CLINICAL PROTOCOL

STUDY TITLE:	Randomized, Double-Blind, Multi-Center, Parallel-Group Comparison of the Efficacy and Safety of the C213 (Zolmitriptan Intracutaneous Microneedle System) to Placebo for the Acute Treatment of Cluster Headaches	
PROTOCOL NUMBER:	CP-2019-001	
PROTOCOL VERSION:	Version 4.0	
PROTOCOL DATE:	Original:	27 June 2019
	Amendment 1:	16 July 2019
	Amendment 2:	01 October 2019
	Amendment 3:	15 April 2020
STUDY DRUG:	C213 (Zolmitriptan Intracutaneous Microneedle System)	
SPONSOR:	Zosano Pharma, Corporation 34790 Ardentech Court Fremont, CA 94555 Tel: 510-745-1200	
MEDICAL MONITOR:	Pete Schmidt, MD, MSc Zosano Pharma Corporation Tel: 510-745-1251	

ZOSANO PHARMA

Clinical Protocol
SPONSOR APPROVAL PAGE

Protocol CP-2019-001

Study Title: Randomized, Double-Blind, Multi-Center, Parallel-Group Comparison of the Efficacy and Safety of the C213 (Zolmitriptan Intracutaneous Microneedle System) to Placebo for the Acute Treatment of Cluster Headaches

Protocol Version: Amendment 3, Version 4 dated: 15 April 2020

Protocol approved by:

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

Donald J. Kellerman	04/15/2020

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

	04/15/2020

Pete Schmidt, MD
Medical Monitor **Date**

Peter Schmidt	04/15/2020

PROTOCOL SIGNATURE PAGE -PRINCIPAL INVESTIGATOR

Protocol Number: CP-2019-001

Study Title: Randomized, Double-Blind, Multi-Center, Parallel-Group Comparison of the Efficacy and Safety of the C213 (Zolmitriptan Intracutaneous Microneedle System) to Placebo for the Acute Treatment of Cluster Headaches

Protocol Version: 4.0

Protocol Date: 15 April 2020

I have received and read the protocol dated 15 April 2020. I agree to undertake the protocol as defined therein, and I will work according to the principles of GCP as described in 21 CFR parts 50, 54, 56, and 312, and according to applicable local requirements. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or informed consent form must first be approved by Zosano Pharma and the Institutional Review Board/Ethics Committee, except those changes necessary to eliminate apparent immediate hazards to subjects. Failure to adhere to these stipulations may constitute a breach of United States (U.S.) Federal Regulations and may result in termination of the study.

Principal Investigator

_____ _____

Signature Date

_____

Printed Name

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

5-HT receptors	5-hydroxytryptamine receptors
AE	Adverse event
ALT	Alanine transferase (same as SGPT)
AST	Aspartate aminotransferase (same as SGOT)
AUC	Area Under the Curve
AUC_{last}	Area under the curve calculated from minute 0 to the last measurable plasma concentration
$AUC_{0\text{-}2\ hr}$	Area under the curve calculated from 0 hour to the 2-hour plasma concentration
BP	Blood Pressure
C	Celsius
CAD	Coronary artery disease
CDMS	Clinical data management system
CFR	Code of Federal Regulations
cm^2	Centimeter squared
C_{max}	Maximum observed plasma concentration
CPK	Creatinine phosphokinase
CRF	Case report form
eCRF	Electronic Case report form
CRO	Contract Research Organization
CTA	Clinical Trials Authorization
CTM	Clinical trial material
CVA	Cerebral vascular accident
C213	Zolmitriptan Intracutaneous Microneedle System
dL	Deciliter
DMP	Data Management Plan
ECG	Electrocardiogram
F	Fahrenheit
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HDL	High-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IHS	International Headache Society
IND	Investigational New Drug
IRB	Institutional Review Board
IWRS	Interactive Web Randomization System
J	Joules

Kg	Kilogram
LDH	Lactate dehydrogenase
M207	Zolmitriptan Microneedle System
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mITT	Modified Intent-to-Treat
mL	Milliliter
MM	Medical Monitor
NDA	New drug application
PCP	Phencyclidine
PE	Physical examination
PRSPB	Patch-related superficial punctate bruising
PV	Pharmacovigilance
RDC	Remote Data Capture
RR	Respiratory Rate
RTSM	Randomization and Trial Supply Management system
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SEM	Standard error of the mean
SOP	Standard operating procedures
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
TIA	Transient ischemic attacks
TMF	Trial master file
U/L	Units per liter
U.S.	United States
WOCBP	Women of child-bearing potential
ZP-Zolmi	Zosano Pharma Zolmitriptan Microneedle System

PROTOCOL SYNOPSIS

TITLE	Randomized, double-blind, multi-center, parallel-group comparison of the efficacy and safety of the C213 (Zolmitriptan Intracutaneous Microneedle System) to placebo for the acute treatment of cluster headaches
SPONSOR	Zosano Pharma Corporation
CLINICAL PHASE	Phase 2/3
INDICATION	Acute treatment of cluster headaches in adults
OBJECTIVES	• To compare the efficacy of C213 at doses of 1.9 mg and 3.8 mg (1.9 mg x 2 patches) to placebo in the acute treatment of cluster headaches • To compare the safety of C213 at doses of 1.9 mg and 3.8 mg (1.9 mg x 2 patches) to placebo in the acute treatment of cluster headaches • To assess the dose-response relationship of C213 on efficacy and tolerability
TRIAL DESIGN	Multi-center, multiple dose, randomized, double-blind, placebo-controlled, parallel-group
INVESTIGATIONAL TREATMENT	Single-dose treatment (to be applied for 30 minutes) of the following: • C213, 1.9 mg on a 3 cm^2 patch and one placebo patch or • C213, 3.8 mg on two 3 cm^2 patches (1.9 mg x 2) or • Placebo microneedle system: two 3 cm^2 patches
BLINDING	Double-blind
RANDOMIZATION	1:1:1 (placebo, 1.9 mg, 3.8 mg)
STUDY POPULATION	Adults who suffer from chronic or episodic cluster headache
NUMBERS OF SUBJECTS	Approximately 120 subjects will be randomized at approximately 13 US sites.
ELIGIBILITY	<u>Inclusion Criteria:</u> Subjects presenting with all of the following may be included in the study: 1. Able to provide written informed consent 2. Women or men 18 to 65 years of age 3. Greater than 1-year history of episodic or chronic cluster headache with onset prior to 50 years of age. Diagnosis must comply with ICHD-3 (International Headache Society (IHS)

diagnostic criteria). Diagnostic criteria must include a history of at least 5 attacks not attributed to any other disorder that include all of the following criteria:

a) Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 45-180 minutes (average, when untreated)
b) Either or both of the following:
    (1) At least one of the following symptoms or signs, ipsilateral to the pain:
        (a) Conjunctival injection and/or lacrimation
        (b) Nasal congestion and/or rhinorrhea
        (c) Eyelid edema
        (d) Forehead and facial sweating
        (e) Miosis and or/ptosis
    (2) A sense of restlessness or agitation
c) Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active.
d) Not better accounted for by another ICHD diagnosis

4. Cluster history during the 12-month period prior to the screening visit must include:
    a) At least 1 cluster period
    b) Averaging 2-6 headaches per day
    c) Lasting at least 7 days
5. Subject can distinguish cluster headaches from other headaches (i.e., migraine and tension-type headaches)
6. Women of child-bearing potential must not be pregnant, must agree to avoid pregnancy during the trial, and must use one of the following or be surgically sterilized: intrauterine device, or a hormonal contraceptive
7. Able to understand the operation of the electronic diary and able to apply the demo study drug patch correctly.

<u>Exclusion Criteria:</u>

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

1. Contraindications to triptans
2. Use of any prohibited concomitant medications within 7 days of screening
3. History of hemiplegic migraine or migraine with brainstem

aura

4. Participation in another investigational trial within 30 days or 5 half-lives of investigational product (whichever is longer).
5. Previous M207/C213 exposure in a clinical trial
6. Subject has other significant pain problems that might confound the study assessments in the opinion of the investigator
7. Diagnosis of any malignant disease (other than adequately treated or excised non-metastatic basal cell carcinoma or squamous cell carcinoma of the skin) within the 5 years prior to screening
8. History of unstable psychiatric illness requiring medication or hospitalization in the 12 months prior to study screening
9. Subjects who have a known allergy or sensitivity to zolmitriptan or its derivatives or formulations
10. Subjects who have a known allergy or sensitivity to adhesives
11. Subjects who have skin lesions or tattoos covering the entire potential area(s) of C213 application
12. Woman who are pregnant, breast-feeding or plan a pregnancy during this study
13. Clinically significant liver disease (ALT > 150 U/L; AST > 130 U/L or bilirubin > 2x ULN)
14. Clinically significant kidney disease (eGFR < 60 ml/min / 1.73 m^2 or to creatinine > 1.5 x ULN)
15. Subject has clinically significant ECG findings, defined by:
    a) ischemic changes (defined as > 1mm of down-sloping ST segment depression in at least two contiguous leads)
    b) Q-waves in at least two contiguous leads
    c) clinically significant intra-ventricular conduction abnormalities (left bundle branch block or Wolf-Parkinson-White syndrome)
    d) clinically significant arrhythmias (e.g., current atrial fibrillation)
16. History of coronary artery disease (CAD), coronary vasospasm (including Prinzmetal's angina), aortic aneurysm, peripheral vascular disease or other ischemic diseases (e.g., ischemic bowel syndrome or Raynaud’s syndrome)
17. Three or more of the following CAD risk factors:
    a) Current tobacco use
    b) Hypertension (systolic BP > 140 or diastolic BP > 90)

or receiving anti-hypertensive medication for treatment of hypertension

c) Hyperlipidemia – LDL > 159 mg/dL and/or HDL < 40 mg/dL (or on prescribed anti-cholesterol treatment)

d) Family history of premature coronary artery disease (CAD) (< 55 years of age in male first-degree relatives or < 65 years of age in female first degree relatives)

e) Diabetes mellitus

18. History of cerebral vascular accident (CVA), transient ischemic attacks (TIA), or seizures
19. History of concurrent illness that requires hospitalization within 30 days prior to study screening
20. Any other household member currently participating in a C213 study or relative of site staff member
21. Any reason to believe that compliance with the study requirements and completion of evaluations required for this study will not be possible
22. Any language barrier that, in the opinion of the Investigator, would preclude communication and compliance with the study requirements
23. History or current abuse of or dependence on alcohol or drugs that would interfere with the results or adherence to study requirements, and/or current tobacco cigarette smoking
24. Any positive drug screens for phencyclidine (PCP), MDMA (ecstasy), cocaine, and/or meth/amphetamine(s)
25. Current or planned use of hallucinogens (e.g. psilocybin) during the trial
26. Any clinically relevant abnormal findings in the physical exam, vital signs or laboratory tests that, in the opinion of the Investigator, may put the subject at risk

