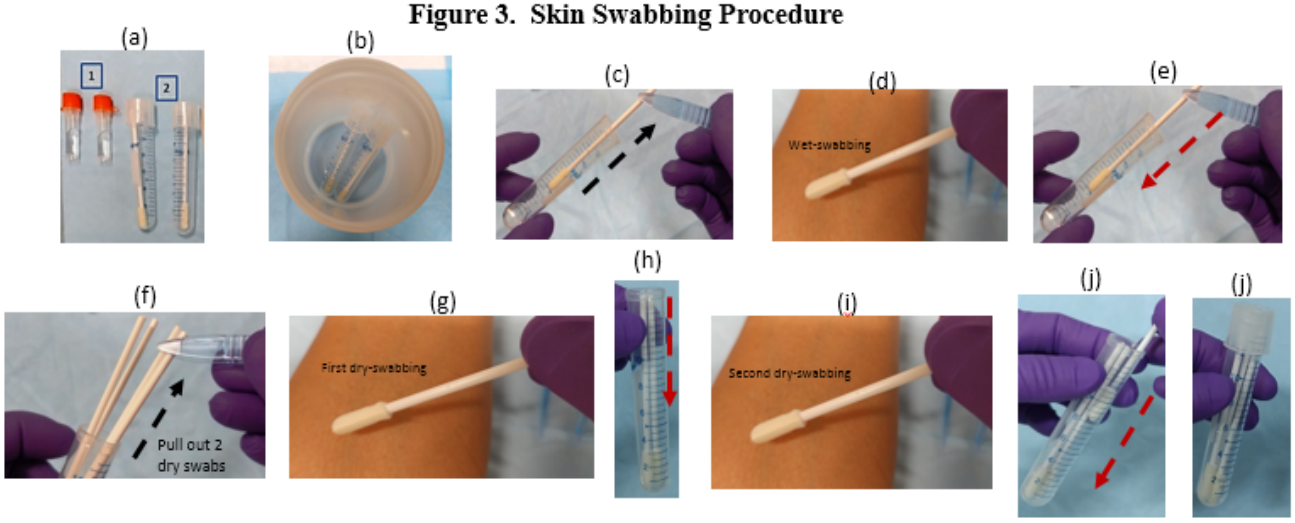
3) Try to complete used patch removal and skin swabbing, for first and second patch, within 5 minutes of the removal of the first used patch.

4) Wetted swab should not be dripping with excess buffer when pulled out for swabbing. Keep all swabs clean until used.

5) Apply the wetted swab over the treated skin site by rolling (back-and-forth) the swab with slight pressure in several directions (e.g., left to right and up and down) and around the periphery of the treatment site. Once swabbing is done, place the wetted swab back into the swab buffer vial.

6) Apply two additional swabs (dry), one at a time, over the wetted skin site using the same rolling motions to absorb all residual buffer on the skin. Once swabbing is done, place both swabs into the same swab buffer vial.

Figure 3. Skin Swabbing Procedure



1) Refer to Appendix 3 Section B1 for details.
2) Remove the wetted swab from one swab buffer vial and swab the upper arm site; use rolling motion to spread the buffer over the treated skin area. Once done, return the swab to the original swab buffer vial.
3) Using forceps, remove two dry swabs (f) from the dry swab vial, Item 6. Use one swab at-a-time to swab the buffer-wetted skin site. Once completed, place both swabs into the specific swab buffer vial, cap vials (g-j) and check labeling of vial.
4) Place swab buffer vials, each with three (3) swabs, into dry ice or -80°C freezer for storage

C. Packing of Used Patches and Skin Swabs

Refer to Figure 4 for packing illustration. Use the Kit tub to pack the used patch vials (2) and swab buffer vials (2) collected from each dosed patient. Pack all tubs in dry ice for shipping and ship upon authorization from Zosano Pharma.

Figure 4. Short-Term and Long-Term Storage and Labeling

1) Transfer the 2 frozen used patch vials and two frozen swab buffer vials from each individual subject into the white Kit tub.

