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I confirm that I have reviewed this document and agree with the content.

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ACT	Assessment of Current Therapy
AE	Adverse event
ALT	Alanine transferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C	Celsius
cm	Centimeter
CPK	Creatinine phosphokinase
CTM	Clinical trial material
CRF	Case report form
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
HDL	High-density lipoprotein
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
Kg	Kilogram
LDH	Lactate dehydrogenase

Abbreviation	Description
LDL	Low-density lipoprotein
M207	Intracutaneous Microneedle System (M207)
MBS	Most Bothersome Symptom
Mg	Milligrams
mITT	Modified Intent-to-Treat
mL	Milliliter
NSAID	Nonsteroidal anti-inflammatory drug
PCP	Phencyclidine
PE	Physical examination
PT	Preferred Term or Prothrombin
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard deviation
SGPT	Serum glutamic pyruvic transaminase
SGOT	Serum glutamic oxaloacetic transaminase
SNRI	Serotonin-norepinephrine reuptake inhibitors
SOC	System Organ Class
SSRI	Selective serotonin reuptake inhibitors
TEAE	Treatment-emergent adverse event
TLFs	Tables, Listings, and Figures
WOCBP	Women of child-bearing potential

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings (TLFs).

2.2. TIMINGS OF ANALYSES

The final analysis will be conducted by Syneos Health after all subjects complete the final study visit or terminate early from the study, and the database has been locked.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

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

3.2. SECONDARY OBJECTIVES

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

3.3. BRIEF DESCRIPTION

This is an open-label, twelve-month safety study. There is a screening period followed by a run-in period (14 to 21 days) to determine eligibility for treatment with study medication based on daily eDiary data collection. Qualified subjects will receive study medication on Day 1 for up to twelve months for the treatment of migraine headaches. Migraines will be treated with a single dose, consisting of two patches, but subjects can treat multiple migraine attacks throughout the 12 months. Using the eDiary to confirm they are experiencing a qualified migraine, subjects will self-administer the patches and continue to respond to questions in the eDiary for 48 hours post treatment administration.

3.4. SUBJECT SELECTION

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

3.4.1. Inclusion Criteria

The inclusion criteria are detailed in Sections 3.2.2 of protocol amendment 2.0

3.4.2. Exclusion Criteria

The exclusion criteria are detailed in Sections 3.2.3 of protocol amendment 2.0

3.5. DETERMINATION OF SAMPLE SIZE

The sample size chosen for this study was selected without statistical considerations. It has been determined adequate to meet the study objectives.

3.6. TREATMENT ASSIGNMENT & BLINDING

This study is an open label study. There is no blinding of treatment assignment in this study.

3.7. ADMINISTRATION OF STUDY MEDICATION

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

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

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

3.8. STUDY PROCEDURES AND FLOWCHART

All study visits and procedures will be performed according to the Schedule of Study Procedures as listed in Table 1. Subject visits should be scheduled as soon as possible within the specified windows.

A screening visit 1 will be conducted up to one week prior to start of the run-in-period.

The following assessments will be performed at screening to determine subject's eligibility. Demographic data (including name, sex, age, race, ethnicity, height, and weight), Fitzpatrick Skin Scale Questionnaire, Medical history, Migraine History, Prior and concomitant medications, Physical Examination (PE) including body weight (kg), height (cm) and BMI (kg/m^2) will be reported. Each subject will have vital sign measurements; heart rate (HR), blood pressure (BP), temperature (TEMP), and respiratory rate (RR), 12-lead Electrocardiogram (ECG), laboratory tests for hematological, chemistry, and additional laboratory tests.

A screening visit 2 (start of run-in-period) will be conducted within two to three weeks prior to dispensation of study medication.

The following assessments and activities will be performed during visit 2. Vital sign measurements (HR, BP, TEMP, and RR), Concomitant medications, training of eDiary, and dispense of eDiary.

