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A phase 3, multicenter, open-label study to evaluate the safety of oliceridine (TRV130) in patients with acute pain for which parenteral opiod therapy is warranted

Statistical Analysis Plan

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

ACEP	American College of Emergency Physicians
AEs	adverse events
ALT	alanine aminotransferase
AST	Asparate aminotransferase
ASA	American Society of Anesthesiologists
bmi	body mass index
BP	blood pressure
bpm	beats per minute
cm	centimeters
℃	Celsius
CRF	case report form
CYP	cytochrome P450 enzyme (e.g. CYP2D6)
DBP	diastolic blood pressure
DOB	date of birth
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDs	emergency departments
ESI	Emergency Severity Index
FDA	Food and Drug Administration
°F	Fahrenheit
HR	heart rate
ICD	International Classification of Diseases
ICF	informed consent form
IP	investigational product
IV	intravenous
kg	Kilograms
max	Maximum
MedDRA	medical dictionary for regulatory activities
mg	Milligram
min	Minimum
MRPSS	Moline-Roberts Pharmacologic Sedation Scale
NPRS	numeric pain rating scale
PACU	post-anesthesia care unit
PCA	patient-controlled analgesia device
PCSA	Potentially Clinically Significant Abnormality
PK	pharmacokinetic
PRN	as needed
PT	preferred term

QT_c	Q-T interval corrected for heart rate
QT_cF	Q-T interval corrected for heart rate using Frederica's formula
RR	respiration rate
SAEs	erious adverse events
SAS®	statistical analysis software
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SOP	standard operating procedures
SOWS	Subjective Opiate Withdrawal Scale
TEAE	treatment-emergent adverse event
TEMP	Temperature
t_x	Time from the start of dose (t_0)
WHO	World Health Organization

2. INTRODUCTION

Inadequately treated pain has significant short- and long-term consequences, including prolonged emergency stays, psychological disturbances, and dissatisfaction with medical care. Opioid analgesics like morphine, fentanyl, and hydromorphone are mainstays of acute pain management; however, their use is hampered by well-known adverse events (AEs), such as respiratory depression, nausea, vomiting, and sedation (Lubawski, 2008) (Philip, 2002). Ultimately, the unmet medical need in acute pain therapy is an increased level of efficacy with acceptable tolerability.

This is a phase III, multicenter, open-label study to evaluate the safety of oliceridine (TRV130) in patients with moderate to severe acute pain for which parenteral opioid therapy is warranted.

This study will be conducted in inpatient hospitals, outpatient hospital departments, ambulatory surgical care centers, and emergency departments (EDs). Patients recruited in EDs may continue oliceridine treatment if hospitalized and parenteral opioid therapy is warranted.

Representative surgeries include orthopedic, abdominal, gynecological, vascular, soft tissue, and surgical procedural pain.

Representative medical conditions include acute pancreatitis, acute exacerbation of existing noncancerous chronic pain, musculoskeletal pain, sickle-cell disease, inflammatory orofacial muscle pain, and renal colic. Medical conditions that could confound the evaluation of oliceridine are excluded, such as acute pain without a specific etiology, undifferentiated acute abdominal pain, acute breakthrough pain in palliative "end of life" care, and pain associated with advanced cancer (somatic, visceral, or neuropathic) or with concurrent use of chemotherapeutic or biologic agents for the treatment of cancer.

Representative ED conditions include visceral pain (eg, renal colic, upper abdominal pain, abdominal pelvic pain); nonvisceral pain (eg, traumatic and atraumatic acute musculoskeletal pain, chest wall pain, burns, orofacial pain/headache, cutaneous and soft tissue pain); procedural analgesia (eg, reduction of orthopedic fractures and dislocations, abscess incision and drainage); acute painful episodes associated with a medical condition (eg, sickle cell painful vaso-occlusive episode). Oliceridine will not be used to intentionally suppress a patient's level of consciousness (procedural sedation and analgesia as defined by the American College of Emergency Physicians [ACEP]).

3. STUDY OBJECTIVES

The primary objective is to evaluate the safety and tolerability of oliceridine in patients with moderate to severe acute pain for which parenteral opiod therapy is warranted.

The secondary objective is to evaluate the analgesic efficacy of oliceridine.

4. STUDY DESIGN

4.1 General Design

This is a phase III, multicenter, open-label study to be conducted in four phases: Screening/Baseline, Treatment (consisting of a pre-dose period and a dosing period), End-of-Treatment, and Follow-up.

During the screening phase, patients will provide written informed consent before any protocol-specified procedures or assessments are performed. All screening procedures will be completed within 14 days before the first oliceridine dose. Select standard of care assessments (e.g., chemistry, hematology, urine or serum pregnancy test, urine or serum toxicology screen, electrocardiogram (ECG)) obtained before informed consent may be used as study data if protocol specifications and timeframes are met (see Protocol Section 3.6.1). When screening and baseline procedures are anticipated to occur within 48 hours of each other, they may be executed as a single procedure, unless the clinical condition of the patient has significantly changed since screening.

The treatment phase begins with the pre-dose period and ends when the investigator documents that the last dose of oliceridine was administered and that the patient will no longer be treated with oliceridine. The duration of treatment for each patient will be determined by the clinical need for parenteral opioid therapy. In current practice, parenteral opioids are used as-needed for up to several days. Although preclinical toxicology studies support intravenous (IV) administration of oliceridine for up to 14 days, it is unlikely that patients will receive oliceridine for that duration in the context of this study.

Before dosing with oliceridine, vital signs, oxygen saturation, and somnolence/sedation will be measured. Pre-dose period procedures will occur within 30 minutes before the first oliceridine dose and if the dosing period is delayed, pre-dose period procedures will be repeated. An

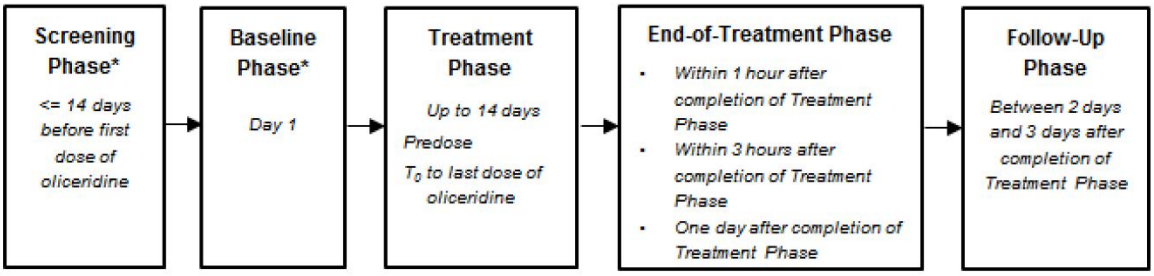
additional post-surgical ECG will be performed only in surgical patients. Prior medications and AEs/SAEs will be recorded. Pain intensity will be measured using a 0-10 point numeric pain rating scale (NPRS).

Oliceridine IV infusion may be administered either by clinician-administered bolus, patient-controlled analgesia device (PCA), or both bolus and PCA, according to the clinical situation. During dosing with oliceridine, vital signs, oxygen saturation, and somnolence/sedation will be measured at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid. An ECG will be obtained 60 minutes after the first dose of oliceridine, and at every 24 hours of oliceridine treatment. Blood will be collected for clinical laboratory tests, oliceridine pharmacokinetics and future cytochrome P450 2D6 (CYP2D6) genotyping. Concomitant medications and AEs/SAEs will be recorded. NPRS assessment will also be completed at 30 minutes +/-10 minutes after the first dose of oliceridine and at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid.