CENTERS	Multicenter in the United States
STUDY DURATION	Screening: 1 to 7 days, Double-blind Period: Subject has up to 48 weeks to administer study medication, End of Study Visit is 1-8 days following administration of study drug
STUDY PROCEDURES	• Screening activities may be performed in 1 to 7 days [+ 3 days] • Double-blind period for up to 48 weeks [+ or – 7 days] • Phone contacts monthly [every 28 days + or – 3 days] • Pregnancy urine testing for WOCBP monthly [every 28 days + or – 7 days] • Rescue therapy allowed at or after 20 min post dose • One single treatment by subject with symptom recording at pre-dose, 5 min, 10 min, 15 min, 20 min, 30 min, and 60 min • End of study or early discontinuation Visit 3 is 1-8 days post-cluster headache treatment
CRITERIA FOR EVALUATION: **EFFICACY AND SAFETY**	**<u>Co-Primary Efficacy Endpoints</u>:** • Proportion of subjects who achieve pain relief at 15 minutes. Headache pain is assessed using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Pain relief is defined by a decrease in pain from severe to mild or none without the use of acute rescue medication. • Proportion of subjects who achieve sustained pain relief from 15 minutes to 60 minutes post patch application. Sustained pain relief requires a pain rating of mild or none at each timepoint from 15 minutes to 60 minutes without the use of acute rescue medication. **<u>Secondary Efficacy Endpoints</u>:** • Proportion of subjects that achieve pain relief at 5, 10, 20, and 30 minutes post patch application • Proportion of subjects that achieve sustained pain relief from 5 to 60 minutes and from 10 to 60 minutes post patch application • Proportion of subjects that achieve pain freedom at 10- and 15-minutes post patch application • Proportion of subjects that achieve sustained pain freedom from 10 to 60 minutes and from 15 to 60 minutes post patch application • Proportion of subjects with rescue therapy use within 20 minutes post patch application • Proportion of subjects able to perform their usual daily activities as assessed by the subject

SAFETY

- Incidence of adverse events
- Physical exam including height and weight
- Vital signs including blood pressure
- Serum chemistries and hematological parameters
- Serum and urine pregnancy for women of child-bearing potential
- 12-lead ECGs
- Assessment of concomitant medications
- Investigator visual skin Assessments

STATISTICAL METHODS:

EFFICACY ANALYSIS:

For the primary efficacy analysis, the proportion of subjects achieving pain relief at 15 minutes and sustained pain relief from 15 minutes to 60 minutes post-dose will be analyzed separately using a Cochran Mantel Haenszel test stratified by cluster headache subtype (chronic or episodic). A significance test of the treatment difference comparing each C213 dose to placebo will be tested at the two-sided 0.05 level, and odds ratios and their corresponding 95% confidence intervals will be calculated. Secondary endpoints will be analyzed using similar methods. A fixed sequence procedure will be applied to the two C213 arms and the primary and secondary efficacy endpoints to adjust for multiplicity and to control for overall type I error.

Safety Analyses:

Adverse events will be summarized overall and by preferred term and system organ class. Adverse events will also be summarized by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized. 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.

Sample Size:

It is anticipated that 20% of subjects receiving placebo and 55% of subjects receiving active treatment will achieve pain relief at 15 minutes and sustained pain relief from 15 minutes to 60 minutes post-dose. Based on a two-sided chi-square test with continuity correction and an alpha level of 0.05, 40 patients/arm will provide approximately 80% power to detect this same difference between two treatment groups, assuming a 15% dropout rate.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

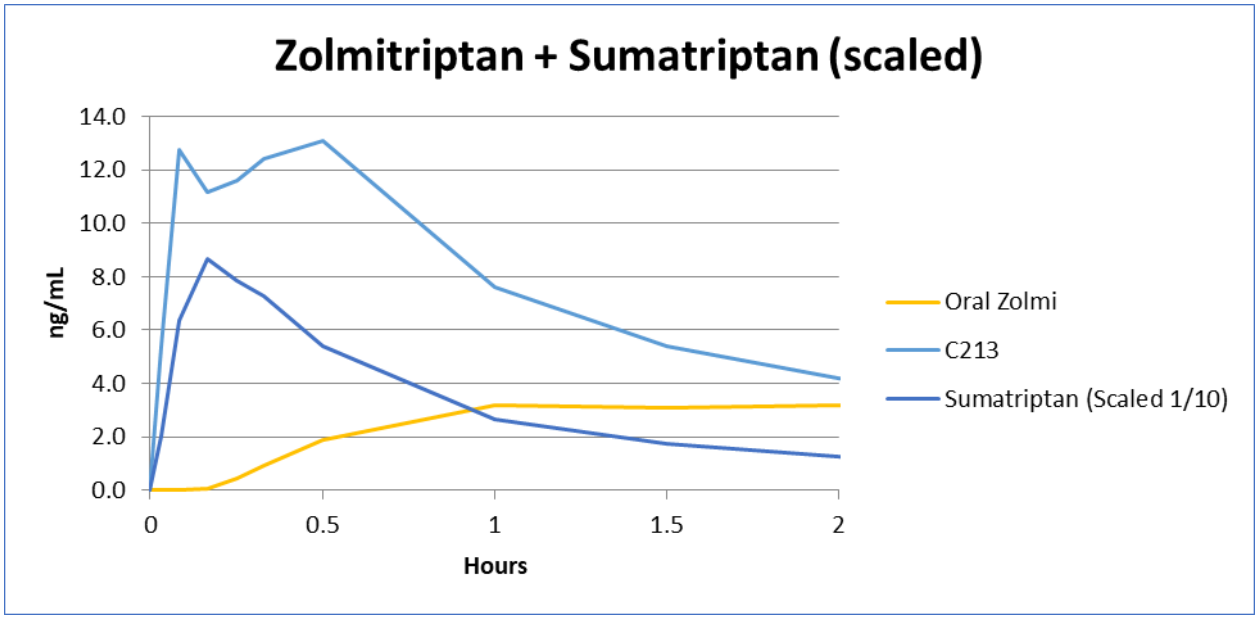
1 INTRODUCTION

1.1 Background C213 for the Acute Treatment of Cluster Headache

Cluster headache is a debilitating and painful disorder that affects approximately 0.1% of the U.S. population. The excruciating headaches, lasting from 15 minutes to 3 hours and averaging 45-60 minutes, and are often described as the worst pain the sufferer has ever experienced. A number of acute treatments have been utilized, including injectable triptans, inhaled oxygen and neurostimulation. Perhaps the most important attribute for an acute treatment of cluster headache is rapid onset of pain relief or freedom (Rozen et al 2012).

Zosano is evaluating C213 for the acute treatment of cluster headache (both episodic and chronic). Intranasal and oral zolmitriptan products have been evaluated for the treatment of cluster headache, in randomized, placebo-controlled trials and found to be effective. Unfortunately, these trials only demonstrated significant efficacy at 30 minutes, which is not ideal for these intense and short-lived attacks (Cittadini et al 2006, Bahra et al 2000, Hedlund et al 2009).

Subcutaneous (SC) sumatriptan is also effective for the treatment of cluster headache and relieves headache pain in a significant percentage of sufferers (Ekbom et al 1993). This is likely due to the rapid absorption of sumatriptan following injection. Zosano conducted a pharmacokinetic study (CP-2015-007) comparing plasma concentrations of sumatriptan following subcutaneous administration with several dose levels of C213 and oral zolmitriptan 2.5 mg. The mean plasma concentrations following C213 3.8 mg, oral zolmitriptan 2.5 mg, and subcutaneous sumatriptan 6.0 mg are shown below. Note that the plasma concentrations of sumatriptan were divided by 10 to account for differences in potency, as the slide is intended to illustrate the comparative pharmacokinetic curves.



By visual inspection, one can see that plasma concentrations of zolmitriptan were detectable very quickly after C213 administration, and the time to maximum concentration is similar to subcutaneous sumatriptan. As has been described several times, time to maximum concentration of oral zolmitriptan is approximately one hour (Seaber et al 1998), which is far less desirable for treating cluster headaches.

If the rapid absorption of zolmitriptan following C213 administration results in fast relief of the severe pain of cluster headache, C213 would be a valuable addition to the therapeutic options currently available to cluster headache sufferers. The goal of this trial is to compare C213 doses of 1.9 mg and 3.8 mg (administered as two patches of 1.9 mg) to placebo for the treatment of acute cluster headache.

1.2 Clinical Pharmacology, Efficacy, and Safety of zolmitriptan and other studies of Cluster Headache

Human Pharmacokinetics

A Phase 1 study compared the PK of intracutaneous zolmitriptan and its metabolites as well as the tolerability of various doses of intracutaneous zolmitriptan to a standard oral dose (2.5 mg) of zolmitriptan (CP-2015-007). Additionally, since onset of effect may be an important attribute of the intracutaneous system, the study included a comparison of T_{max} values with SC sumatriptan 6.0 mg. The study provided preliminary information on the potential advantages of the C213 system use for the treatment of cluster headaches.

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

Table 1: Key Pharmacokinetic Parameters

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

Perhaps most relevant to the potential utility of this product for the treatment of cluster headache is the T_{max} for the ZP-Zolmitriptan regimens, showing much more rapid absorption of the zolmitriptan from intracutaneous administration than from oral administration.

Efficacy Measurements

The efficacy of C213 for the acute treatment of cluster headaches has not been established. The efficacy of zolmitriptan given by oral tablet or nasal spray has been demonstrated in large placebo-controlled trials (Rapoport et al 1997, Dawson et al 2005, Dahlof et al 1998). In a meta-analysis of zolmitriptan nasal spray for cluster headache, the authors found that headache response was observed at 30 minutes (primary endpoint) in a larger proportion of subjects than placebo for both 5 mg and 10 mg doses (48.3% vs 29.5%, P = .0004, and 63.1% vs 29.5%, P ≤ .001, respectively). Furthermore, significantly more subjects were pain free at 30 minutes in both dose groups as compared to placebo (34.8% vs 19.3%, P = .007 for 5 mg, and 44% vs 19.3%, P ≤ .001 for 10 mg). Similarly, oral zolmitriptan was found to be effective in episodic cluster headache at both the 10 mg (59.5%) and 5mg (56.6%) doses versus placebo (42.2%, P ≤ 0.01 for both doses) Bahra et al 2000. The oral formulation was not found to be significantly different from placebo in chronic cluster.