Table 1: Schedule of Study Procedures

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

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

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

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

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

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

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

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

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

4. ENDPOINTS

4.1. EFFICACY ENDPOINTS

- Proportion of Migraines that are pain free at 30 minutes, 2 hours, 12 hours, 24 hours, and 48 hours post-dose
- Proportion of subjects with pain freedom at 30 minutes, 2 hours, 12 hours, 24 hours, and 48 hours post-dose for the 1st, 5th,15th, and 25th migraine a subject experiences
- Proportion of migraines with most bothersome other symptom freedom at 30 minutes, 2 hours, 12 hours, 24 hours, and 48 hours post-dose
- Proportion of subjects with most bothersome other symptom freedom at 30 minutes, 2 hours, 12 hours, 24 hours, and 48 hours post-dose for the 1st, 5th, 15th, and 25th migraine a subject experiences
- Proportion of migraines with pain relief at 30 minutes, 2 hours, 12 hours, 24 hours and 48 hours post-dose
- Proportion of migraines with nausea freedom at 30 minutes, 2 hours, 12 hours, 24 hours and 48 hours post-dose
- Proportion of migraines with photophobia freedom at 30 minutes, 2 hours, 12 hours, 24 hours and 48 hours post-dose
- Proportion of migraines with phonophobia freedom at 30 minutes, 2 hours, 12 hours, 24 hours and 48 hours post-dose
- Proportions of migraines that require rescue medication within 2 hours post-dose
- Proportion of migraines that recurred within 24 and 48 hours post-dose
- Proportion of migraines with sustained pain freedom from 2 to 24 hours post-dose and from 2 to 48 hours post-dose
- Frequency of responses on the migraine assessment of current therapy (ACT)

4.2. SAFETY ENDPOINTS

- Changes from baseline in physical examination findings at Months 6 and 12
- Changes from baseline in vital signs at Months 1, 2, 3, 6, 9, 12, and at the 2-week post-study visit
- Changes from baseline in clinical laboratory parameters at Month 12
- Changes from baseline and/or shifts in 12-lead ECG parameters at Months 6 and 12
- Frequency of concomitant medications

- Incidence of treatment-emergent systemic and skin AEs (TEAEs)
- Frequencies of type of redness, severity of swelling, amount of bruising, and amount of bleeding (30 minutes only) at the application site as reported by the subject at 30 minutes, 2 hour, 12 hour, 24 hour, and 48 hours post-dose
- Frequencies of amount of skin itching and severity of pain at the application site as reported by the subject at 48 hours post-dose
- Frequencies of amount of bruising, erythema, and edema at the application site as assessed by the Investigator at Months 1, 2, 3, 6, 9, 12, and at the 2-week post-study visit
- Proportion of subjects with presence of skin signs and symptoms as assessed by the Investigator at Months 1, 2, 3, 6, 9, 12, and at the 2-week post-study visit

5. ANALYSIS SETS

5.1. SAFETY SET

The Safety Population will include all subjects who receive any amount of study drug (applied at least one patch).

All safety analyses will be based on the Safety Population.

5.2. MODIFIED INTENT-TO-TREAT

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

All efficacy analyses will be based on the mITT Population.

5.3. PROTOCOL DEVIATIONS

Protocol deviations will be captured during monitoring visits or via remote monitoring. All deviations will be recorded in the Syneos Health clinical trial management system and will be categorized as major or minor. Major protocol deviations will be summarized by deviation type using frequency counts. All deviations will be listed by subject.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

The statistical analysis will be conducted following the principles specified in the International Council for Harmonisation (ICH) Topic E9 Statistical Principles for Clinical Trials (CPMP/ICH/363/96).

All statistical tabulations and analyses will be done using SAS®, Version 9.4 or higher.

All results collected in the database will be presented in listings.

Unless otherwise stated, summary statistics including the number of subjects (n), mean, standard deviation (SD), median, minimum and maximum will be presented for continuous variables. Generally, the minimum and maximum values will be presented to the same decimal precision as the raw values, the mean and median values to one more, and the standard deviation, to two more decimal places than the raw values. This decimal place convention may be followed for all data elements. For categorical variables, per category, the absolute counts (n) and percentages (%) of subjects with data, and if appropriate, the number of subjects with missing data, will be presented. Percentages will be presented to one decimal place.