When the investigator documents that the last dose of oliceridine was administered and that the patient will no longer be treated with oliceridine, the treatment phase is complete and the end-of-treatment phase begins. A physical examination will be performed at this time. Within 1 hour after completion of the treatment phase, vital signs, oxygen saturation, and somnolence/sedation will be measured, and concomitant medications and AEs/SAEs will be recorded. Within 3 hours after completion of the treatment phase, blood will be collected for clinical laboratory tests. Concomitant medications and AEs/SAEs will be recorded. Patients will be observed for at least 3 hours after the last dose of oliceridine; however, medically-required transfer of an ED patient to another facility takes precedence over study procedures. The Subjective Opioid Withdrawal Scale (SOWS) will be administered to detect symptoms of opioid withdrawal. If the patient is discharged or transferred before the time when the SOWS is to be performed, it will be performed 1 day after completion of the treatment phase and returned to the site by mail or in person.

A follow-up contact will be made between 2 and 3 days after completion of the treatment phase. The contact may be conducted in person or by telephone. Concomitant medications and AEs/SAEs will be recorded. The surgical procedure, medical diagnosis or ED diagnosis for which parenteral opioid therapy was warranted will be captured using the International Classification of Diseases, 10th Revision (ICD-10) terminology.

A flow chart of the study design is presented below:



Abbreviations: t_0 = time of first dose of oliceridine; h = hours
* Combined if occurring within 48 hours of each other, unless the clinical condition of the patient has significantly changed since screening.

4.2 Method of Assignment of Patients to Cumulative Dose Groups

This is an open-label study therefore the method of assigning patients to dose groups will be based on the actual dose received by the patient.

Depending on the clinical considerations for which parenteral opioid therapy is warranted (e.g., anticipated duration of therapy, clinical site/setting), a patient could receive oliceridine using clinician-administered bolus dosing or PCA dosing. For clinician-administered bolus dosing, the oliceridine initial dose is 1 mg to 2 mg. If clinically indicated, a 1 mg supplemental dose may be administered as early as 15 minutes after the initial dose. Subsequent doses are 1 to 3 mg every 1 to 3 hours PRN based on individual patient need and previous response to oliceridine. In settings where rapid analgesia is targeted (e.g., ED or post-anesthesia care unit (PACU)), the oliceridine initial dose is 1 mg to 3 mg. If clinically indicated, 1 mg to 3 mg supplemental doses may be administered every 5 minutes PRN. Subsequent doses are 1 to 3 mg every 1 to 3 hours PRN based on individual patient need and previous response to oliceridine. For PCA dosing, the oliceridine regimen will consist of a loading dose, a demand dose, and a lockout interval without a continuous baseline infusion.

Oliceridine PCA regimen:

- Loading dose: 1.5 mg.
- Demand dose: 0.5 mg.
- Lockout interval: 6 minutes.

If clinically indicated, throughout the treatment phase, a 1 mg supplemental dose may be administered PRN, taking into account the patient's utilization of PCA demand doses, individual patient need and previous response to oliceridine.

For purposes of analysis the cumulative dose groups will be grouped in the following categories where cumulative dose group will be defined as the sum of all individual doses:

Oliceridine <= 4 mg	Oliceridine >4 to 8 mg	Oliceridine >8 to 16 mg	Oliceridine >16 to 36 mg	Oliceridine > 36 mg	All Treated Patients

4.3 Blinding

This is an open-label trial in which all patients will receive oliceridine; therefore, blinding is not applicable.

4.4 Determination of Sample Size

No formal sample size calculations were made. Approximately 1000 patients will be treated with oliceridine.

5. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

At the time of the writing of this document, protocol amendment 5 has been approved. For changes in the conduct of the study or planned analyses, please see the individual protocol amendments.

6. BASELINE, SAFETY & TOLERABILITY, EFFICACY and PHARMACOKINETIC EVALUATIONS

6.1 Schedule of Evaluations

Procedures	Screening phase[1] (<= 14 days before first dose of oliceridine)	Baseline phase[1] (Day 1)	Treatment phase (up to 14 days)		End-of-treatment phase[2]				Follow-up phase[3] (Between 2 days and 3 days after completion of treatment phase)
			Predose (Day 1)	T0 to last dose of oliceridine[4]	End-of-treatment documentation[2]	Within 1hour after completion of treatment phase[2]	Within 3 hours after completion of treatment phase[2]	One day after completion of treatment phase	
Informed consent[5]	X								
Demographics	X								
Medical history	X	X							
Eligibility criteria	X	X							
ASA physical status classification[6]	X	X							
ESI[7]	X								
Physical examination[2]	X	X			X				
Clinical laboratories[8]	X	X					X		
Blood sample for future CYP2D6 genotyping				X					
Urine or serum pregnancy test[9]	X	X							
Urine or serum toxicology screen[10]	X								
Weight	X	X							
Height[11]	X								
ECG	X	X	X[12]	X[13]					
PK sampling[14]				X					
PCA patient training[15]	X	X	X	X					
Oliceridine dosing				X					
NPRS[16]		X	X	X		X			
Vital signs[17]	X	X	X	X		X			
MRPSS[18]			X	X		X			
SOWS[19]								X	
Oxygen saturation[20]			←----------X----------→						
Prior, concomitant medications[21]	←----------X----------→		←----------X----------→						
AE/SAE reporting[22]	←----------X----------→								

Abbreviations: AE = adverse event; ASA = American Society of Anesthesiologists; CYP2D6 = cytochrome P450 2D6; ECG = electrocardiogram; ESI = Emergency Severity Index; MRPSS = Moline-Roberts Pharmacologic Sedation Scale; NPRS = Numeric Pain Rating Scale; PCA = patient-controlled analgesia device; PK = pharmacokinetic; SAE = serious adverse event; SOWS = Subjective Opiate Withdrawal Scale; T0 = time of first oliceridine dose.