Subcutaneous sumatriptan 6 mg was evaluated in two double-blind, placebo-controlled, crossover trials of individuals with cluster headache. Pain relief rates at 15 minutes for SC sumatriptan were 74% and 75% compared with placebo pain relief rates of 26% and 35%. In both trials, SC sumatriptan was significantly more effective than placebo. Thus, pain relief rates appeared higher with the more rapidly absorbed product (Imitrex product information).

Safety Assessments

As with efficacy, the safety of various formulations of zolmitriptan has been extensively studied, predominantly in migraine patients.

The safety of oral zolmitriptan at significantly higher doses (and presumably higher plasma concentrations) than those proposed for the C213 program, has been evaluated in two large placebo-controlled studies of migraine. Dahlof et al 1998 evaluated 1181 subjects who received zolmitriptan doses of 5 mg, 10 mg, 15 mg or 20 mg (more than 200 subjects per dose group). The incidence of adverse events was 61%, 75%, 79% and 76% respectively. \The most commonly reported adverse events were asthenia, dizziness, paresthesia and feelings of heaviness. Most of the adverse events were mild or moderate in intensity, not serious, transient and resolved without intervention. The incidence of chest-related adverse events i.e., tightness, pain, heaviness, and pressure was low. Administration of zolmitriptan, even at the highest dose, was not associated with significant effects on clinical laboratory tests or ECGs.

Rapoport et al 1997 compared oral doses ranging from 1 mg to 10 mg of zolmitriptan to placebo in 1258 migraine patients and found that efficacy increased as a function of dose, and that all doses of zolmitriptan were well-tolerated, although the incidence of adverse events was dose-related.

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

Long-Term Safety Studies of Zolmitriptan

Two large long-term studies have established the long-term safety of oral zolmitriptan and intranasal zolmitriptan. The International Zolmitriptan Study group studied 2058 patients who treated 31579 migraines with 5 mg oral zolmitriptan over one year and found the drug to be well-tolerated. Dawson et al evaluated 538 patients who treated 20717 attacks over 1 year with intranasal zolmitriptan 5 mg, and also found a high degree of tolerability. Therefore, the long-term safety of frequent administration of zolmitriptan administered from two different formulations has been well established.

Zosano Pharma Protocol CP-2016-001 Safety Data

1.2.1 Safety Results of Protocol CP-2016-001

Study CP-2016-001 was a dose ranging study comparing the safety and efficacy of M207/C213 to placebo in the acute treatment of migraine attacks. 365 subjects were enrolled in this study. No serious adverse events occurred in the efficacy and safety study CP-2016-001 in subjects with migraine. Adverse events including investigator and subject-reported dermal events at the patch site were generally mild and transient. Treatment-emergent adverse events that occurred in two or more subjects summarized by System Organ Class/Preferred Term are shown in Table 2, and Investigator Dermal Adverse Events are shown in Table 3.

Table 2: Treatment Emergent Adverse Events Occurring in Two or More Subjects

	Treatment Group				
	Placebo (N=83)	**C213 1 mg (N=80)**	**C213 1.9 mg (N=87)**	**C213 3.8 mg (N=83)**	**Total (N=333)**
System Organ Class/Preferred Term	**No. (%) Subjects**	**No. (%) Subjects**	**No. (%) Subjects**	**No. (%) Subjects**	**No. (%) Subjects**
General disorders and administration site conditions	12 (14.5%)	23 (28.8%)	31 (35.6%)	38 (45.8%)	104 (31.2%)
Application site erythema	9 (10.8%)	13 (16.3%)	17 (19.5%)	22 (26.5%)	61 (18.3%)
Application site bruise	3 (3.6%)	5 (6.3%)	12 (13.8%)	12 (14.5%)	32 (9.6%)
Application site pain	1 (1.2%)	2 (2.5%)	2 (2.3%)	8 (9.6%)	13 (3.9%)
Application site hemorrhage	0 (0.0%)	3 (3.8%)	5 (5.7%)	4 (4.8%)	12 (3.6%)
Application site swelling	3 (3.6%)	1 (1.3%)	3 (3.4%)	2 (2.4%)	9 (2.7%)
Application site edema	0 (0.0%)	1 (1.3%)	3 (3.4%)	2 (2.4%)	6 (1.8%)
Application site discoloration	1 (1.2%)	1 (1.3%)	1 (1.1%)	1 (1.2%)	4 (1.2%)
Musculoskeletal and connective tissue disorders	0 (0.0%)	1 (1.3%)	2 (2.3%)	4 (4.8%)	7 (2.1%)
Muscle tightness	0 (0.0%)	0 (0.0%)	1 (1.1%)	2 (2.4%)	3 (0.9%)
Musculoskeletal stiffness	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (1.2%)	2 (0.6%)
Myalgia	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (1.2%)	2 (0.6%)
Gastrointestinal disorders	1 (1.2%)	2 (2.5%)	2 (2.3%)	1 (1.2%)	6 (1.8%)
Nausea	0 (0.0%)	2 (2.5%)	1 (1.1%)	1 (1.2%)	4 (1.2%)
Vomiting	1 (1.2%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
Investigations	1 (1.2%)	1 (1.3%)	1 (1.1%)	0 (0.0%)	3 (0.9%)
Blood creatine phosphokinase increased	1 (1.2%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	2 (0.6%)
Infections and infestations	0 (0.0%)	1 (1.3%)	1 (1.1%)	0 (0.0%)	2 (0.6%)

Table 3: Investigator Visual Dermal Adverse Events

Patch-Related Superficial Punctate Bruising (PRSPB)	N	Treatment Group			
		Placebo (N=83)	C213 1 mg (N=80)	C213 1.9 mg (N=87)	C213 3.8 mg (N=83)
		83	78	84	83
	None	82 (98.8%)	73 (93.6%)	72 (85.7%)	74 (89.2%)
	≤ 25% ZP patch application site has punctate bruising spots	1 (1.2%)	5 (6.4%)	9 (10.7%)	4 (4.8%)
	≥ 26% to < 50% ZP patch application site has punctate bruising spots	0 (0.0%)	0 (0.0%)	2 (2.4%)	2 (2.4%)
	> 50% ZP patch application site has punctate bruising spots	0 (0.0%)	0 (0.0%)	1 (1.2%)	3 (3.6%)
Edema	N	83	78	84	83
	None	83 (100.0%)	77 (98.7%)	81 (96.4%)	82 (98.8%)
	Slight Edema	0 (0.0%)	1 (1.3%)	3 (3.6%)	1 (1.2%)
	Moderate Edema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe Edema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Erythema	N	83	78	84	83
	None	78 (94.0%)	71 (91.0%)	71 (84.5%)	64 (77.1%)
	Mild Redness	5 (6.0%)	7 (9.0%)	10 (11.9%)	16 (19.3%)
	Well-defined Redness	0 (0.0%)	0 (0.0%)	3 (3.6%)	3 (3.6%)
	Beet Redness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

1.3 Study Rationale and Choice of Design

C213 is a novel formulation of zolmitriptan for intracutaneous delivery, which when administered results in rapid systemic absorption of zolmitriptan and time to maximum concentration of plasma zolmitriptan of approximately 15 minutes. This product was evaluated in a previous migraine trial (CP-2016-001), and the 3.8 mg dose was superior to placebo for both co-primary endpoints. The 1.9 mg dose was superior to placebo for 1 of 2 co-primary endpoints (pain freedom at 2 hours). Tolerability was good, and the most common adverse reactions were application site reactions, that all resolved over a course of hours to days.

Cluster headaches are severe, debilitating and exquisitely painful, but the attacks are of shorter duration than in migraine. Given the characteristics of the attacks, any drug administered to abort the attacks must be rapidly absorbed to be of benefit. Previous trials of subcutaneous sumatriptan have demonstrated that a rapidly absorbed triptan can relieve the pain associated with a cluster attack. Thus, C213 with observed T_{max} ranging from 2-30 minutes seen in a

previous Phase 1 study, may be absorbed rapidly enough to produce systemic levels of zolmitriptan, sufficient to relieve a cluster headache attack.

The doses of C213 used in this study are 3.8 mg, that was found to be effective in a previous migraine efficacy trial and 1.9 mg, that was effective for pain reduction in the same trial. There is anecdotal clinical evidence that lower doses of injected triptans may be effective for cluster headache attacks.

Sample size determination was estimated based on the characteristics of C213 and the results of previous trials of pharmacologic agents for the treatment of cluster headache. The only product approved for treating cluster headache is subcutaneous sumatriptan, and the effect size in those trials was significant. However, the trials were crossover designs utilizing paper diaries conducted in the 1990s. The more recent trials with zolmitriptan (particularly nasal spray) had smaller effect sizes, perhaps due to slower absorption than seen with SC sumatriptan. C213 has pharmacokinetics more similar to SC sumatriptan than the zolmitriptan formulations. Therefore, we estimated the effect size of C213 to be somewhere between that of SC sumatriptan and that of intranasal zolmitriptan.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To compare the efficacy of C213 at doses of 1.9 mg and 3.8 mg (1.9 mg x 2 patches) to placebo in the acute treatment of cluster headache attacks

2.2 Secondary Objectives

- To compare the safety of C213 at doses of 1.9 mg and 3.8 mg (1.9 mg x 2 patches) to placebo in the acute treatment of cluster headache attacks
- To assess the dose-response relationship of C213 on efficacy and tolerability

3 INVESTIGATIONAL PLAN

3.1 Study Design

The study is outlined in Figure 1.

Figure 1: Study Design

SCREENING PERIOD **1-7 days**		**DOUBLE BLIND TREATMENT PERIOD –** **DAY 1 – DAY 336**	
Up to one week prior to Randomization		Starts on Day 1 = Randomization	Up to 48 weeks from Day 1
Obtain ICF and all required screening procedures. If subject qualifies for randomization, schedule visit 2.	→	If the subject still qualifies for randomization at visit 2, the subject will be assigned by the Medidata RTSM randomization system one of the following kits: 1. C213 1.9 mg patch and placebo patch administered upon confirmed cluster headache or → Subject will have up to 48 weeks to confirm and treat a cluster headache attack. Subject will answer questions about his/her headache symptoms in the eDiary. Upon confirmation of a qualifying cluster headache, the subject will self-administer the patches. The subject will continue to complete the eDiary at specified time points out to 60 minutes post dose. 2. C213 3.8 mg (1.9 mg x 2 patches) administered upon confirmed cluster headache or → 3. Placebo (two patches) administered upon confirmed cluster headache →	
If preliminary entry criteria indicate that the subject is <u>not</u> eligible for randomization, register the subject as a screen failure.		If the subject does not meet all the inclusion and/or meets one or more of the exclusion criteria, record the subject as a screen failure in the Medidata EDC system.	Subject will be seen for their final visit within 1-8 days post C213 application.