For adverse events, medical history and concomitant medications reported on a per-subject basis, the denominator for the percentage calculation will be the number of subjects at risk in each treatment group. A subject will be considered at risk if the subject is in the analysis set and in the subgroup of interest.

All p-values will be rounded to 4 decimal places. If a p-value is less than 0.0001 it will be displayed as "< 0.0001".

Due to technical issues with the eDiary, any duplicate eDiary entries for a given time point will utilize the earliest recorded entry for analyses.

Unless otherwise specified all efficacy analyses will be based upon the modified intent-to-treat population and all safety as well as demographic and baseline characteristic analyses will be based upon the safety population.

Only data from nominal protocol scheduled visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables but will be included in the listings. Subjects who withdraw/drop out from the study will have their collected ET visit data included in the analysis based on the closest visit window. Visit windows will be assigned by splitting the periods between visits at the midpoint between the visits. If more than one record falls within the window, the one closest to the target date will be used in the analysis.

6.2. KEY DEFINITIONS

6.2.1. Baseline

Baseline assessment for migraine and headache endpoints will be based upon the data recorded in the eDiary at time 0, prior to the first administration of Investigational Product. Baseline MBS is recorded at Visit 2. For other variables, the baseline assessment will be the latest available valid measurement taken prior to the first administration of Investigational Product.

6.2.2. Age

Age, in completed years, at screening will be calculated for each subject and will be defined as:

Age (years) = integer value ((Date of Screening – Date of Birth + 1) / 365.25).

6.2.3. Study Day

Study Day 1 is the day when a subject enters the treatment period. Study Day -1 is the day before the subject enters the treatment period, all assessments prior to study Day -1, including the Screening and Admission visits, will have negative study days.

If the date of interest occurs on or after the first study drug administration date, study day will be calculated as (date of interest – first study drug administration date + 1). If the date of interest occurs prior to the first study drug administration date, study day will be calculated as (date of interest – first study drug administration date).

6.3. MISSING DATA

There will be no imputation for missing data, unless otherwise specified.

AEs and CMs with incomplete start dates will be considered as treatment-emergent or prior/concomitant, respectively, according to the following algorithm:

1. If the AE occurrence type is specified for the AE on the eCRF, it will be used to determine treatment-emergence. This will be verified using the algorithms below (steps 3 through 5).
2. If a medication started and stopped prior to the start of study treatment, the medication will be considered prior. This will be verified using the algorithms below (steps 3 through 5).
3. Only the start year is reported: If the year is after or the same as the year of the first dose date, the event will be considered treatment-emergent.
4. Only the start month and year are reported: If the month/year is after or the same as the month/year of the first dose date, then the event will be considered treatment-emergent.

5. If the event occurred or medication was started on or after the date of the first dose date, then the event will be considered treatment-emergent.

The missing severity of an AE will be imputed to “severe”; the missing relationship to study drug of an AE will be imputed to “probably related”.

6.4. VISIT WINDOWS

Nominal Visits will be used in the analyses as reported on the eCRF. As per section 6.1, the subjects who withdraw/drop out from the study will have their ET visit data collected included in the analysis based on the closest visit window.

6.5. POOLING OF CENTRES

There will be no adjustment for multiple centers.

6.6. SUBGROUPS

No subgroups analysis will be performed.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

The number of subjects who were screened, entered run-in, entered the treatment phase, treated, completed 6 months, completed 12 months, and terminated from the study early will be summarized. The reasons for early termination of treatment or from the study will be summarized. Subjects who sign informed consent but do not enter the treatment phase will be listed along with failure type (screening or run-in) and reason for failure. Additionally, a summary of subjects present at each visit will be summarized. The number of subjects in each analysis population will be reported.

Inclusion/exclusion criteria definitions and violations will be listed. If no inclusion/exclusion criteria violations are reported, this will be noted in place of the listing.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

Age at Study day 1 = (Study day 1 visit date - date of birth + 1) / 365.25 and truncated to complete years.

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m^2) = Weight (kg)/[Height$(m)^2$].