1. When screening and baseline procedures are anticipated to occur within 48 hours of each other, they may be executed as a single procedure, unless the clinical condition of the patient has significantly changed since screening.
2. When the investigator documents that the last dose of oliceridine was administered and that the patient will no longer be treated with oliceridine, the treatment phase is complete and the end-of-treatment phase begins. A physical examination will be performed at this time.
3. Follow-up contact may be conducted in person or by telephone.
4. Procedures will be performed at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid.
5. Written informed consent.
6. If a surgical or medical patient. Refer to Section 9.3 of the protocol for the ASA scale.
7. If an ED patient. Refer to Section 9.4 of the protocol for the ESI scale.
8. Blood chemistry and hematology will be obtained using local laboratories and local laboratory range values.
9. Female patients of childbearing potential only.
10. If an ED patient.
11. Height may be obtained by measurement or patient attestation.
12. During the pre-dose period, an additional, post-surgical ECG will be performed only in surgical patients.
13. ECG will be obtained during the Treatment Phase at 60 minutes after the first dose of oliceridine, and at every 24 hours of oliceridine treatment.
14. PK samples will be collected at two times during the treatment phase: sample 1 at 30 minutes (+/- 10 minutes) after the first dose; sample 2 between 1 and 2 hours after the first dose. Unscheduled PK samples may be required. Refer to Sections 3.5.2.3 and 3.6.3 of the protocol.
15. PCA patient training is required before PCA use. If PCA is planned, training will occur during the screening and baseline phases; if PCA is started during the treatment phase, training will occur before PCA use. Training is repeated according to patient need.
16. NPRS will be measured during the pre-dose period, at 30 minutes +/-10 minutes after the first dose of oliceridine, and at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid (see Section 9.2 of the protocol).
17. Blood pressure, heart rate, respiratory rate, and temperature. Temperature will be measured at screening and baseline only.
18. Refer to Section 9.1 of the protocol for the MPRSS.
19. Refer to Section 9.5 of the protocol for the SOWS. If the patient is discharged or transferred before the time when the SOWS is to be performed, it will be performed one day after completion of the treatment phase and returned to the site by mail or in person.
20. Oxygen saturation monitoring will be continuous but will be recorded at any and all times during the dosing period consistent with individual patient need and institutional standards of care for a patient receiving a parenteral opioid. The date and time of initiation and discontinuation of continuous oxygen saturation monitoring will be recorded in the source documents.
21. Prior medications are defined as those taken before the first dose of oliceridine. Concomitant medications are defined as those taken after the first dose of oliceridine. Prior medications taken or administered within the 14 days before the first dose of oliceridine will be recorded in source and will also be recorded in eCRF. Supplemental oxygen will be recorded as a prior and/or concomitant medication.
22. AEs occurring from time of informed consent to the follow-up phase will be recorded in source and will also be recorded in eCRF if the patient receives oliceridine. SAEs occurring from time of informed consent to the follow-up phase or 7 days after the last dose of oliceridine (whichever occurs later) will be recorded in source and eCRF; ongoing SAEs after this time frame will be followed until the investigator, medical monitor, and sponsor agree that the SAE is satisfactorily resolved. SAEs considered by the investigator to be related to oliceridine, regardless of the time of onset after treatment, should be reported.

6.2 Time Point Algorithms

6.2.1. Baseline Assessments

Baseline assessments are listed in Section 3.6.1 of the study protocol. In general, baseline values will be defined as the last non-missing value (scheduled, unscheduled or repeat) prior to the patient receiving the first dose of oliceridine.

The following assessments will have a baseline value:

- NPRS
- Clinical Laboratories
- Vital Signs
- MRPSS Total Score
- ECG

6.2.2. Initial Setting and Condition Category

During the screening phase, the initial setting (Surgical, Medical and ED) will be recorded. The condition category for which parenteral opioid therapy was warranted will be captured using the International Classification of Diseases, 10th Revision (ICD-10) terminology.

6.2.3. Relative Day

The date of the first dose of oliceridine will be considered relative day 1, and the day before the first dose of oliceridine will be relative day -1. Relative days for events on or after the first dose will be calculated as date of event - date of first dose of oliceridine + 1. Relative days for events before the first dose will be calculated as date of event - date of first dose of oliceridine.

Study hour will be calculated relative to the first dose of oliceridine also: date/time of event - date/time of first dose of study drug.

6.2.4. Analysis Windows

All NPRS, PK, ECG, Cumulative Exposure, Laboratory Assessments, Vital Signs, Oxygen Saturation, and MRPSS data collected during the treatment period will be windowed to an appropriate analysis time window based on the following time intervals.

Analysis Windows for Exposure, Laboratory Assessments, Vital Signs, Oxygen Saturation, and MRPSS

Windowed Time Point	Analysis Window	Midpoint of Analysis Window
Baseline	<0 minutes	NA
T30 minutes	≥0 – <1 hour	30 minutes
T2.5 hours	≥1 – <4 hours	2 hours and 30 minutes
T8 hours	≥4 – <12 hours	8 hours
T18 hours	≥12 – <24 hours	18 hours

T30 hours	≥24 – <36 hours	30 hours
T42 hours	≥36 – <48 hours	42 hours
T60 hours	≥48 – <72 hours	60 hours
T84 hours	≥72 – <96 hours	84 hours
T96 hours	≥96 hours	96 hours

Analysis Windows for ECG

Windowed Time Point	Analysis Window	Midpoint of Analysis Window
Baseline	<0 minutes	NA
T60 minutes	≥0 – <1.5 hours	1 hour
T6 hours	≥1.5 – <12 hours	6 hours
T24 hours	≥12 – <36 hours	24 hours
T48 hours	≥36 – <63 hours	48 hours
T72 hours	≥63 – <96 hours	72 hours
T96 hours	≥96 hours	96 hours

Analysis Windows for NPRS

Windowed Time Point	Analysis Window	Midpoint of Analysis Window
Baseline	<0 minutes	NA
T20 minutes	≥0 - <40 minutes	30 minutes
T1 hour	≥40 – <1.5 hour	1 hour
T3.5 hours	≥1.5 – <6 hours	3 hours and 45 minutes
T12 hours	≥6 – <14 hours	10 hours
T19 hours	≥14 – <24 hours	19 hours
T24 hours	≥24 hours	24 hours

Analysis Windows for PK

Windowed Time Point	Analysis Window	Protocol Allowed Window
Baseline	≤0 minutes	NA
T30 minutes	>0 – <1 hour	±10 minutes
T1.5 hours	≥1 – <2 hours	≥1 – <2 hours
T14 hours	≥2 – <24 hours	NA
T36 hours	≥24 – <48 hours	NA
T60 hours	≥48 – <72 hours	NA
T84 hours	≥72 – <96 hours	NA

Unless stated otherwise, if multiple observations fall within the same analysis window, the measurement closest to the midpoint of the analysis time point will be selected. If there are more than 1 assessments equal distant from the midpoint of the analysis time point, the later of the data points will be used in the analysis. All selected observations will be flagged in the listings and only the flagged observation will be used in the descriptive summary statistics over time for each parameter.

In addition to the windowed values collected during the treatment phase, the protocol specified assessments for vital signs, oxygen saturation, MRPSS and laboratory End-of-Treatment values will be summarized using descriptive statistics. The End-of-Treatment values are defined as the first observation after the end of study date/time.

6.3 Safety Assessments

6.3.1 Extent of Exposure

Depending on the clinical considerations for which parenteral opioid therapy is warranted, a patient could receive oliceridine using clinician-administered bolus dosing or PCA dosing. Patients will have the method of administration categorized as PCA if they received at least 1 PCA dosing. Otherwise the method of administration will be categorized as bolus.

Duration is defined as the difference in total hours from the first dose to the last dose of study medication.

6.3.2 Adverse Events

Adverse events includes any newly occurring event or previous condition that increased in severity or frequency from time of informed consent. AEs occurring from time of informed consent to the follow-up phase will be recorded in source documentation and will also be recorded in the EDC system if the patient receives oliceridine. All AEs must be recorded irrespective of whether or not they are considered medication-related. All AEs that are possibly or probably related to study medication will be followed until resolution or database lock, whichever occurs first. Changes in intensity or frequency of AEs should be recorded as separate events (i.e., a new record started).

Treatment emergent adverse events (TEAEs) are defined as AEs with onset at the time of or following the start of treatment with study medication until 7 days after the last dose of study medication or any pre-existing AEs that have worsened in severity on or after the first dose of study medication and through 7 days after the last dose of study medication.

Adverse events will be designated as treatment-emergent according to the following algorithm:

- If both the start date and start time of an AE are known, then:
- If the AE starts at any time prior to the time of the first dose on Day 1, then the AE will not be designated as treatment-emergent and hence will not be summarized.
- If the AE starts on or after the time of the first dose on Day 1 through 7 days after the last dose, then the AE will be designated as treatment-emergent.