This is a randomized, double-blinded, placebo-controlled study. Subjects who have consented and meet the entry criteria will be randomized to receive one of three blinded treatments.

Qualified subjects will randomize to the double-blind treatment period at Day 1 and will have up to 48 weeks to confirm and treat a cluster headache. Using the eDiary to confirm the subject is experiencing a cluster headache, subjects will self-administer the patches and continue to respond to questions in the eDiary for 1-hour post treatment administration.

3.2 Selection of Study Population

3.2.1 Number of Subjects

Approximately 120 subjects will be randomized into the study at approximately 13 study sites.

3.2.2 Inclusion Criteria

Inclusion Criteria:

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

1. Able to provide written informed consent
2. Women or men 18 to 65 years of age
3. Greater than 1-year history of episodic or chronic cluster headache with onset prior to 50 years of age. Diagnosis must comply with ICHD-3 (International Headache Society (IHS) diagnostic criteria. Diagnostic criteria must include a history of at least 5 attacks not attributed to any other disorder that include all of the following criteria:
    a) Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 45-180 minutes (average, when untreated)
    b) Either or both of the following:
        1. At least one of the following symptoms or signs, ipsilateral to the pain:
            (a) Conjunctival injection and/or lacrimation
            (b) Nasal congestion and/or rhinorrhea
            (c) Eyelid edema
            (d) Forehead and facial sweating
            (e) Miosis and or/ptosis
        2. A sense of restlessness or agitation
    c) Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active
    d) Not better accounted for by another ICHD diagnosis
4. Cluster history during the 12-month period prior to the screening visit must include:
    a) at least 1 cluster period
    b) averaging 2-6 headaches per day
    c) lasting at least 7 days
5. Subject can distinguish cluster headaches from other headaches (i.e., migraine and tension-type headaches)

6. Women of child-bearing potential must not be pregnant, must agree to avoid pregnancy during the trial, and must use one of the following or be surgically sterile: intrauterine device or a hormonal contraceptive
7. Able to understand the operation of the electronic diary and able to apply the demo study drug patch correctly.

3.2.3 Exclusion Criteria:

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

1. Contraindication to triptans
2. Use of any prohibited concomitant medications within 7 days prior to screening (See Table 6 Prohibited Concomitant Medications)
3. History of hemiplegic migraine or migraine with brainstem aura
4. Participation in another investigational trial within 30 days or 5 half-lives of investigational product (whichever is longer)
5. Previous M207/C213 exposure in a clinical trial
6. Subject has other significant pain problems that might confound the study assessments in the opinion of the Investigator.
7. Diagnosis of any malignant disease (other than adequately treated or excised non-metastatic basal cell carcinoma or squamous cell carcinoma of the skin) within the 5 years prior to screening
8. History of unstable psychiatric illness requiring medication or hospitalization in the 12 months prior to study screening
9. Subjects who have a known allergy or sensitivity to zolmitriptan or its derivatives or formulations
10. Subjects who have known allergy or sensitivity to adhesives
11. Subjects who have skin lesions or tattoos covering the entire potential area(s) of C213 application
12. Women who are pregnant, breast-feeding or plan a pregnancy during this study
13. Clinically significant liver disease (ALT > 150 U/L; AST > 130 U/L or bilirubin > 2x ULN)
14. Clinically significant kidney disease (eGFR < 60 ml/min /1.73 m^2 or to creatinine > 1.5 x ULN)
15. Subject has clinically significant ECG findings, defined by:
    a) ischemic changes (defined as > 1mm of down-sloping ST segment depression in at least two contiguous leads)
    b) Q-waves in at least two contiguous leads

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

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

16. History of coronary artery disease (CAD), coronary vasospasm (including Prinzmetal's angina), aortic aneurysm, peripheral vascular disease or other ischemic diseases (e.g., ischemic bowel syndrome or Raynaud's syndrome)
17. Three or more of the following CAD risk factors:
    a) Current tobacco use
    b) Hypertension (systolic BP > 140 or diastolic BP > 90) or receiving anti-hypertensive medication for treatment of hypertension
    c) Hyperlipidemia – LDL > 159 mg/dL and/or HDL < 40 mg/dL (or on prescribed anti-cholesterol treatment)
    d) Family history of premature coronary artery disease (CAD) (< 55 years of age in male first-degree relatives or < 65 years of age in female first degree relatives)
    e) Diabetes mellitus
18. History of cerebral vascular accident (CVA), transient ischemic attacks (TIA), or seizures
19. History of concurrent illness that requires hospitalization within 30 days prior to study screening
20. Any other household member currently participating in a C213 study or relative of site staff member
21. Any reason to believe that compliance with the study requirements and completion of evaluations required for this study will not be possible
22. Any language barrier that, in the opinion of the Investigator, would preclude communication and compliance with the study requirements
23. History or current abuse of or dependence on alcohol or drugs that would interfere with the results or adherence to study requirements, and/or current tobacco cigarette smoking
24. Any positive drug screens for phencyclidine (PCP), MDMA (ecstasy), cocaine, and/or meth/amphetamine(s)
25. Current or planned use of hallucinogens (e.g. psilocybin) during the trial
26. Any clinically relevant abnormal findings in the physical exam, vital signs or laboratory tests that, in the opinion of the Investigator, may put the subject at risk

3.2.4 Eligibility Criteria for Randomization

To be eligible for randomization and the double-blind period, subjects must meet all inclusion and exclusion criteria. In addition, the following must be confirmed on the day of randomization:

1. Demonstrated ability to properly use the eDiary
2. Willing to enter eDiary data to determine if he/she is experiencing a qualifying cluster headache attack and complete the eDiary questions after applying the patches
3. Demonstrated ability to apply the demonstration study drug patches
4. Confirmation of continuing good general health, or stable non-serious disease that in the opinion of the Investigator will not place the subject at risk

3.2.5 Prior and Concomitant Medications Allowed During the Study

Medications that are considered necessary for the subject's welfare and are not specifically prohibited (Section 6.2.10*)*, may be given at the discretion of the investigator. The administration of such medication must be recorded in the appropriate source document and in the electronic case report form (eCRF) for the duration of the study.

For the cluster headache to be qualifying for study medication, no medications specifically taken for the subject's headache symptoms are allowed within 24 hours prior to onset of the current cluster headache symptoms. If rescue therapy is required by the subject, rescue therapy other than a triptan or ergot is permitted at or after 20 minutes post study drug administration.

Oxygen will be provided in an "E" cylinder (680L), with a flow-rate adjustable regulator and a non-rebreather facemask.

3.2.6 Early Termination

3.2.6.1 Withdrawal of Subjects

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

- At their own request or at the request of their legally authorized representative;
- If, in the investigator's opinion, continuation of treatment would be detrimental to the subject's well-being;
- If the subject experiences any AE believed to be possibly or probably related to study drug and severe enough to warrant withdrawal of treatment;
- If the subject starts and continues to use a prohibited drug, as listed in Section 6.2.10; or
- If the subject is non-compliant with the study drug and dosing schedule, or any other requirement of this protocol.

For all subjects who are withdrawn from the study, the reason must be recorded on the appropriate source document and on the appropriate eCRF. The subject must be followed up to establish whether the reason was an AE, and, if so, this must be reported in accordance with the procedures in Section 8.3. Subjects with ongoing systemic and skin AEs at study termination will be followed until all significant changes have resolved or become medically stable.

To the extent possible, all examinations scheduled and all data normally collected at completion of the study (the final study visit) must be performed on all subjects who receive study drug, but do not complete the study according to protocol (see Section 6.1.4). This can be done until study closure but preferably as close as possible to the time of the subject's early termination.

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

3.2.6.2 Replacement of Subjects

Subjects who discontinue after being randomized will not be replaced.

3.2.6.3 Premature Discontinuation of the Trial

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

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

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

4 STUDY TREATMENTS

4.1 Identity of Investigational Products

4.1.1 C213

The C213 patches will be manufactured by Zosano Pharma in Fremont, CA (see Investigator's Brochure for more information).

4.1.2 Comparator Product: ZP-Placebo

The Placebo will be manufactured by Zosano Pharma. The placebo patch is a single use, 3 cm^2 Placebo (intracutaneous microneedle) system that contains no active ingredients.

The Placebo patch is supplied and packaged in an identical fashion as the C213 1.9 mg coated patch thereby maintaining the blinding.

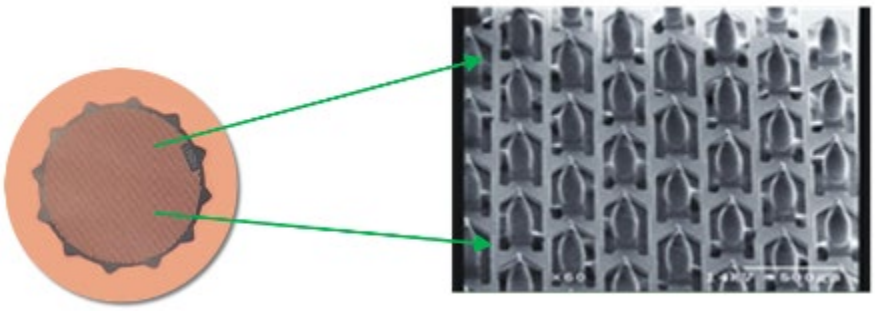
4.1.3 Product Description and Patch Application

The Zosano C213 Microneedle System is a novel drug delivery technology which consists of a disposable titanium patch centered on an adhesive backing with microneedles that are dry-coated with the drug product formulation, and a reusable handheld applicator that ensures that the patch is applied with a defined application speed and energy to the site of administration.

The C213 System is a proprietary disposable patch and a reusable applicator. The zolmitriptan-coated titanium microneedle array (3 cm^2 array) is attached to a 5 cm^2 adhesive patch. A magnified image of the zolmitriptan-coated microneedles is shown in Figure 2. The patch system is composed of several parts. The patch is mounted inside a polycarbonate plastic ring with a co-molded desiccant (Figure 3).

The completed system is packaged in a nitrogen purged foil cup. The reusable applicator is shown in Figure 3 and Figure 4 with a lock-out function to avoid accidental firing. The applicator provides a spring-driven piston to apply the patch with consistent impact energy of 0.26 Joules. The user presses the handheld reusable applicator onto the patch ring assembly for attachment, then the applicator is un-locked by twisting the cap. The user applies the patch by pressing the applicator/patch ring assembly onto the skin site and holding it to the arm for 3 seconds (Figure 4). The system was used in the Zosano Pharma Phase 1 study CP-2015-007, conducted in Australia under Clinical Trials Authorization (CTA), two phase 1 PK studies, CP-2018-002 and CP-2019-001 conducted in the US, a Phase 2 efficacy study CP-2016-001 and a long-term safety study CP-2017-001, conducted in the US. The intended regimens for this clinical study will be 1.9 mg plus one placebo patch, two patches of 1.9 mg (3.8 mg total dose), or two placebo patches delivered to the upper arm.