Baseline characteristics, including medical history, Fitzpatrick skin scale results, migraine history, headache/migraine medication history and current drug or alcohol usage will also be summarized descriptively for the safety population.

7.3. MEDICAL HISTORY AND CONCOMITANT DISEASES

A summary table of the number and percentage of subjects by medical history system organ class (SOC) and preferred term (PT) will be produced using the safety population. Previous and concurrent diseases/conditions will be sorted alphabetically by SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, version 20.0 or higher. For the summary tables, a subject will be counted only once within preferred term if he/she experienced multiple episodes of the same event.

A separate by-subject listing for medical history data will also be provided.

7.4. OTHER BASELINE CHARACTERISTICS

The Fitzpatrick Skin Scale Questionnaire will be completed by the subjects at baseline will also be listed for each subject.

7.5. MEDICATION

All medications including Concomitant medications, prohibited medications, and Rescue Medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification and preferred drug names from the World Health Organization Drug Dictionary (WHO-DD), version March 2016.

Summaries of medications will be presented in tabular form using the highest level ATC term as an upper classification and the preferred drug name as a lower classification level. All medications will be summarized and sorted by descending counts in the upper classification term and the lower classification term within the upper. For each subject, the medication will be counted only once within the upper classification level and only once within the lower classification level.

Separate listings will be provided for concomitant, prohibited, and rescue medications taken during the study separately.

7.5.1. Prior, Concomitant Medications, and Prohibited Medications

All medications taken within 30 days of screening and throughout the study, including over the counter medications, topical skin ointments and/or creams, prescription medications, herbal supplements, and/or vitamins will be reported as concomitant medications or prior medications.

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

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

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

Below is the list of all prohibited concomitant medications taken within 10 days prior to the Run-in Period and for the duration of this study (table 2):

Table 2: Prohibited Concomitant Medications

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

Medications with a stop date before the treatment dosing date will be considered prior medications. Medications with a start or stop date on or after the treatment dosing date will be considered concomitant medications. All medications marked as ongoing are concomitant medications.

A medication with an incomplete stop date will be considered concomitant if

- Month is missing and year is equal to or after the year of treatment dosing date
- Day is missing and year is equal to the year of the treatment dosing date and month is equal to or after the month of the treatment dosing date.

All medications will be provided in a listing.

7.5.2. Rescue Medications

Rescue medications are defined as medications taken to treat a migraine attack (in addition to the study drug) within 2 hours after taking the study drug. Rescue medications taken during the study will be reported in the eCRF as concomitant medications.

8. EFFICACY

All efficacy analyses will be based on the mITT Population.

8.1. EFFICACY ENDPOINTS AND ANALYSIS

The following efficacy endpoints will be summarized using descriptive statistics:

8.1.1. The Proportion of Migraines and Subjects Experiencing Pain Freedom

The proportion of subjects who are pain-free without the use of rescue medication (i.e., a pain severity score of 0 and no rescue medication reported within the given timeframe) at 30 minutes, 2 hours, 12 hours, 24 hours, and 48 hours after dosing for the 1st, 5th, 15th, and 25th migraine a subject experiences will be summarized descriptively;

The proportion of migraines that are pain-free without the use of rescue medication (i.e., a pain severity score of 0 and no rescue medication reported within the given timeframe) at 30 minutes, 2 hours, 12 hours, 24 hours, and 48 hours after dosing will be summarized descriptively.

8.1.2. The Proportion of Migraines and Subjects Experiencing Most Bothersome Other Symptom Freedom

The proportion of subjects with absence of the most bothersome (MBS) other symptom among nausea, photophobia, and phonophobia at 30 minutes, 2 hours, 12 hours, 24 hours, and 48 hours after dosing for the 1st, 5th, 15th, and 25th migraine a subject experiences will be summarized descriptively. In order to be MBS free, the subject must not have taken a rescue medication up until the specified time point.

The proportion of migraines that are MBS free without the use of rescue medication at 30 minutes, 2 hours, 12 hours, 24 hours, and 48 hours after dosing will be summarized descriptively.