- If only the start date of an AE is known and the start time of the AE is unknown, then:
- If the AE starts on Day 0, then the AE will not be designated as treatment-emergent and hence will not be summarized.

• If the AE starts on Days 1 through 7 days after the last dose, then then the AE will be designated as treatment-emergent.

All AEs will be assessed on two descriptive parameters: intensity and relationship to the study medication:

• Intensity refers to the severity of an event and references impact on a patient's functioning. The following categories will be used to classify intensity:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Incapacitating with inability to work or perform usual activity

• Relationship refers to the likelihood that the event being assessed was caused by the study medication. The following categories will be used to classify relationship:

Not Related	There is no reasonable association between the study treatment and the suspected event.
Unlikely Related	It is doubtful that there is an association between the study treatment and the suspected event. The event could have been produced by the patient's clinical state or other modes of therapy administered to the patient.
Possibly Related	The suspected AE may or may not follow a reasonable temporal sequence from study treatment administration. The event could have been produced or mimicked by the patient's clinical state or by other modes of therapy concomitantly administered to the patient.
Probably Related	The suspected AE follows a reasonable temporal sequence from study treatment administration, abates upon discontinuation of the treatment, and cannot be reasonably explained by the known characteristics of the patient's clinical state.

For summaries by relationship, possibly and probably related will also be combined into one "related" summary.

6.3.3 Clinical Laboratory Evaluations

Baseline values are defined as the last measurements taken before the first dose of oliceridine. Change from baseline will be defined as the post baseline value minus the baseline value.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

Liver chemistry thresholds have been designed to assure patient safety. When patients meet the hepatic transaminase threshold criteria (AST or ALT >=3 × upper limit of normal [ULN]), the patient should undergo close observation, including monitoring for symptoms (clinical symptoms of hepatitis or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash) and hepatic function (AST, ALT, alkaline phosphatase, and fractionated bilirubin) at least every 48 hours, until symptoms and/or hepatic function abnormalities resolve, stabilize, or return to baseline values. The following thresholds will be derived and presented for hepatic chemistry:

- AST ≥ 3 x ULN
- ALT ≥ 3 x ULN
- AST or ALT ≥ 3 x ULN
- AST ≥ 5 x ULN
- ALT ≥ 5 x ULN
- AST or ALT ≥ 5 x ULN
- BILI ≥ 2 x ULN

6.3.4 Vital Signs

Baseline values are defined as the last measurements taken before the first dose of oliceridine. Change from baseline will be defined as the post baseline value minus the baseline value. Vital signs will include blood pressure (BP), heart rate (HR), respiratory rate (RR), and temperature. Temperature will be measured at screening and baseline only.

Potentially clinically significant abnormal (PCSA) vital signs parameter criteria is defined below:

Parameter	Criterion value	Change relative to baseline
Systolic blood pressure (mmHg)	≥ 180 mmHg	25% increase
Systolic blood pressure (mmHg)	≤ 80 mmHg	25% decrease
Diastolic blood pressure (mmHg)	≥ 110 mmHg	25% increase
Diastolic blood pressure (mmHg)	≤ 40 mmHg	25% decrease
Pulse rate (bpm)	≥ 120 bpm	15 bpm increase
Pulse rate (bpm)	≤ 40 bpm	15 bpm decrease

6.3.5 Electrocardiogram (ECG)

ECG summaries will include HR, PR interval, RR interval, QRS interval, QT interval, and QTcF interval. Baseline values are defined as the last measurements taken before the first dose of oliceridine. Change from baseline will be defined as the post baseline value minus the baseline value.
In addition to the observed values for these parameters, the following will be categorized:

- Change from Baseline QTcF > 30 milliseconds
- Change from Baseline QTcF > 60 milliseconds
- Increase of QTcF to > 500 milliseconds

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal finding is clinically significant.

6.3.6 Physical Examination

The physical examination will include general appearance. Results from screening/baseline will be recorded as medical history events while changes from screening/baseline in the physical examination will be recorded as AEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal finding is clinically significant.

6.3.7 Subjective Opiate Withdrawal Scale (SOWS)

The Subjective Opioid Withdrawal Scale (SOWS) will be administered one day after completion of the treatment phase to detect symptoms of opioid withdrawal. Patients will score each of the 16 symptoms on an intensity scale ranging from 0 “not at all” to 4 “extremely”.

If the patient is discharged or transferred before the time when the SOWS is to be performed, it will be performed one day after completion of the treatment phase and returned to the site by mail or in person.

Each patient should have exactly one SOWS administered during the study. However, if multiple SOWS results are collected for any given patent, the record with the most extreme total score will be used for summary purposes.

6.3.8 Oxygen Saturation

Baseline values are defined as the last measurements taken before the first dose of oliceridine. Change from baseline will be defined as the post baseline value minus the baseline value.

Potentially clinically significant abnormal (PCSA) oxygen saturation criteria is defined below:

Parameter	Criterion value	Change relative to baseline
Oxygen Saturation	< 90 %	NA

6.3.9 Somnolence/Sedation

The Moline-Roberts Pharmacologic Sedation Scale (MRPSS) will be used to measure somnolence/sedation. Baseline values are defined as the last measurements taken before the first dose of oliceridine. Six levels describe the range of sedation from "none to minimal" to "general anesthesia":

Presentation	Auditory Stimulus	Tactile Stimulus	Response	Sedation
Awake, aware, alert Airway and ventilation adequate	None	None	Spontaneous, sustained interaction	1 None to Minimal
Restful, drowsy, dozing, lightly sleeping Airway and ventilation adequate	Soft voice or ambient noise	None or light touch, rubbing or tapping	Sustains interaction	2 Anxiolysis
Sleeping Airway and ventilation adequate	Soft to normal voice	Light touch, rubbing or tapping	Limited or brief interaction	3 Moderate Sedation
Sleeping Airway and ventilation adequate	Normal to loud voice	Light touch, rubbing or tapping	Follows simple commands	4 Moderate Sedation
Sleeping Airway and ventilation may be impaired	**Loud voice**	**Intense to noxious**	**Purposeful response or non-purposeful**	**5 Deep Sedation**
Sleeping Airway and ventilation likely impaired	**Loud voice**	**Noxious**	**No response, unarousable**	**6 General Anesthesia**

6.4 Drug Concentration Measurements and Pharmacokinetic Parameters

For all samples, the actual sampling time will be recorded.

6.5 Efficacy Variables

6.5.1. Numeric Pain Rating Scale (NPRS)

The NPRS is a generic, unidimensional questionnaire of pain intensity in adults. In the NPRS, a respondent selects a whole number (0-10 integers) on a single 11 point scale that best reflects the intensity of their pain. In this scale, the 0 is anchored with the descriptor "no pain" and the 10 is anchored with the descriptor "worst pain imaginable". Baseline values are defined as the last measurements taken before the first dose of oliceridine. Change from baseline will be defined as the post baseline value minus the baseline value.

7. STATISTICAL METHODS

7.1 General Methodology

Data will be summarized using descriptive statistics (number of patients [N], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and using frequency and percentage for discrete variables. Unless specified otherwise, all summaries will be performed using SAS® Version 9.3 or higher.

7.2 Adjustments for Covariates

Not applicable to this study.

7.3 Handling of Dropouts or Missing Data

All dates presented in the individual patient listings will be as recorded on the eCRF, not as per the rules below. All rules explained below for partial/missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

7.3.1. Adverse Events

If the AE stop date is completely missing and the AE has resolved, the stop date will be imputed as the date of the patient's last visit in the study.

- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the patient's last clinic visit in the study if in the same year.

- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the patient's last clinic visit in which case the date of patient's last clinic visit in the study will be used instead.

If the start date is completely missing it will be imputed as follows:

- If the stop date occurs on or after the start of study medication or the event is ongoing, the start date will be imputed as the date of the first dose of study medication.

- If the stop date occurs before the start of study medication, the start date of the event will be imputed as the patient's screening date or the stop date of the event, whichever the earlier.

If the start time is missing it will be imputed only in the case where the start date of the event corresponds to the date of the first dose of study medication. In this case the time will be imputed as the same time as the first dose of study medication. In all other cases the time will not be imputed. Imputed dates will be used for calculations, however the actual date collected will be presented in listings.

7.3.2. Concomitant Medications

If the stop date is completely missing and the patient has stopped taking the CM, the stop date will be imputed as the date of the patient's last visit in the study.

- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the patient's last clinic visit in the study if in the same year.

- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the patient's last clinic visit in which case the date of patient's last clinic visit in the study will be used instead.

If the start date is completely missing it will be imputed as follows:

- If the stop date occurs on or after the start of study medication or the concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study medication.

- If the stop date occurs before the start of study medication, the start date of the medication will be imputed as the patient's screening date or the stop date of the medication whichever the earlier.

If the start time is missing it will be imputed only in the case where the start date of the medication corresponds to the date of the first dose of study medication. The time will be imputed as the same time as the first dose of study medication. In all other cases the time will not be imputed. Imputed dates will be used for calculations, however the actual date collected will be presented in listings.

7.3.3. Study Medication Dosing

The start date/time of first dose of study medication is not expected to be missing for any patient in the Safety Analysis Set. If the stop date/time of last dose of study medication is completely missing, then the date/time of last dose of study medication will be assigned as the earliest of the 5 options below for analysis purposes:

1. Start date/time of last dose
2. Date/time from end of treatment phase declaration
3. Date/time of patient's first end-of-treatment phase assessment in the study
4. Early termination
5. Death (assuming time of death of 23:59 if only date is available; time may be obtained from stop time of associated AE with fatal outcome)

7.3.4. Medical History

If the month and year are present but the day is missing, the diagnosis date will be set to first day of the relevant month. If only the year is recorded, the diagnosis date will be set as "01-Jan" for that year. If the entire date is missing, the start date of diagnosis will remain missing.

7.3.5. Numeric Pain Rating Scale

For patients who have no NPRS assessments recorded prior to the first dose of study medication, the baseline will be imputed with a score of 4. Otherwise, there will be no imputation of missing data for NPRS.

7.3.6. Subjective Opioid Withdrawal Scale

Opioid withdrawal will be measured using the Subjective Opioid Withdrawal Scale (SOWS) consisting of 16 symptoms rated in intensity (0=Not at all, 1=A little, 2=Moderately, 3=Quite a bit, 4=Extremely). The total score will be derived by summing the individual symptom intensities and will range from 0 to 64. If there are no more than half of the symptoms that are missing from the SOWS, imputation with the mean score of the non-missing questions will be used to calculate total score. SOWS with more than half of the symptoms missing will have total score missing.

7.4 Interim Analyses and Data Monitoring

No data monitoring committees are planning for this study. An interim analysis is expected to be performed in order to support regulatory discussions. No statistical testing will be performed.

7.5 Multi-Center Studies and Pooling of Centers

This study will be conducted at approximately 60-90 study centers located in the United States. No pooling of the sites will be performed since no formal statistical tests will be performed for the different centers.

7.6 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons or multiplicity will be made.

7.7 Examination of Subgroups

The analysis of safety will be examined by looking at the following subgroups: sex (females vs. males); age grouping 1 (<65 years vs. ≥65 years); age grouping 2 (≥18 to <study median years of safety analysis set population vs. ≥study median years of safety analysis set population); race (white vs non-white); median baseline NPRS score (< median vs. ≥ median); initial setting, BMI (<25 vs. >=25), and CYP2D6 metabolizer status.

No statistical testing will be performed for the subgroup analyses but any differences in treatment effect noticed in subgroups may be explored.

8. STATISTICAL ANALYSIS

The standard operating procedures (SOPs) of Chiltern, International, will be followed in the creation and quality control of all data displays and analyses.

8.1 Disposition of Subjects

The number of patients in each analysis set will be tabulated for all the Enrolled Analysis Set. Safety Analysis Set will be further summarized by each site and by cumulative dose group and all groups combined.

In addition, summary of reasons for screen failure will be tabulated for the Enrolled Analysis Set. The inclusion and exclusion criteria will be summarized in two separate categories. The inclusion criteria will be further categorized to patients not meeting the NPRS threshold and those not meeting other inclusion criteria. Patients with multiple reasons for failure or termination will be counted in each reason category.

Safety Analysis Set will be further summarized by cumulative dose group and all groups combined. The number of patients that completed the study, the number of patients that discontinued early, the number of patients for each reason for ealy discontinuation and the number of patients discontinuing at each study window will be summarized. Study window will be defined as the date and time of termination minus the date and time of first dose of oliceridine. The time point intervals are defined in section 6.2.4

Because the duration of treatment for each patient in this study will be determined by the clinical need for parenteral opioid therapy, a patient will be considered to be a completer if no early termination reason (e.g, AE to discontinuation, lack of efficacy) is indicated.

A listing with each patient's first/last dose of oliceridine, date/time of end of treatment, date of study completion and a potential reason for early termination will be provided. An additional listing with each patient's inclusion/exclusion criteria that caused the patients to be screen failures will be provided.

8.2 Protocol Deviations

Protocol deviations will be listed by patient and summarized in a table based on protocol deviation categories as collected by the Kestrel clinical trial management system. This summary will be based on the Enrolled Analysis Set. Deviation categories will include procedure window, inclusion/exclusion criteria, unapproved medication, visit window, missed procedure, informed consent, and incorrectly performed procedure. A categorization of major or minor for each deviation will be determined by Trevena and recorded in the Kestrel database, as well as included as part of the summary table.

Protocol deviations will be summarized by cumulative dose groups based on their cumulative dose received. Screening failures will not be included in this summary. The categories will be sorted by descending count of patients in the all treated patients column.

8.3 Analysis Populations

8.3.1. Enrolled Analysis Set

The enrolled population will include all patients that signed the informed consent form irrespective of whether they received oliceridine or not.

8.3.2. Safety Analysis Set

The safety analysis population will include all enrolled patients receiving at least 1 dose of oliceridine.

8.3.3. Efficacy Analysis Set

The efficacy analysis set will include all enrolled patients who received at least 1 dose of oliceridine and have at least 1 post-dose NPRS score.

8.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics including age, height, weight, BMI, and baseline pain intensity will be summarized for each cumulative dose group and for all groups combined for the Safety Analysis Set with descriptive statistics (number of patients [n], mean, standard deviation [SD], median, minimum [min], and maximum [max]). No statistical comparisons will be performed for demographic and baseline characteristics.

Initial setting, gender, age groupings 1 and 2, race, race group, ethnicity, CYP2D6 metabolizer status, and BMI group will be summarized for each cumulative dose group and for all groups combined for the Safety Analysis Set using counts and percentages.

Data listings including demographic and baseline characteristics will be produced.