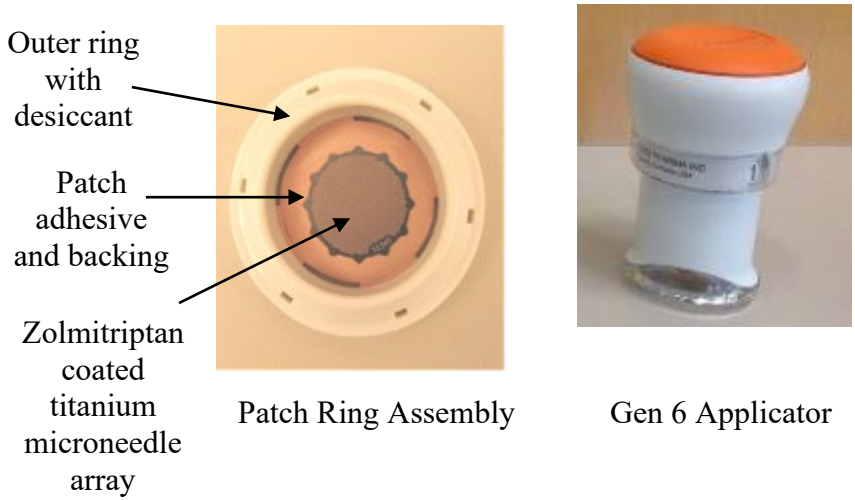
Figure 2: 5 cm^2 Patch with Zolmitriptan Coated Titanium Microneedle Array



C213 Intracutaneous Patch with Titanium Array

Magnified section – C213 Intracutaneous Patch with Titanium Array

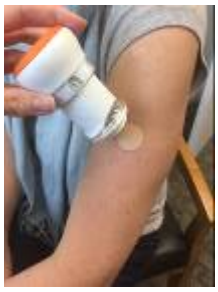
Figure 3: Handheld Gen 6 Patch Ring Assembly and Applicator

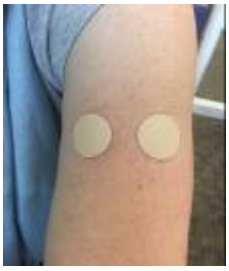


Patch Ring Assembly

Gen 6 Applicator

Figure 4: *C213 Patch Application

	Open the foil cups.
	Snap one patch-ring assembly onto the applicator.
	Twist applicator cap clockwise from Position 1 to Position 2 to unlock for patch application.
	Press applicator downward to apply patch to upper arm. Press down firmly against the skin until you hear a click then hold for 3 seconds. Patches are left on for 30 minutes.
 	Remove the outer ring in order to load and apply the second patch.

	Repeat the above steps to apply second patch next to the first patch. Both patches are to be removed at 30 minutes post application, and should be discarded and not returned to the clinic.

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

4.2 Method of Assigning Subjects to Treatment Group

Approximately 120 subjects will be randomly assigned to receive one of the three treatments in a 1:1:1 ratio: C213 1.9 mg administered as one active and one placebo patch, C213 3.8 mg administered as two active patches, or placebo administered as two placebo patches. Randomization will be stratified by study center and cluster headache subtype (chronic or episodic). Zosano will employ RTSM randomization system for randomization and subsequent clinical trial material (CTM) kit assignments. A contract research organization will be responsible for generating the randomization schedule.

At randomization (Day 1), once it has been established that a subject qualifies for the study, study staff will log in to Medidata using appropriate credentials and input subject-specific information. In accordance with the randomization schedule, the RTSM will assign the randomization number and the unique CTM kit number to the subject. Each subject must be given only the CTM kit assigned by the RTSM randomization system. The study staff will document the kit number assigned in the eCRF. Subjects are to be randomized in the order in which they qualify from the screening phase for inclusion in the study.

4.3 Dose, Dose Schedule, and Route of Administration

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

When a subject experiences a qualifying headache (as confirmed by answering questions in the eDiary), the subject will self-administer the study drug. Subjects will be trained on how to administer the patches using the C213 applicator supplied in the kit.

4.4 Packaging, Labeling, and Receipt of Supplies

In this study, C213 active and placebo patches will be double-blinded.

The C213 patches (active or placebo) are individually packaged in cups. Two patches per dose and one applicator will be packaged in a CTM kit based on the randomization schedule. The kit labels will contain at minimum the manufacturer's name, CTM kit number, storage conditions, and a statement indicating that the study drug is for investigational use only.

The on-site pharmacist or designee will inventory and acknowledge receipt of all shipments of study drug. The study site personnel will access the RTSM in Medidata to confirm receipt of each study drug shipment.

4.5 Study Drug Stability, Storage, and Retention

C213 patches are stable at 20-25°C. The patches and handheld applicators, packaged in individual subject kits, should be stored at controlled room temperature (20-25°C/68°F-77°F). All CTM kits must be kept in a locked area with access restricted to designated study personnel. Sites do not need to report excursions in the range of 15°C to 20°C. Sites must report all excursions under 15°C and over 25°C.

4.6 Study Drug Kit Assignment, Dispensation, and Accountability

A kit will be supplied to each subject based on the kit number assigned by the RTSM in Medidata. The pharmacist or designee will record the CTM kit number dispensed to each subject on the drug accountability record. The designated site monitor will periodically check the supplies of CTM to ensure accountability of used applicators and unused kits. Final study drug accountability will be completed after the last subject visit. All drug accountability records will be filed in the site file and TMF as appropriate. The kits dispensed and used for each subject must be documented. Any discrepancies must be documented.

4.7 System Performance

A C213 Site User's Manual will be provided. An applicator associated with field observations of atypical appearance or system performance that cannot be resolved after consulting the C213 Site User's Manual should be returned directly to Zosano Pharma following the instructions provided in the manual. A description of the field observation should accompany the shipment. Only defective applicators will be returned to Zosano. At the end of the study, all unused kits will be dispositioned per Zosano Pharma instructions.

4.8 Medication Compliance

The investigator will emphasize the importance of correctly self-administering the study medication once a qualifying cluster headache is confirmed through the eDiary. Subjects will be instructed to bring the following items to the final clinic visit following administration of their dose:

- eDiary
- C213 applicator
- Any unused C213 patches

Subjects may discard used patches. Date and time of dose and information regarding the subject's study drug administration will be recorded in the eDiary.

5 EFFICACY AND SAFETY ANALYSIS VARIABLES

5.1 Efficacy

The co-primary efficacy endpoints are the proportion of subjects who achieve pain relief at 15 minutes and the proportion of subjects who achieve sustained pain relief from 15 minutes to 60 minutes. Headache pain is assessed using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Pain relief is defined by a decrease in pain from severe to mild or none without the use of acute rescue medication. Sustained pain relief requires a pain rating of mild or none at each timepoint from 15 minutes to 60 minutes without the use of acute rescue medication.

The secondary efficacy endpoints for this study are:

- Proportion of subjects that achieve pain relief at 5, 10, 20, and 30 minutes post patch application
- Proportion of subjects that achieve sustained pain relief from 5 to 60 minutes and from 10 to 60 minutes post patch application
- Proportion of subjects that achieve pain freedom at 10 minutes and 15 minutes post patch application
- Proportion of subjects that achieve sustained pain freedom from 10 to 60 minutes and from 15 to 60 minutes post patch application
- Proportion of subjects using rescue therapy within 20 minutes post patch application
- Proportion of subjects able to perform their usual daily activities as assessed by the subject

5.2 Safety

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

Safety will be assessed through the following:

- Incidence of adverse events
- Physical exam including height and weight
- Vital signs including blood pressure
- Clinical laboratory determinations including coagulation studies
- Serum pregnancy and urine pregnancy for women of child-bearing potential
- 12-lead ECGs

- Assessment of concomitant medications
- Investigator visual skin assessments

6 STUDY PROCEDURES AND SCHEDULE

6.1 Study Schedule

A schedule of study procedures is presented in Table 4.

Table 4: Schedule of Study Procedures

Procedure	VISIT 1[1] Screening [+3 days] Up to 1 week prior to Randomization	VISIT 2 Randomization Day[1] Day 1 – start of double-blind period	48 Week Double-blind Period [+ or – 7 days] Day 1 – Day 336	VISIT 3 End of Study (or Early Discontinuation) [+ 3 days] Day 1-8
Informed Consent	X			
Inclusion/Exclusion Criteria	X	X		
Medical History including Cluster headache, nicotine, alcohol use, and substance abuse history	X			
Demographics	X			
Randomization		X		
Physical Exam	X	X		X
Weight[2]/Height	X	X[2]		X[2]
Vital Signs	X	X		X
Adverse Events Collection		X		X
Concomitant meds/therapies Collection	X	X		X
Chemistry, coagulation & Hematology (fasting) [3]	X[3]			X
Serum or Urine Pregnancy [4] (only for WOCBP)	X - Serum	X – Urine dipstick	X – Urine dipstick[4]	X - Serum
Drug Abuse Testing	X			
12-lead ECG	X			X
Train on patch application using demonstration patches		X		
Train/dispense eDiary		X		
Dispense CTM		X		
Study Drug Self-Administration			X	
Subject eDiary Assessments			X	
Investigator Skin Assessment		X		X
Investigator Phone call to subject [5, 6]			X[5, 6]	
Collect Unused Patch(es) and Applicator/Perform Drug Accountability				X
Collect eDiary				X

[1] Qualifying headache and treatment of a cluster headache must occur within 48 weeks of randomization

[2] Both height and weight at screening only and weight only at visit 2 and 3

[3] Clinically significant abnormal lab values may be repeated and if not clinically significant on repeat, subject may be eligible for randomization

[4] Urine pregnancy for WOCBP will be collected monthly [+ or – 7 days] after randomization day 1 to ensure no pregnancy prior to study drug administration.

[5] Following randomization, the investigator (or designee) will contact the subject monthly [+ or – 3 days] to assess for adverse events, concomitant medications and to provide study related reminders regarding eDiary use and/or C213 application instructions in advance of the qualifying cluster attack.

[6] The investigator (or designee) will contact the subject within 2 days after C213 application to assess for Adverse Events and to schedule the subject for a final visit 1-8 days after C213 application.