The MBS is the symptom other than pain that is most bothersome most of the time with their migraine. (Sick to their stomach, sensitive to light, sensitive to sound/noise). Patients are asked to identify their most bothersome migraine-associated symptom in addition to pain at Visit 2.

A subject's MBS is obtained via the eDiary, and must be present pre-dose in order to be included in the analysis.

8.1.3. The Proportion of Migraines with Nausea Freedom, Photophobia Freedom, and Phonophobia Freedom

Regardless of the associated symptom identified as MBS, all three important migraine-associated symptoms (i.e., nausea/vomiting, photophobia, and

phonophobia) will be assessed separately. A binary scale (present or absent) will be used for associated symptoms. The proportion of migraines that are nausea-free, photophobia-free, and phonophobia-free without the use of rescue medication at 30 minutes, 2 hours, 12 hours, 24 hours, and 48 hours after dosing will be summarized descriptively. Both nausea and vomiting must be absent in order for the migraine to be considered nausea-free.

8.1.4. The Proportion of Migraines with Pain-Relief

In addition to all above, the proportion of migraines with pain relief without rescue medication use (improvement of pain severity to mild or none from moderate or severe at baseline, or to none from mild at baseline) at 30 minutes, 2 hours, 12 hours, 24 hours, and 48 hours after dosing will also be summarized descriptively.

8.1.5. The Proportion of Migraines Requiring Rescue Medication within 2 Hours Post-Dose

Rescue medications are defined as medications taken to treat a migraine attack (in addition to the study drug) within 2 hours after taking the study drug. Rescue medication data will be obtained from the eDiary. The proportion of migraines requiring rescue medication within 2 hours of initial treatment will be summarized descriptively.

8.1.6. The Proportions of Migraines with Sustained Pain Freedom from 2 to 24 Hours Post-Dose and from 2 to 48 Hours Post-Dose

The proportion of migraines that are “sustained pain-free”, defined as having no headache pain at 2 hours after dose, with no use of rescue medication, and no relapse of headache pain within 24 hours (24-hour sustained pain-free) post-dose will be summarized descriptively.

The proportion of migraines that are sustained pain-free from 2 to 48 hours will also be summarized descriptively.

8.1.7. The Proportion of Migraines with Migraine Recurrence within 24 and 48 Hours Post-Dose

Migraine recurrence between 2 to 24 hours (or 2 to 48 hours) is defined as pain-free at 2 hours post-dose, with pain (mild, moderate, or severe) reported within 24 hours (or 48 hours) post-dose or with rescue medication taken at any time 2 to 24 hours (or 48 hours).

The proportion of migraines that have recurred between 2 to 24 hours post-dose (and 2 to 48 hours post-dose) will be summarized.

8.1.8. Migraine-ACT Questions (Assessment of Current Therapy)

The frequencies and percentages will be provided for all subject responses on the ACT by visit. Note that if a subject has not treated any migraine attacks since the most recent in clinic study visit, the ACT response will be missing. Missing data will not be imputed.

9. ANALYSIS OF PHARMACOKINETICS

Not Applicable

10. ANALYSIS OF PHARMACODYNAMICS

Not Applicable

11. SAFETY

Safety will be assessed through the following:

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

All safety analyses will be based on the Safety Population. Adverse events will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 20.0 or higher) 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.

Clinical laboratory test results and ECG parameters will be summarized at each visit using shift tables or listings of abnormal results as appropriate. The number and percentage of subjects experiencing Bruising, Erythema, Edema and other skin assessments will also be summarized.

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

11.1. EXTENT OF EXPOSURE AND COMPLIANCE

Treatment duration will be calculated as (number of days=last dose date - first dose date+1). First and last dose dates will be determined from the dates of patch application recorded in the eDiary. Average treatment duration per subject in days will be summarized. Frequencies of duration, 0-6 months, 6-12 months, and >12 months will be provided.