2) Make sure each vial is labeled accordingly. Cap the tub with the yellow lid (Item 8) provided, label tub accordingly and put tub **in** dry ice for short-term storage, -80°C for long-term storage, and **in** dry ice for shipping.

3) For labeling, include at minimum the following: subject ID, patch location (upper arm or thigh and number or side (eg, 1 and 2, or left and right), sample collection date and time, and protocol number.

APPENDIX 4: SHIPPING PROCEDURES FOR UNUSED PATCHES AND NEW APPLICATORS

1. Unused Patch Collection and Shipment

Collection: All unused systems should be stored in their original cups and shipping box, at room temperature until shipment to Zosano Pharma.

Shipment: All unused systems should be combined into one shipment and shipped at room temperature - upon authorization from Zosano Pharma.

Shipments should be made via World Courier using the Zosano Pharma World Courier Account number 13334.

All returned packages should contain the statement: "For research purposes only. Not for human use."

Complete the Product Return Form (provided by Sponsor) and include with each return shipment:

- Insert 1 copy in a separate plastic bag in the sample container box which will act as a packing slip.
- Keep 1 copy in the Regulatory binder
- Fax or email one copy to Zosano Pharma, Lu Liu (LuLiu@zosanopharma.com) and Whitney Halladay (whalladay@zosanopharma.com), Fax: +1-510-952-4632, Phone: +1-510-745-1289

Unused Patch shipments to Zosano Pharma should be addressed to:

Zosano Pharma
ATTN: Lu Liu
Senior Director, Manufacturing and Supply Chain
34790 Ardentech Court
Fremont, CA 94555 USA
Phone: + 1 510-745-1289
Fax: +1-510-952-4632

2. New Applicator Collection and Shipment

Collection: At the completion of the study, place the used applicators back into the original applicator box or equivalent. Place the applicator boxes into a Ziploc bag and label bag with "Used Applicators." Place all unused applicators into another Ziploc bag and label bag with "Unused Applicators." Store used and unused applicators at room temperature until shipment to Zosano Pharma. All samples should be shipped in one shipment.

Shipment: Securely pack the bags of used and/or unused applicators into suitable boxes containing shipping materials (e.g., Styrofoam "popcorn" or bubble-wrap). Both used and unused applicators may be shipped back to Zosano Pharma at ambient temperature.

Shipments should be made via World Courier using the Zosano Pharma World Courier Account 13334.

All returned packages should contain the statement: "For research purposes only. Not for human use."

Complete the Product Return Form (provided by Sponsor) and include with each return shipment:

- Keep 1 copy in the Regulatory binder
- Place another copy of the Form in a Ziploc back and place the Ziploc bag inside the shipping container; this copy will be used as the packing slip for the shipment.
- Fax or email one copy to Zosano Pharma, Lu Liu (LuLiu@zosanopharma.com) and Whitney Halladay (whalladay@zosonopharma.com), **Fax: +1-510-952-4632**, Phone +1-510-745-1289

Applicator shipments to Zosano Pharma Corporation:

Zosano Pharma Corporation
ATTN: Lu Liu
Senior Director, Manufacturing and Supply Chain
34790 Ardentech Court
Fremont, CA 94555 USA
Phone: +1510-745-1289
Fax: +1-510-952-4632

APPENDIX 5: DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October

1996and the52nd WMA General Assembly, Edinburgh, Scotland, October 2000

INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other subjects in medical research involving human subjects. Medical research involving human subjects include research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

Medical progress is based on research that ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well being of the human subjects should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

In current medical practice and medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subjects.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research that may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be dearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the Investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the county in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even thought the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefit or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed subjects in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be adequately informed to the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If consent cannot be obtained in writing, non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the Investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the Investigator must obtain that assent in addition to the consent of the legally authorized representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the Investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE.

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

At the conclusion of the study, every patient entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.

The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or

alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.