All study visits and procedures will be performed according to the Schedule of Study Procedures as listed in Table 4. Screening activities may be completed over a period as short as one day or spread out over up to one week. Subject visits should generally be scheduled as soon as possible within the specified windows.

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

6.1.1 Screening Visit 1: Up to 1 Week [+ 3 days] Prior to Randomization and Start of the Double-Blind Period

In order to determine if a subject meets entry criteria, the following activities and evaluations will be performed during screening. Screening activities may be completed over a period as short as one day or spread out over up to one week. Once lab and ECG reports are available and reviewed by the investigator and eligibility is confirmed, the subject may be scheduled for Visit 2 and randomization.

The following procedures are to be performed during screening:

- Provide informed consent discussion; collect signed ICF (must be done prior to commencing screening assessments)
- Assess subject eligibility based on inclusion/exclusion criteria
- Record demographics
- Record medical history including cluster headache, drug, alcohol, nicotine, and substance abuse history
    - Record year of subject's first cluster attack, approximate number of attacks per day during the last cluster period, average duration (in days) of cluster period, approximate number of cluster headache periods during the past 12 months, type of cluster headache (chronic or episodic), and the subject's usual signs and symptoms
    - Record whether the subject has a history of illicit drug use in the past year, currently uses alcohol, and/or whether the subject is a nicotine user and frequency of use.

- Perform PE, including height and weight
- Record vital signs: temperature, respiratory rate (RR), blood pressure (BP), and heart rate (HR)
- Collect blood (4-hr fasting) for clinical laboratory measurements including clinical chemistries, hematology, and coagulation
- Collect blood for serum pregnancy for all women of child-bearing potential (WOCBP). WOCBP is defined as women who are neither 1 year post-menopausal or surgically sterile.
- Collect urine for urine drug screen
- Perform 12-lead electrocardiogram (ECG)
- Record concomitant medications taken within 60 days prior to Screening
- Register in IWRS all subjects who become screen failures

6.1.2 Visit 2, Day 1 Randomization

- Perform physical exam, including weight
- Perform investigator skin assessment of the upper arm where patches are intended to be applied
- Record vital signs: temperature, respiratory rate (RR), blood pressure (BP), and heart rate (HR)
- Record concomitant medications, including medication taken to treat cluster headaches
- Urine pregnancy for all WOCBP
- Record Adverse events
- Train the subject on how to apply the patches to the upper arm with the demo applicator and have the subject practice applying the demo patches to his/her arm 2-3 times (more is allowable, if necessary)
- Review the definition of a qualifying cluster headache for the study with the subjects
- Record that the subject can apply patches with the applicator unaided
- Reconfirm subject's eligibility based on inclusion/exclusion criteria
- Randomize subject
- Dispense CTM kit that includes the applicator and one dose (each dose consists of 2 patches) as assigned by the RTSM in Medidata

- Provide instructions for scheduling the next visit within 1-8 days of experiencing and treating a qualifying cluster headache with C213
- Remind the subject that if rescue therapy is required, rescue therapy other than a triptan or ergot is permitted at or after 20 minutes post study drug administration.
- Provide eDiary training necessary and dispense the eDiary

6.1.3 Double-Blind Treatment Phase: Day 1 through up to 48 Weeks [336 Days + or – 7 days]

Subjects will have up to 48 weeks to confirm and treat a qualifying cluster headache. Subjects will be instructed to complete the eDiary at the time of a suspected cluster headache. Once the eDiary confirms that the subject has a "qualifying" cluster headache, the subject will follow the steps provided to self-administer the study drug.

6.1.3.1 Day 1 through Week 48: Treatment of a Qualifying Cluster Headache

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

- Severe unilateral orbital, supraorbital and/or temporal pain
- Either or both of the following:
    1) at least one of the following symptoms or signs, ipsilateral to the pain:
        - conjunctival injection and/or lacrimation
        - nasal congestion and/or rhinorrhea
        - eyelid edema
        - forehead and facial sweating
        - miosis and/or ptosis
    2) a sense of restlessness or agitation

The following procedures are to be performed by the subject for a cluster headache from Day 1 through 48 weeks of the double-blind period:

- Using the eDiary, the subject will record the following to confirm the headache meets the qualifications for a cluster headache:

  Cluster headache symptoms and pain assessment
- Once the qualifying cluster headache has been confirmed, subject self-administers the study drug patches. Subjects will apply two patches to the upper arm.
- Subject will continue to record the following in the eDiary, post self-administration of the patches at 5 min, 10 min, 15 min, 20 min, 30 min and 60 mins.

Cluster headache symptoms, pain assessment, and whether rescue therapy was needed

- For the cluster headache to be qualifying for study medication, no triptans or ergots are allowed within 24 hours prior to onset of cluster headache. If rescue therapy is required by the subject, rescue therapy other than a triptan or ergot is permitted at or after 20 minutes post study drug administration.
- Subject will contact the site to schedule a Visit 3 follow-up visit within 1-8 days of study drug treatment following administration of study drug.

6.1.4 Pregnancy Tests (every 4 weeks ± 7 days)

- A urine pregnancy test will be collected on WOCBP every month from the day of randomization during the double-blind period to ensure the subject is not pregnant prior to administration of study medication.
    - Due to the COVID-19 pandemic, a urine pregnancy test kit will be sent to WOCBP for in-home testing on a monthly basis. The Investigator (or designee) will contact the subject to review and document the result.

6.1.5 Investigator (or designee) Phone Contact to Subjects (every 4 weeks ± 3 days)

Following randomization, the investigator (or designee) will contact the subject monthly to assess for:

- Adverse events, concomitant medications and to provide study related reminders regarding eDiary use and/or C213 application instructions in advance of administering study medication for the qualifying cluster attack.

6.1.6 Investigator (or designee) Phone Contact to Subject– Following application of C213 (+ 2 days)

The investigator (or designee) will contact the subject within 2 days after C213 application to assess for:

- Adverse events and to schedule the subject for a final visit 1-8 days after C213 application.

6.1.7 Visit 3 - Day 1-8 Following Treatment of Cluster Headache / End of Study (or Early Discontinuation) Visit (+3 days)

The following procedures will be performed at the Day 1-8 / end of study (or early discontinuation):

- Collect the applicator and any unused patches and perform drug accountability
- Perform physical exam, including weight
- Record vital signs: temperature, respiratory rate (RR), blood pressure (BP), and heart rate (HR)
- Collect blood (4-hr fasting) for clinical laboratory measurements including clinical chemistries, coagulation, hematology, and serum pregnancy for WOCBP
- Collect serum pregnancy for all WOCBP
- Perform 12-lead electrocardiogram (ECG)
- Collect and review subject's eDiary data with the subject for the following:

  Subject compliance with study drug treatment and/or rescue therapy use
- Investigator Skin Assessment
- Record concomitant medications
- Review of adverse events

Due to the COVID-19 pandemic, if any subjects cannot or elect not to be seen in clinic, the Visit 3/End of Study Visit may take place via a virtual video (such as FaceTime, WhatsApp, Skype, Zoom). Any procedure such as vital signs, blood collection, and ECG, which cannot be collected on site or remote will be indicated as 'not done' in both the source documents and if prompted to specify a reason in the eCRF as due to the pandemic.

During this call, the following procedures will be performed:

- Perform drug accountability and confirm with subject that both patches were applied and arrange to have the applicator and eDiary sent back to the clinical site
- Review subject's eDiary data with the subject for the following:

  Subject compliance with study drug treatment and rescue therapy use
- Investigator Skin Assessment
- Record concomitant medications
- Review of adverse events

- Investigator to verify results of in-home urine pregnancy test (WOCBP only)

6.2 Study Procedures

6.2.1 Informed Consent

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

6.2.2 Inclusion/Exclusion Criteria

All inclusion criteria and none of the exclusion criteria must be satisfied prior to randomization and assignment of a CTM kit number to the subject and the start of study drug dosing.

6.2.3 Medical History, Substance Use, Cluster Headache History and Demographics

Demographic information and a medical history, including history of menopausal status, will be obtained during screening. The medical history should include all current conditions, including recent illnesses and relevant past medical history. Subjects will be asked about current use of illicit drugs, nicotine containing products, and alcohol. Information will also be obtained on the subject's history of cluster headache therapy.

6.2.4 Randomization

Randomization will be conducted at Day 1 after verifying that the participant meets all inclusion criteria and has none of the exclusion criteria. Participants who meet the study eligibility criteria and give informed consent will be randomized to one of three doses (1.9 mg, 3.8 mg, or placebo).

6.2.5 Physical Examination

A PE will be performed during screening for inclusion, at Day 1 and End of Study (or early discontinuation). The physical exam will include, but is not limited to, HEENT, dermatologic (investigator skin assessment), brief neurological, general appearance, lymph nodes, cardiovascular, respiratory, gastrointestinal and musculoskeletal examination.

6.2.6 Height and Weight

Subjects will have both height and weight measured at screening, and weight only will be collected at Day 1, and the End of Study visit (or early discontinuation). The subject must not wear shoes during the height measurement.

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

6.2.7 Vital Signs

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

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

6.2.8 Clinical Laboratory Tests

Blood samples will be collected for clinical laboratory tests at screening and at the End of Study visit (or early discontinuation). Subjects must be fasting (i.e., nothing by mouth for at least 4 hours before the visit; drinking water during the 4-hour fast before clinical laboratory assessments is permitted). All samples will be processed by a central laboratory. The following parameters will be assessed:

Table 5: Clinical Laboratory Tests

Serum Chemistry	Hematology	Additional Tests
▪ Aspartate aminotransferase (AST) ▪ Alanine aminotransferase (ALT) ▪ Cholesterol (HDL and LDL) ▪ Bilirubin ▪ Creatinine ▪ Glomerular filtration rate (GFR) ▪ Triglyceride ▪ Alkaline phosphatase	▪ Hematocrit ▪ Hemoglobin ▪ Red Blood Cell Count ▪ White Blood Cell Count ▪ Platelet Count	▪ Serum and Urine Pregnancy (WOCBP only)* ▪ Urine drug screen ▪ Coagulation** ▪ PT/INR ▪ PTT

* WOCBP is defined as women who are neither 1 year post-menopausal or surgically sterile.
**Coagulation sample is to be sent to Eurofins on the day of collection on dry ice.

Laboratory tests will be performed at screening and at the End of Study visit (or early discontinuation). Clinically significant abnormal values at screening may be repeated to confirm eligibility. Pregnancy tests will be performed on all women of child-bearing potential every month [+ or – 7 days] after randomization to ensure no pregnancy prior to study drug administration.

The urine drug abuse screen will be performed at screening and will test for amphetamines, barbiturates, cocaine, phencyclidine (PCP), and meth/amphetamines.