8.5 Prior and Concomitant Medications

Prior and concomitant medications will be summarized separately using the Safety Analysis Set for each cumulative dose group and for all groups combined. The World Health Organization (WHO) Drug Dictionary, version March 2016, will be used to classify medications by preferred name and WHO ATC classification of ingredients.
The number and percent of patients who took prior medications will be shown by WHO ATC classification of ingredients and by preferred term. The number and percent of patients who took concomitant medications will be shown in the same manner.

Data listings including prior and concomitant medications will be produced. Prior and concomitant medications will be distinguished directly in the listing.

8.6 Analysis of Safety

The Safety Analysis Set will be used for all safety summaries. Summaries will be tabulated by cumulative dose group and for all groups combined.

8.6.1. Medical History

The reasons for receiving oliceridine will be summarized by the number and percentage of patients from each initial setting, specialty, and ICD-10 category for each cumulative dose group and for all groups combined using the Safety Analysis Set.

Other medical history collected will be summarized by the number and percentage of patients from each body system and medical condition for each cumulative dose group and for all groups combined using the Safety Analysis Set. All medical hisotry events will be coded using MedDRA version 19.0

Data listing including all medical history regardless of whether or not it was the reason for receiving oliceridine will be produced.

8.6.2. Extent of Exposure and Compliance to Study Treatment

8.6.2.1. Extent of Exposure

Each exposure summary will be summarized for each cumulative dose group and for all groups combined using the Safety Analysis Set.
The method of administration will be summarized by the number and percentage of patients using each method. Patients will have the method of administration categorized as PCA if they received at least 1 PCA dosing. Otherwise the method of administration will be categorized as bolus.
Then, regardless of the method of administration, the duration of exposure to study medication will be displayed by summary statistics (mean, standard deviation, median, minimum, and maximum). This duration will be computed as the difference in total hours from the start of the first dose of study medication to the end-time for the last dose of study medication administration.

The total amount of oliceridine administered will be computed regardless of the method of administration within the windows defined in Section 6.2.4. Subsequently, the total amount of oliceridine administered to patients over these periods will be summarized (mean, standard deviation, median, minimum, and maximum) by summary statistics.

Exposure summaries will be repeated by sex, age grouping 1, age grouping 2 , race, median baseline NPRS score, BMI, CYP2D6 metabolizer status and initial setting subgroups.

Exposure data including the date, time, method of administration, dose in mg for each administration of oliceridine and the cumulative dose will be listed for each patient.

Boxplots for each cumulative dose and dose duration will be generated by site. A scatterplot will also be generated depicting all patient by duration of treatment and cumulative oliceridine dose.

8.6.2.2. Measurements of Treatment Compliance

Treatment consists of parenteral opioid therapy administered by qualified medical personnel. There is no opportunity for self-administration outside of the confines of PCA, and the study drug is not dispensed to an enrolled patient outside of the confines of the investigative site. No summaries of compliance will be performed.

8.6.3. Adverse Events

The MedDRA version 19.0 will be used to classify all verbatim AE terms with respect to SOC and PT. Summaries will include only TEAEs and will be summarized for the Safety Analysis Set for each cumulative dose group and for all groups combined.

An overall summary of TEAEs will be performed with the following categories: any TEAE, serious TEAEs, TEAEs with the outcome of fatal, and TEAEs leading to early discontinuation. Severity rating and relationship to study medication categories will also be summarized. The summary will include unique patient counts and percentages based on the number of patients in the cumulative dose group, and the total event count. Overall summary of TEAEs will be repeated by sex, age grouping 1, age grouping 2 , race, median baseline NPRS score, BMI, CYP2D6 metabolizer status and initial setting subgroups.

The number and percentage of patients with TEAEs for each cumulative dose group and overall will also be displayed by SOC and PT and will be repeated by BMI and CYP2D6 metabolizer status subgroups. These 3 summary tables will also be repeated for serious TEAEs and TEAEs leading to early discontinuation.
TEAEs will also be summarized by PT only. This summary table will be repeated y BMI and CYP2D6 metabolizer status subgroups.

TEAEs, serious TEAEs and TEAEs resulting in early discontinuation will be summarized by cumulative dose and cumulative time based on the time point intervals defined in section 6.2.4. TEAEs by cumulative dose and cumulative time based on the time point intervals will also be summarized by PTs.

A summary of most common TEAEs will be presented, where PTs occurring in at least 5% of the all treated patients group will be included. Summaries will be sorted by PT in descending frequency in the all treated patients column.

Summaries of TEAEs by maximum severity (mild, moderate, or severe) will be performed by SOC and PT. Patients with missing severities will be counted as severe. Summaries of TEAEs by maximum relationship will be performed by SOC and PT. Patients with missing relationship will be counted as probably related.

The denominator for percentages will be the number of patient within the cumulative dose group for the Safety Analysis Set. The total number of events will be presented

along with the patient count and percentage. For summaries by SOC and PT, SOCs will be sorted alphabetically. For summaries only by PT, the sort will be by descending frequency in the all treated patients column. PTs with the same frequency count will be sorted alphabetically.

AE data including start/end time, intensity, any action taken, outcome and whether or not it's serious will be listed for each patient by cumulative dose groups.
Lastly, scatterplots will be generated depicting patients' cumulative dose by duration of treatment for patients with at least 1 TEAE, patients with at least 1 related TEAE, patients with at least 1 TEAE leading to early discontinuation and patients with at least 1 SAE.

No statistical inference testing between the treatments will be performed for AEs.

8.6.4. Clinical Laboratory Evaluations

All clinical laboratory evaluations will be summarized for the Safety Analysis Set for each cumulative dose group and for all groups combined. Descriptive summaries (mean, SD, median, minimum, and maximum) of absolute values and changes from baseline values will be presented for clinical laboratory values at each time point. Summaries will be performed using the standard units for each analyte. These summaries will be conducted over time using the windows specified in Section 6.2.4.

The number of patients with clinical laboratory values below, within, or above normal ranges for each time point will be tabulated (shift tables) for each clinical laboratory analyte by cumulative dose group.

The proportion of patients who have a clinically significant laboratory result will be summarized by time point for each parameter using frequencies and percentages.

Specific liver-related laboratory results will be summarized by cumulative dose groups and by time point. The specific results summarized will be AST $\geq$ 3 x ULN, ALT $\geq$ 3 x ULN, and AST or ALT $\geq$ 3 x ULN; AST $\geq$ 5 x ULN, ALT $\geq$ 5 x ULN, and AST or ALT $\geq$ 5 x ULN; and BILI $\geq$ 2 x ULN.

For clinically significant and shift summaries, the worst overall value reported will displayed. These "worst" results will be calculated as the maximum absolute change from baseline.

In addition, laboratory measurements listing will be presented for each patient.

No statistical inference between the treatments will be performed for laboratory evaluations.

8.6.5. Vital Signs

All vital signs will be summarized for the Safety Analysis Set for each cumulative dose group and for all groups combined. Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline values for systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR), and oxygen saturation will be presented at each time point defined in Section 6.2.4.

Patients meeting the PCSA criterion value or change relative to baseline will be summarized for the Safety Analysis Set for each cumulative dose group and for all groups combined also.

In addition, a listing of each vital signs parameter will be presented for each patient.

8.6.6. Physical Examination

Patient listings of whether physical examination was performed or not will be presented for the Safety Analysis Set.

8.6.7. ECG

Continuous descriptive summaries (n, mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for HR, PR interval, RR interval, QRS interval, QT interval, and QTcF interval for the Safety Analysis Set. These summaries will be provided by time point in accordance with the windoing defined in Section 6.2.4.