Study drug exposure will be captured as the total number of doses. Patch application is captured in the eDiary, and a subject is considered as having received one dose regardless if one or two patches are applied. The average number of treated migraines per month per subject for months 1-12 and overall will also be summarized, as well as frequencies provided for ≥12 doses and ≥24 doses. Also, the frequency of the number of subjects with at least 2 doses per month on average for at least 6 months will be provided.

Compliance will be assessed as the percentage of subjects treating at least 2 migraines per month. Months will be defined starting with the day IP was provided to the subject and calculated as each consecutive 30-day period following the day IP was first provided.

All study drug dosing information will be listed.

11.2. ADVERSE EVENTS

All systemic and skin AEs, regardless of suspected causal relationship to the investigational products, will be reported. Subject assessed skin adverse events such as skin redness (erythema), skin swelling (edema), skin bruising, skin bleeding, skin itching and skin pain are collected through the eDiary and will also be recorded as adverse events in the eCRF.

All Adverse Events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 20.0 or higher). Migraine headaches will not be captured as AEs.

All AEs will be listed by subject. The following listings of AEs will be provided:

- All AEs,
- Study-drug related AEs,
- Serious adverse events (SAEs),
- AEs leading to death, and
- Adverse events leading to study-drug withdrawal.

Only TEAEs will be included in summary tables. An Overview summary table of TEAEs will be produced showing the following categories:

- Any TEAE,
- Study-drug related TEAEs,
- Serious TEAEs,
- TEAEs leading to study-drug withdrawal, and
- TEAEs leading to death.

All TEAEs will be classified by system organ class (SOC) and preferred term (PT). Frequency count and the number of unique subjects of a TEAE will be tabulated by treatment received. For the number of unique subjects reporting, if a subject reported more than one AE that was coded to the same SOC or PT, the subject will be counted only once for that specific SOC or PT.

The following summaries of TEAEs will also be provided:

- TEAEs by SOC and PT,
- Study-drug related TEAEs by SOC and PT,

- Serious TEAEs by SOC and PT,
- TEAEs by maximum severity (mild, moderate, severe or missing) by SOC and PT, and
- TEAEs by strongest causality relationship (not related, possibly related, probably related, definitely related or missing) by SOC and PT.

For TEAEs presented by relationship to study treatment(s), the strongest relationship to study treatment(s) during the study will be presented for each subject if coded to the same SOC or PT. For TEAEs presented by severity, the worst severity during the study will be presented for each subject if coded to the same SOC or PT. TEAEs with missing causality will be counted as related. TEAEs with missing severity will be counted as severe. The same will be true in the individual summaries.

TEAEs by SOC and PT and by severity and causality will be presented 3 ways: subject reported AEs from the eDiary, other subject reported AEs, and all AEs combined (eDiary and other). For subject reported AEs from the eDiary, the average time to resolution in days will be summarized.

11.2.1. Subject Assessed Skin Adverse Events

Subject reported skin bruising, skin bleeding (at 30 minutes only), skin redness (erythema), skin swelling (edema), skin itching and skin pain at the application site are collected through the eDiary and will also be recorded as adverse events in the eCRF.

The frequencies of type of redness, severity of swelling, amount of bruising, and amount of bleeding (30 minutes only) at the application site as reported by the subject at 30 minutes, 2 hour, 12 hour, 24 hour, and 48 hours post-dose will be summarized.

The frequencies of amount of skin itching and severity of pain at the application site as reported by the subject at 48 hours post-dose will also be summarized.

Frequency tables of eDiary skin assessments will be provided using the greatest severity or greatest amount for each parameter as reported by the subject at any time during the study. The denominator will be the number of subjects in the safety population. Tables will also be generated using the data from all treated migraines so the denominator will be the number of treated migraines that have eDiary data.

The proportion of attacks and the proportion of subjects with no skin findings will be summarized by time point. Also, the proportion of attacks and subjects with any amount of all 3 symptoms (redness, swelling, and bruising) at the same time and all combinations of the 3 symptoms will be summarized by time point.

All subject assessed skin adverse events will also be listed.