The central laboratory will provide a laboratory manual and appropriate supplies (containers and labels). Laboratory values that are out of range will be identified and may be repeated at the investigator's discretion with sponsor approval. The investigator will determine if any out-of-

range laboratory values that emerge during treatment are clinically significant and if so, record these on the appropriate source document and on the AE eCRF page if applicable. All clinically significant out-of-range laboratory values will be followed until they return to normal or become medically stable.

6.2.9 Twelve-Lead Electrocardiogram

The ECG, done at screening and at the End of Study visit (or early discontinuation), and will be sent to a central ECG laboratory for interpretation. ECG equipment and an ECG manual will be provided by the central ECG lab.

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

6.2.10 Previous, Concomitant and Prohibited Medications

Concomitant medications will be recorded on the appropriate source document and on the appropriate eCRF at all visits including screening, randomization day, and end of study (or early discontinuation). All previous and concomitant medications taken within 90 days prior to the screening visit must be recorded in the source document and eCRF. When new medications are started and come to the attention of the investigator between scheduled visits, they will be recorded that day on the appropriate source document and on the appropriate eCRF.

No triptans or ergots are allowed within 24 hours prior to onset of current cluster headache symptoms. If rescue therapy is required by the subject, rescue therapy other than a triptan or ergot is permitted at or after 20 minutes post study drug administration. Ergots and triptans may be resumed 24 hours after dosing with study medication.

No lotions, ointments or powders applied to the skin immediately before (within an hour) or for 24 hours after applying the patches are allowed.

Table 6 lists all prohibited medications. Medications listed in Table 6 are prohibited from 7 days prior to screening through the final visit.

Table 6: Prohibited Concomitant Medications

Drug Type	Medication
Prescription anticoagulants	Entire class
Monoamine oxidase inhibitors	Entire class
Potent CYP450 3A4 Inhibitors	Ketoconazole Erythromycin Clarithromycin Cimetidine Grapefruit
CYP450 1A2 Inhibitors/Inducers	Ciprofloxacin

Drug Type	Medication
	Enoxacin Fluvoxamine Alpha-Naphthoflavone Furafylline Omeprazole (OTC) Lansoprazole (OTC) Fluvoxamine Enoxacin Phenytoin Rifampin Ritonavir teriflunomide Methoxsalen Mexiletine Tobacco Cigarettes

6.2.11 Assessment of Adverse Events

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

6.2.12 Investigator Skin Assessment

The investigator will perform a visual skin assessment of bruising, erythema, and edema at the randomization visit and at the End of Study (or early discontinuation) visit. Any adverse events including application site reactions will be documented on the appropriate eCRF page and must be followed until resolution or medically stable.

At the End of Study (or early discontinuation) visit, the entire surface area of the outer upper arm where the two patches were applied will be assessed for the following skin signs or symptoms.

Any findings with an intensity rating of 1 (Mild intensity), 2 (Moderate intensity), or 3 (Severe intensity) must be recorded as an adverse event in the eCRF and followed to resolution. The investigator will use the definitions of AE Severity Ratings for Mild, Moderate, Severe, Life-Threatening (Section 8.2.1.3) to assess the Severity of the AE.

For further instructions, photographs and descriptors are in Photograph and Appendix 1 (Investigator Assessments – Rating for Bruising, Erythema, Swelling and Photographs).

1.1.1.1 Bruising

The Bruising assessment will be performed by the investigator at Visit 3 End of Study or Early discontinuation.

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

Symptom	Intensity Rating (circle)
Bruising where C213 was applied?	0 = Clear 1 = Mild intensity 2 = Moderate intensity 3 = Severe intensity

1.1.1.2 Erythema and Edema

Erythema and Edema will be assessed by the investigator at Visit 3 End of Study or early termination.

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

Symptom	Rating (circle)
Skin Erythema where C213 was applied?	0 = Clear 1 = Mild intensity 2 = Moderate intensity 3 = Severe intensity

Symptom	Rating (circle)
Skin Edema where C213 was applied?	0 = Clear 1 = Mild intensity 2 = Moderate intensity 3 = Severe intensity

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

6.2.13 Medication Compliance

Subject compliance with study drug administration will be reviewed at the End of Study (or early discontinuation) visit. The applicator and any unused patches will be collected.

7 STATISTICS

A full description of the statistical analyses to be performed at study completion will be provided in a Statistical Analysis Plan (SAP), which will be finalized prior to database lock and unblinding of the study.

Unless otherwise noted, significance tests of treatment differences will be tested at the two-sided 0.05 level.

7.1 Analysis Populations

Modified Intent-to-Treat (mITT) Population

All randomized patients who have a qualifying headache and at least one post-application pain score recorded within the first 15 minutes post-application will be included in the mITT population. This is the primary population for efficacy analyses and patients will be analyzed based on their randomized treatment.

Safety Population

The safety population will include all patients who received any amount of study drug. All safety analyses will be performed using this population, analyzed as treated.

7.2 Estimate of Sample Size

It is anticipated that 20% of subjects receiving placebo and 55% of subjects receiving active treatment will achieve pain relief at 15 minutes and sustained pain relief from 15 minutes to 60 minutes post-dose. Based on a two-sided chi-square test with continuity correction and an alpha level of 0.05, 40 subjects/arm will provide approximately 80% power to detect this same difference between two treatment groups, assuming a 15% dropout rate.

7.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics such as age, gender, race/ethnicity, height, and weight, will be summarized by treatment group using descriptive statistics. Medical History will be coded using MedDRA and summarized by SOC and Preferred Term using frequency counts. Baseline disease characteristics will also be summarized.

7.4 Efficacy Analysis

7.4.1 Primary Analysis

The co-primary efficacy endpoints are the proportion of subjects who achieve pain relief at 15 minutes and the proportion who achieve sustained pain relief from 15 minutes to 60 minutes post patch application. These two endpoints will be analyzed separately using a Cochran Mantel Haenszel test stratified by cluster headache subtype (episodic or chronic) and will utilize the mITT population. A significance test of the treatment difference comparing each C213 dose to

placebo will be tested at the two-sided 0.05 level, and odds ratios and their corresponding 95% confidence intervals will be calculated. Headache pain will be assessed using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe), with pain relief defined by a decrease in pain from severe to mild or none without the use of acute rescue medication. Sustained pain relief requires a pain rating of mild or none at each timepoint from 15 minutes to 60 minutes without the use of acute rescue medication. Handling of missing data as well as sensitivity analyses will be described in the SAP.

7.4.2 Secondary Analyses

Secondary endpoints will be analyzed using similar methods as the primary endpoints and will utilize the mITT population.

To adjust for multiplicity and to control for overall type I error, a fixed sequential testing procedure will be applied to the primary analyses for the two C213 arms and the secondary efficacy analyses. If the primary efficacy analyses for the 3.8 mg arm both produce a result that is statistically significant at the 0.05 level, a significance level of 0.05 will be used for the primary analyses of the 1.9 mg arm and for the secondary efficacy analyses in an ordered fashion. If any subsequent analysis does not produce a statistically significant result at the 0.05 level, then the remaining analyses will automatically be considered non-significant. The order of testing for each endpoint and each C213 dose group will be provided in the SAP.

7.5 Safety Analysis

Safety analyses will be performed using the Safety population. Safety will be assessed by:

- Incidence of adverse events
- Physical exam including height and weight
- Vital signs including blood pressure
- Clinical laboratory determinations including serum chemistries and hematological parameters
- Pregnancy testing for women of child-bearing potential
- 12-lead ECGs
- Assessment of concomitant medications
- Investigator visual skin assessments

Adverse events will be coded using the latest version of MedDRA and will be summarized overall and by preferred term and system organ class. Adverse events will also be summarized by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized.

All safety data will be listed by subject and parameter, separate listings of all abnormal laboratory findings and ECG findings will be provided, and clinically significant abnormalities will be recorded as AEs. Additional safety analyses will be described in the SAP.

8 ADVERSE EVENTS

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

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

Pregnancy: In the event that a pregnancy occurs, it will not be considered an AE but requires notification within 24 hours of investigator awareness to the Medical Monitor and Pharmacovigilance Group by completing a Pregnancy Report Form. The investigator will follow the pregnancy through the time of birth and report the outcome. Information about the subject's newborn or subject's pregnant partner will be followed for up to 1 month after the birth.

8.1 Reporting Period

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

8.2 Adverse Event Definitions

8.2.1 Adverse Events (Adverse Experiences)

An AE is any untoward medical event that occurs in a clinical investigation, where a subject is administered a medicinal (investigational) product or medical device, and which does not necessarily have a causal relationship between the event and the treatment. An AE can be any unfavorable and unintended sign or symptom, including clinically significant abnormal laboratory result, concomitant illness, or worsening of an existing medical condition.

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

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

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

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

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

8.2.1.1 Serious Adverse Event Definitions

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

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

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

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

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

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

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

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

8.2.1.2 Unexpected Adverse Event

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

8.2.1.3 Severity Ratings

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

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

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

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

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

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

8.2.1.4 Relationship to Study Drug

The investigator's assessment of causality must be provided for all systemic and skin AEs (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility or likelihood that the investigational product caused or contributed to an AE. If the investigator's final determination of causality is unknown and the investigator does not know whether the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. Thus, it is imperative that all initial SAE reports include an assessment of causality. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

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

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

Probably Related

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

Possibly Related

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

Not Related

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

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

8.3 Documentation and Reporting of Adverse Events by Investigator

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

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

8.3.1 Reporting Requirements for Serious Adverse Events

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

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

If an SAE occurs, PV and MM are to be notified within 24 hours of awareness of the event by the investigator. In particular, if the SAE is fatal or life-threatening, notification to PV and MM

must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports. An initial assessment of causality must be included in all SAE reports.

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

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

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

The investigator must promptly report to the IRB/IEC or independent ethics committees (IEC) all changes in the research activity and all unanticipated problems involving risk to human subjects or others. This includes all SAEs that have occurred at the study site and all study-related SAEs that have resulted in an expedited safety report to the FDA (serious, unexpected SAEs possibly or probably related to study drug). The investigator must send all IRB/IEC documentation (including notifications and acknowledgements) to the sponsor or its designee. The investigator must not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

8.3.2 Reporting Requirements for Non-Serious Adverse Event

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

8.4 Follow up of Adverse Events

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

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

8.5 Contacts for Serious Adverse Events and Medical Monitoring

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

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

- Fax US Number: 1-866-352-7864
- Scanned and emailed: POISafetyDesk@pharm-olam.com
- Copy Pete Schmidt, MD, MSc, Zosano Pharma Medical Monitor (pschmidt@zosanopharma.com)

9 EMERGENCY PROCEDURES

9.1 Emergency Contact

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

9.2 Unblinding Procedures

If a medical emergency occurs and a decision regarding the subject's clinical treatment requires knowledge of the treatment assignment, the study blind may be broken for the specific subject. Unless the medical emergency is deemed to be life-threatening, the medical monitor must first be consulted before unblinding. The investigator would then access Medidata for unblinding.