The number and percentage of patients with normal and abnormal ECG results will be displayed by each cumulative dose group and for all groups combined.

In addition, a listing of electrocardiogram results will be presented for each patient.

8.6.8. Subjective Opiate Withdrawal Scale (SOWS)

SOWS total score will be summarized with descriptive statistics (number of patients [N], mean, standard deviation [SD], median, minimum, and maximum) for the Safety Analysis Set. All SOWS results will also be listed by treatment.

8.6.9. Pharmacokinetic Procedures

Plasma concentration values (scheduled and unscheduled) will be summarized for the Safety Analysis Set over time using descriptive summary statistics and the analysis windows described in section 6.2.4. All plasma concentration values will be listed at each time point where an assessment has occurred.

8.7 Analysis of Efficacy Parameters

The Efficacy Analysis Set will be the population for all efficacy variables. Descriptive summary statistics will be tabulated by time interval, by cumulative dose group and for all groups combined. No formal statistical testing will be performed on the efficacy endpoints.

8.7.1. Analysis of NPRS

Continuous descriptive summaries (n, mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for the NPRS values for the Efficacy Analysis Set. All NPRS assessments will be listed for each actual time point where an assessment has occurred.

8.7.2. Exploratory Analyses

No exploratory analyses of efficacy data are planned.

9. Computer Software

All analyses will be performed by Chiltern, International, using Version 9.3 or later of SAS® software. All summary tables, figures and data listings will be prepared utilizing SAS® software.

10. REFERENCES

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American Journal of Alcohol Abuse, 13, 294-308.

[3]McCaffery, M., Beebe, A. (1989) *Pain: Clinical Manual for Nursing Practice* (UK edition). Aylesbury: Mosby.

[4] Pasero, C. (1994). *Acute Pain Service*: Policy and Procedure Manual. Los Angeles, CA: Academy Medical Systems.

11. APPENDICES

11.1 APPENDIX 1: VARIABLE DEFINITIONS

Age will be calculated as the informed consent date minus the date of birth divided by 365.25 [Age=(ICF Date-DOB)/365.25].

Body mass index (BMI; kg/m2) is calculated as: weight (kg) / [height (m)]2, rounded to one decimal place.

Height and weight are collected in imperial units and will be converted using the following conversion factors:
Height (cm) = height (inches) x 2.54
Weight (kg) = weight (lb) x 0.454

Temperature is collected in degrees Fahrenheit and will be converted to degrees Celcius using the following formula:

$$\text{Temp (°C)} = [\text{temp (°F)} - 32] \times \frac{5}{9}$$

Protocol Number CP130-3003

A phase 3, multicenter, open-label study to evaluate the safety of oliceridine (TRV130) in patients with acute pain for which parenteral opiod therapy is warranted

Mock Data Displays
Final Version 1.0
Date: 20Dec 2016

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Table 14.1.1
Protocol Deviations
(Safety Analysis Set)

Protocol Deviation Deviation Criticality	Oliceridine <= 4 mg N=XXX n(%)[E]	Oliceridine >4 to 8 mg N=XXX n(%)[E]	Oliceridine >8 to 16 mg N=XXX n(%)[E]	Oliceridine >16 to 36 mg N=XXX n(%)[E]	Oliceridine >36 mg N=XXX n(%)[E]	All Treated Patients N=XXX n(%)[E]
Number of Patients with a Protocol Deviation	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Minor	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Major	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Procedure Window	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Minor	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Major	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Inclusion/Exclusion Criteria	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Minor	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Major	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Unapproved Medication	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Minor	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Major	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Missed Procedure	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Minor	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Major	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]

Note: E = Number of deviation events.
Percentages are based on the number of patients in each cumulative dose group.

Table 14.1.1 *(Continued)*
Protocol Deviations
(Safety Analysis Set)

Protocol Deviation Deviation Criticality	Oliceridine <= 4 mg N=XXX n(%)[E]	Oliceridine >4 to 8 mg N=XXX n(%)[E]	Oliceridine >8 to 16 mg N=XXX n(%)[E]	Oliceridine >16 to 36 mg N=XXX n(%)[E]	Oliceridine >36 mg N=XXX n(%)[E]	All Treated Patients N=XXX n(%)[E]
Informed Consent	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Minor	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Major	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Incorrectly Performed Procedure	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Minor	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]
Major	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]	xxx (xxx.x)[E]

Note: E = Number of deviation events.
Percentages are based on the number of patients in each cumulative dose group.

Table 14.1.2.1
Patient Populations
(Enrolled Analysis Set)

Population	All Enrolled Patients N=XXX n(%)
Enrolled Analysis Set	xxx (xxx.x)
Safety Analysis Set	xxx (xxx.x)
Efficacy Analysis Set	xxx (xxx.x)

Note: Percentages based on the total number of enrolled patients.

Table 14.1.2.2
Summary of Safety Analysis Set
(Safety Analysis Set)

Population Site Number	Oliceridine <= 4 mg N=XXX n(%)	Oliceridine >4 to 8 mg N=XXX n(%)	Oliceridine >8 to 16 mg N=XXX n(%)	Oliceridine >16 to 36 mg N=XXX n(%)	Oliceridine >36 mg N=XXX n(%)	All Treated Patients N=XXX n(%)
Safety Analysis Set	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Site 1	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Site 2	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...						

Note: Percentages are based on the number of patients in each cumulative dose group.

Table 14.1.2.3
Summary of Reasons for Screen Failure
(Enrolled Analysis Set)

Parameter	All Enrolled Patients N=XXX n(%)
Number of Screen Failure Patients	xxx (xxx.x)
Number of Patients with Inclusion Criteria not Met	xxx (xxx.x)
Number of Patients not Meeting NPRS of >= 4	xxx (xxx.x)
Number of Patients not Meeting Other Inclusion Criteria	xxx (xxx.x)
Number of Patients with Exclusion Criteria Met	xxx (xxx.x)
Missing	xxx (xxx.x)

Note: Percentages based on the total number of enrolled patients.
Patients may fail screening for more than one reason.

Table 14.1.3
Summary of Reasons for Receiving Oliceridine
(Safety Analysis Set)

Initial Setting Specialty ICD-10 Category	Oliceridine <= 4 mg N=XXX n(%)	Oliceridine >4 to 8 mg N=XXX n(%)	Oliceridine >8 to 16 mg N=XXX n(%)	Oliceridine >16 to 36 mg N=XXX n(%)	Oliceridine >36 mg N=XXX n(%)	All Treated Patients N=XXX n(%)
Surgical	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Specialty 1>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<ICD-10 Category>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Specialty 2>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Medical	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Specialty 1>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<ICD-10 Category>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Specialty 2>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
ED						
<Specialty 1>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<ICD-10 Category>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Specialty 2>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)

Note: Percentages are based on the number of patients in each cumulative dose group.
Patient are only counted in the category if finding is the reason for patient's participation in the study.

Programmers Note: Sort by initial setting (Surg, Med then ED) and by decreasing frequency(all treated patients column) of ICD-10 category.

Table 14.1.4
Medical History by Body System and Medical Condition
(Safety Analysis Set)

Body System Medical Condition	Oliceridine <= 4 mg N=XXX n (%)	Oliceridine >4 to 8 mg N=XXX n (%)	Oliceridine >8 to 16 mg N=XXX n (%)	Oliceridine >16 to 36 mg N=XXX n (%)	Oliceridine >36 mg N=XXX n (%)	All Treated Patients N=XXX n (%)
Number of Patients with at Least 1 Medical History	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Body System 1>						
<Condition 1>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Condition n>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Body System 2>						
<Condition 1>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Condition n>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...						