The type of redness, severity of swelling, amount of bruising, amount of bleeding, amount of skin itching, and severity of pain will be collected using eDiary cards and assessed as follows:

Skin Symptom/ Time Points	Assessment
Redness (Erythema)/ at 30 minutes, 2 hour, 12 hour, 24 hour, and 48 hours post-dose	None Mild redness Moderate colored redness Beet colored redness
Swelling (Edema)/ at 30 minutes, 2 hour, 12 hour, 24 hour, and 48 hours post-dose	None Slight swelling Moderate swelling Severe swelling
Bruising/ at 30 minutes, 2 hour, 12 hour, 24 hour, and 48 hours post-dose	None Less than a quarter of the application site has bruising spots About one-half of the application site has bruising spots More than one-half of the application site has bruising spots
Bleeding/ 30 minutes post-dose only	None Pink color on skin Visible blood drop Active bleeding
Itching/ at 48 hours post-dose only	None Mild itching Moderate itching Sever itching
Pain/ at 48 hours post-dose only	None Mild pain Moderate pain Severe pain

11.2.2. Investigator Skin Assessments

The investigator skin assessment will be made at each in clinic visit starting at month 1. The entire surface area of the outer upper arm from the upper shoulder to the elbow will be assessed for the following skin signs or symptoms.

Investigator reported skin bruising, skin redness (erythema), and skin swelling (edema) at the application site will be collected and will also be recorded in the eCRF.

The amount of bruising, erythema, and edema and the presence of skin signs and symptoms will be categorized and assessed as follows:

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

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

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

Erythema Severity Categories:

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

Edema Severity Categories:

Symptom	Rating (circle)
Skin Edema	0 (clear) = None 1 (mild) = ≤ 25% Present in the upper arm region of all M207

	applications 2 (moderate) = ≥ 26 to ≤ 50% Present in the upper arm region of all M207 applications 3 (severe) = > 50% Present in the upper arm region of all M207 applications

The frequencies of amount of bruising, erythema, and edema at the application site as assessed by the Investigator at Months 1, 2, 3, 6, 9, 12, and at the 2-week post-study visit will be summarized. The proportion of subjects with any amount of all 3 symptoms (erythema, edema, and bruising) and all combinations of the 3 symptoms will be summarized by time point.

The proportions of subjects with presence of skin signs and symptoms as assessed by the Investigator at Months 1, 2, 3, 6, 9, 12, and at the 2-week post-study visit will also be summarized.

All investigator skin assessments will also be listed.

11.3. LABORATORY EVALUATIONS

The lab results for clinical laboratory categories including hematology, serum chemistry as well as results for urine drug screens and serum and urine pregnancy tests will be recorded on the eCRF at the study visits mentioned in Table 1. The parameters given in the Table 3 will be assessed.

Table 3: Clinical Laboratory Tests

Serum Chemistry	Hematology	Additional Tests
Glucose Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase (AP) Lactate dehydrogenase (LDH) Sodium Phosphorus Potassium	Hematocrit Hemoglobin Red Blood Cell Count White Blood Cell Count with Differential Platelet Count Mean corpuscular volume Mean corpuscular hemoglobin	Serum (at screen visit only) and Urine Pregnancy (WOCBP only)[1] [2] Urine drug screens will test for: amphetamines, barbiturates, cocaine, cannabinoids, opioids, phencyclidine (PCP), and methamphetamines

Serum Chemistry	Hematology	Additional Tests
Chloride Creatine phosphokinase (CPK) Globulin Cholesterol (HDL and LDL) Creatinine Blood urea nitrogen (BUN) Prothrombin (PT) and INR (International Normalized Ratio) Serum calcium Total bilirubin Triglyceride Gamma glutamyl transpeptidase (GGT) Serum glutamic pyruvic transaminase (SGPT) Serum glutamic oxaloacetic transaminase (SGOT) Uric acid	Mean corpuscular hemoglobin concentration	

Low, normal, and high classifications will be applied to determine whether the laboratory test value was below (low), within (normal), or above (high) its reference range. The number and percentage of subjects with indicated shifts (low, normal, high) in their results from baseline to post-baseline will be presented.

Separate listings will be produced for each laboratory test group (hematology, serum chemistry, urine drug screens, and serum and urine pregnancy tests). A listing of all abnormal results will be provided.