The date, time, and reason for unblinding must be documented in the source documents and on the applicable eCRF. Investigators should note that the occurrence of a SAE should not routinely trigger immediate unblinding. If the medical monitor was not notified prior to breaking the blind, the investigator must notify the medical monitor of any and **all** blinds broken within 24 hours of each occurrence.

9.3 Emergency Treatment

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

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

10.1 Study Monitoring

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

10.2 Audits and Inspections

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

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

10.3 Institutional Review Board (IRB)/Independent Committee

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

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

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

10.4 Participant Recruitment

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

11 QUALITY CONTROL AND QUALITY ASSURANCE

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

12 ETHICS

12.1 Ethics Review

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

12.1.1 Ethical Conduct of the Study

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

12.2 Written Informed Consent

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

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

The ICF must contain the subject's dated signature or the signed and dated signature of the subject's legally authorized representative (if applicable). In addition, the dated signature of the person who conducted the informed consent discussion will also be documented on the consent form. Each subject's signed ICF must be kept on file by the Investigator and be available for possible inspection by regulatory authorities, and/or the study Sponsor or the regulatory compliance monitor, or the IRB/IEC. All subjects will be informed of the nature of the program, its possible hazards, and their rights to withdraw at any time from the study without prejudice and without jeopardy to the subject's future medical care at the center. Documentation of the

informed consent and subject information discussion must appear in the subject's medical record. HIPAA authorization must also be provided (if applicable).

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

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

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

12.3 Disclosure of Data

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

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

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

13 DATA HANDLING AND RECORDKEEPING

13.1 Inspection of Records

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

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

13.2 Case Report Forms

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

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

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

The eCRF development and database validation programs will be documented in the Data Management Plan (DMP) and will be tested before the database is released for data entry. The validation of the data once entered into the eCRF/database will occur dynamically or nightly dependent upon the type of edit check required. Any data discrepancies identified as a result of this validation routine will be documented.

13.3 Publication 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 C213, 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.

13.4 Retention of Records

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

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

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

14 REFERENCES

Bahra A, Gawel MJ, Hardebo JE, et al. Oral zolmitriptan is effective in the acute treatment of cluster headache. Neurology. 2000 May 9;54(9):1832-9.

Cittadini E, May A. Straube A, et al Effectiveness of Intranasal Zolmitriptan in Acute Cluster Headache. Arch Neurol. 2006:1537-1542

Dahlof C, Diener HC, Goadsby PJ, et al. Zolmitriptan, a 5-HT1B/1D receptor agonist for the acute oral treatment of migraine: a multicentre, dose-range finding study. Eur J Neurol. 1998 Nov;5(6):535-543.

Dawson AJ, Charlesworth BR, Green J, et al. INDEX Study Group. Zolmitriptan nasal spray exhibits good long-term safety and tolerability in migraine: results of the INDEX trial. Headache. 2005 Jan;45(1):17-24.

Ekbom K, Monstad I, Prusinski A, et. Al. Subcutaneous Sumatriptan in the acute treatment of cluster headache; a dose comparison study. The Sumatriptan Cluster Headache Study Group Acta Neurol Scand 1993, July 88(1) 63-69.

Hedlund C, Rapoport AM, Dodick DW, et al. Zolmitriptan nasal spray in the acute treatment of cluster headache: a meta-analysis of two studies. Headache. 2009 Oct;49(9):1315-23.

Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika.* 1988;75:800-2.

Rapoport A, Ramadan N, Adelman J, et al. Optimizing the dose of zolmitriptan (Zomig, 311C90) for the acute treatment of migraine. A multicenter, double-blind, placebo-controlled, dose range-finding study. *Neurology*. 1997;49(5):1210-18.

Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden. Headache. 2012 Jan;52(1):99-113.

Schoenen J, Caekebeke P, Louis, G, et al. An open study to investigate the absorption and tolerability of oral 311C90 and to obtain a preliminary indication of efficacy in migraine patients. *Proceedings of the 10th Migraine Trust Symposium. New advances in headache research.* 1994;vol. 4:11-2.

Seaber E, Peck , Smith D, et al. The absolute bioavailability and effect of food on the pharmacokinetics of zolmitriptan in healthy volunteers. *Br J Clin Pharmacol*. 1998 Nov;46(5): 433–9.

Visser W, Klein K, Cox R, et al. 311C90, a new central and peripherally acting 5-HT_{1D} receptor agonist in the acute oral treatment of migraine: a double-blind, placebo-controlled, dose-range finding study. *Neurology.* 1996 Feb;46(2):522-6.

APPENDIX 1 INVESTIGATOR ASSESSMENTS – RATING FOR BRUISING, ERYTHEMA, EDEMA AND PHOTOGRAPHS

The Bruising, Erythema, and Edema assessment will be performed by the investigator at the final visit 3 (or early discontinuation). Any findings with an intensity rating of 1 (Mild intensity), 2 (Moderate intensity), or 3 (Severe intensity) must be recorded as an adverse event in the eCRF and followed to resolution. The investigator will use the definitions of AE Severity Ratings for Mild, Moderate, Severe, Life-Threatening (Section 8.2.1.3) to assess the Severity of the AE.

Symptom	Intensity Rating (circle)
Bruising spots where C213 was applied?	0 = Clear 1 = Mild intensity 2 = Moderate intensity 3 = Severe intensity

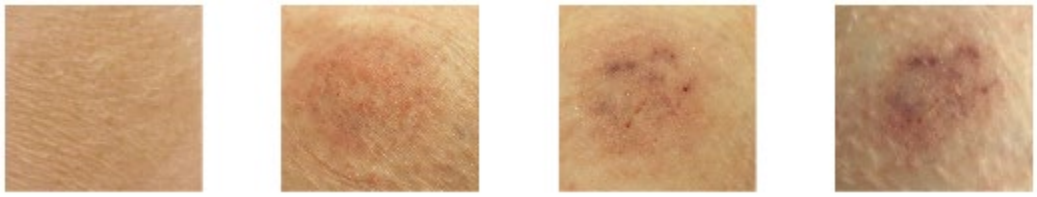
Symptom	Intensity Rating (circle)
Skin Erythema where C213 was applied?	0 = Clear 1 = Mild intensity 2 = Moderate intensity 3 = Severe intensity

Symptom	Intensity Rating (circle)
Skin Edema where C213 was applied?	0 = Clear 1 = Mild intensity 2 = Moderate intensity 3 = Severe intensity

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

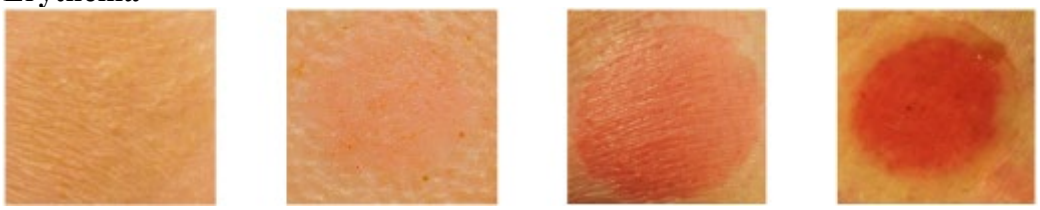
Intensity Ratings

Bruising



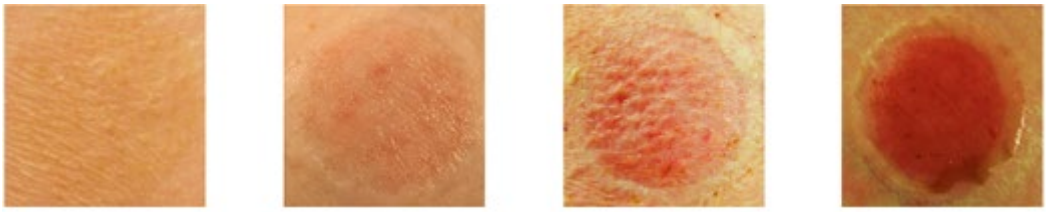
None (Clear) Mild Moderate Severe

Erythema



None (Clear) Mild Moderate Severe

Edema



None (Clear) Mild Moderate Severe

APPENDIX 2 SAMPLE SUBJECT eDIARY QUESTIONS

Qualifying Cluster Headache Double-Blind Period (eDiary is Activated at Visit 2)

- Are you having a cluster headache now? (Yes, No)
- How bad is your headache pain? (Mild, Moderate, Severe)
- Are you experiencing any of the following (please scroll down and select all that apply)?

  Feeling Restless/Agitated? (Yes, No)

  Eye redness or tearing on the same side as pain? (Yes, No)

  Runny or stuffy nose on the same side as pain? (Yes, No)

  Swollen eyelid on the same side as pain? (Yes, No)

  Forehead and face sweating on the same side as pain? (Yes, No)

  Drooping of the upper eye lid, or pupil getting smaller on same side as pain? (Yes, No)

  None of the above (Yes, No)
- Did you treat your cluster headache with a triptan or ergot in the past 24 hours?
- *If a non-qualifying headache:*

  The following text shows - **DO NOT** APPLY THE PATCHES. YOU **HAVE NOT** REPORTED a qualifying cluster headache. Please save your answers and return to the diary next time you think you are experiencing a headache.
- *If a qualifying headache:*

  The following text shows - You have reported a qualifying headache. Please apply the **first patch** now. **After applying the first patch**, please respond to the question below:

  Have you applied your first patch? (Yes, No)

  Please apply the second patch now.

Post Patches Application Questions at: 30 min

- Where were the study drug patches applied? (Both to left arm, Both to right arm, One patch to each arm, One patch to left arm, One patch to right arm)
- Please remove the patches from your upper arm, fold in half, and discard. Press the next button once you have removed both patches.

- *Reminder* Text – You have 1 post treatment questionnaire left to complete. Please do not turn off your device. You may press next to complete this questionnaire.

Post Patches Application Questions/text at: 5, 10, 15, 20, 30, 60 min

- How bad is your headache pain? (None, Mild, Moderate, Severe)
- Did you take any medication, since your last diary entry, other than the patches you applied to treat your headache? (Yes, No)
- Do you feel able to perform your usual daily activities? (Yes/No)
- Your next assessment is due at [time]. Please keep your device with you. (at 5, 10, 15, 20, 30 minute)
- Thank you. You have answered all study related questions and your physician will contact you about setting up your final visit (at 60 minutes only)