11.4. VITAL SIGNS

All subjects will have vital signs including body temperature (TEMP), respiratory rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR)

measured at screening and all subsequent visits. Weight will be collected at selected visits, and height will be collected at screening and final visit only (or early termination visit).

A listing of abnormal vital signs results will be provided using the ranges below. All vital signs measurements will also be listed for each subject.

Vital Sign	Low Cutoff	High Cutoff
Systolic Blood Pressure	90 mmHg	139 mmHg
Diastolic Blood Pressure	60 mmHg	89 mmHg
Heart Rate	50 beats/minute	100 beats/minute
Respiratory rate	12 breaths/minute	20 breaths/minute
Body Temperature	36.1 degrees Celsius	37.5 degrees Celsius

11.5. 12-LEAD ECG

Twelve-lead ECG will be performed at screening, months 6 and 12 study visits. Abnormal ECG results will be listed. All ECG findings collected in the CRF will also be listed.

11.6. PHYSICAL EXAMINATION

Physical examination (PE) which includes (but not limited to) HEENT, Dermatologic, Neurological, General Appearance, Lymph Nodes, Cardiovascular, Respiratory, Gastrointestinal, and Musculoskeletal will be performed at screening, day 1, months 6 and 12 study visits. The overall PE findings (normal, abnormal clinically significant, abnormal not clinically significant) will be listed.

All PE findings collected in the CRF will also be listed.

11.7. OTHER SAFETY

Fitzpatrick skin scales, drug abuse testing, and pregnancy test results collected in the CRF will be listed.

12. INTERIM ANALYSES

No planned interim analysis for this study

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Efficacy endpoints were changed from "the proportion of subjects" to "the proportion of migraines" since this is a multiple dose study. Two efficacy endpoints were added: the proportion of subjects with pain freedom and the proportion of subjects with MBS freedom for the 1st, 5th, 15th, and 25th migraine a subject experiences.

14. REFERENCE LIST

1. A Long-Term, Open-Label Study to Evaluate the Safety of M207 (Zolmitriptan Intracutaneous Microneedle System) in the Acute Treatment of Migraine, Zosano Pharma, Protocol No.CP-2017-0016, amendment 2, 06 Apr 2018.

15. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.4 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

The format of the table shells will be followed as closely as possible; however, in the course of programming and familiarization with the database, some changes may become necessary. All changes will be documented. Major changes will be documented through a formal amendment to this document.

SDTM datasets will be created from the clinical database and external data, following the Study Data Tabulation Model Implementation Guide Version 3.2. Analysis will be based on analysis datasets created from the SDTM datasets.

The below programming considerations will be followed unless already specified in the above text.

15.1. GENERAL CONSIDERATIONS

- One SAS program can create several outputs. / A separate SAS program will be created for each output.
- One output file can contain several outputs. / Each output will be stored in a separate file.
- Output files will be delivered in Word format / pdf format.
- Numbering of TFLs will follow ICH E3 guidance (or other logical order for studies performed according to GPP)

15.2. TABLE, LISTING, AND FIGURE FORMAT

15.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will

not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.

- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

15.2.2. Headers

- All output should have the following header at the top left of each page:
  <Sponsor Name> Protocol XXX (Syneos Health study number xxx)
  Draft/Final Run <date>
- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

15.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination (see also template 03.007C "Table of Contents for Tables Listings and Figures in Statistical Analysis Plan"). A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the
- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Analysis Set

15.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.

- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

15.2.5. Body of the Data Display

15.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

15.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as "-".
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

15.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

15.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

15.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

16. QUALITY CONTROL

"SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Syneos Health SOP 03.010 and 03.013 provide an overview of the development of such SAS programs.

Syneos Health SOP 03.009 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output."

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20. MOCK-UPS

20.1. TABLE MOCK-UPS

Table shells will be provided as a separate document.

20.2. FIGURE MOCK-UPS

Figure shells will be provided as a separate document.

20.3. LISTING MOCK-UPS

Listing shells will be provided as a separate document.