Note: All medical history events were coded using MedDRA version 19.0.
Percentages are based on the number of patients in each cumulative dose group.
Patients are counted once within each body system and condition within each cumulative dose group.

Programmer's Note: Order System Organ Class alphabetically and preferred term alphabetically within each SOC. If SOC wraps to a new page, it shoud be repeated in each page. Sort UNCODED as fist SOC.

Table 14.1.5
Summary of Patient Disposition
(Safety Analysis Set)

Disposition	Oliceridine <= 4 mg N=XXX n(%)	Oliceridine >4 to 8 mg N=XXX n(%)	Oliceridine >8 to 16 mg N=XXX n(%)	Oliceridine >16 to 36 mg N=XXX n(%)	Oliceridine >36 mg N=XXX n(%)	All Treated Patients N=XXX n(%)
Number of Patients That Completed the Study [a]	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Number of Patients That Discontinued Early from Study	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Reason for Early Discontinuation from Study						
ADVERSE EVENT	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
LACK OF EFFICACY	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
LOST TO FOLLOW-UP	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
. . .	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Study Window of Early Discontinuation [b]						
<T30 Minutes>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<T2 Hours>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<T96 Hours>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)

Note: Percentages are based on the number of patients in each cumulative dose group.

[a] Because the duration of treatment for each patient in this study will be determined by the clinical need for parenteral opioid therapy, a patient will be considered to be a completer if no early termination reason is indicated.

[b] Study window is defined as the date and time of termination – date and time of the first dose of oliceridine. See section 6.2.3 of the SAP for windowed time point intervals.

Table 14.1.6
Demographic and Baseline Characteristics
(Safety Analysis Set)

Characteristic	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX
Initial Setting, n(%)						
Surgical	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Medical	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Emergency Department	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Gender, n(%)						
Male	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Female	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Age (Years)						
N	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing	xxx	xxx	xxx	xxx	xxx	xxx
Age Group 1 (Years), n(%)						
< Median	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
>= Median	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)

Note: Percentages are based on the total number of non-missing values in each cumulative dose group.
[a] Extensive Metabolizer = Normal functional levels of CYP2D6 in the liver. Poor Metabolizer = Low functional levels of CYP2D6 in the liver.

Table 14.1.6 (*continued*)
Demographic and Baseline Characteristics
(Safety Analysis Set)

Characteristic	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX
Age Group 2 (Years), n(%)						
< 65	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
>= 65 to < 75	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
>= 75	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Race, n(%)						
<Race 1>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Race n>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Race Group, n(%)						
White	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Non-White	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Ethnicity, n(%)						
<Ethnicity 1>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Ethnicity n>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
CYP2D6 Metabolizer Status [a], n(%)						
Extensive Metabolizer	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Poor Metabolizer	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)

Note: Percentages are based on the total number of non-missing values in each cumulative dose group.
[a] Extensive Metabolizer = Normal functional levels of CYP2D6 in the liver. Poor Metabolizer = Low functional levels of CYP2D6 in the liver.

Table 14.1.6 (*continued*)
Demographic and Baseline Characteristics
(Safety Analysis Set)

Characteristic	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX
Height (cm)						
N	xxx	xxx	xxx	xxx	xxx	Xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing	xxx	xxx	xxx	xxx	xxx	Xxx
Weight (kg)						
N	xxx	xxx	xxx	xxx	xxx	Xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing	xxx	xxx	xxx	xxx	xxx	Xxx
BMI (kg/m**2)						
N	xxx	xxx	xxx	xxx	xxx	Xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing	xxx	xxx	xxx	xxx	xxx	Xxx
BMI Group (kg/m**2), n(%)						
< 25	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
>= 25	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)

Note: Percentages are based on the total number of non-missing values in each cumulative dose group.
[a] Extensive Metabolizer = Normal functional levels of CYP2D6 in the liver. Poor Metabolizer = Low functional levels of CYP2D6 in the liver.

Table 14.1.6 (*continued*)
Demographic and Baseline Characteristics
(Safety Analysis Set)

Characteristic	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX
Baseline Pain Intensity						
N	xxx	xxx	xxx	xxx	xxx	Xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing	xxx	xxx	xxx	xxx	xxx	Xxx

Note: Percentages are based on the total number of non-missing values in each cumulative dose group.
[a] Extensive Metabolizer = Normal functional levels of CYP2D6 in the liver. Poor Metabolizer = Low functional levels of CYP2D6 in the liver.

Table 14.1.7
Summary of Prior Medications by Drug Class and Medication
(Safety Analysis Set)

Drug Class Preferred Name[a]	Oliceridine <= 4 mg N=XXX n(%)	Oliceridine >4 to 8 mg N=XXX n(%)	Oliceridine >8 to 16 mg N=XXX n(%)	Oliceridine >16 to 36 mg N=XXX n(%)	Oliceridine >36 mg N=XXX n(%)	All Treated Patients N=XXX n(%)
Number of Patients Receiving a Prior Medication	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Class 1>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Preferred 1>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Preferred n>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...						
<Class n>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Preferred 1>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Preferred n>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)

Note: Percentages are based on the number of patients in each cumulative dose group.
Patients are counted once within each drug class and preferred name within each cumulative dose group.
[a] All medications were coded using WHO DRUG version Mar 1 2016.

Table 14.1.8
Summary of Concomitant Medications by Drug Class and Medication
(Safety Analysis Set)

Drug Class Preferred Name[a]	Oliceridine <= 4 mg N=XXX n(%)	Oliceridine >4 to 8 mg N=XXX n(%)	Oliceridine >8 to 16 mg N=XXX n(%)	Oliceridine >16 to 36 mg N=XXX n(%)	Oliceridine >36 mg N=XXX n(%)	All Treated Patients N=XXX n(%)
Number of Patients Receiving a Concomitant Medication	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Class 1>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Preferred 1>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Preferred n>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Class n>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Preferred 1>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Preferred n>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)

Note: Percentages are based on the number of patients in each cumulative dose group.
Patients are counted once within each drug class and preferred name within each cumulative dose group.
[a] All medications were coded using WHO DRUG version Mar 1 2016.

Table 14.2.1
Summary of Numeric Pain Rating Scale Change From Baseline
(Efficacy Analysis Set)

Windowed Time Point [a]	Baseline/ Observed/ Change from Baseline	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX
Baseline [b]							
N	Observed	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing		xxx	xxx	xxx	xxx	xxx	xxx
<T30 Minutes>							
N	Baseline[c]	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing		xxx	xxx	xxx	xxx	xxx	xxx
N	Observed	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing		xxx	xxx	xxx	xxx	xxx	xxx
N	Change	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing		xxx	xxx	xxx	xxx	xxx	xxx
...							

[a] See section 6.2.3 of the SAP for windowed time point intervals.
[b] Baseline is the last non-missing value prior to the patient receiving the first dose of oliceridine.
[c] Only patients with both a baseline value and a windowed time point value are summarized at a given windowed time point.

Table 14.3.1.1
Exposure to Study Drug
(Safety Analysis Set)

	Oliceridine <=4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine > 36 mg N=XXX	All Treated Patients N=XXX
Method of Administration, n(%)						
Bolus	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
PCA	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Exposure to Oliceridine [a] (Hours)						
N	Xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Number of Patients Exposed by Study Window [b], n(%)						
<T30 Minutes>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<T96 Hours>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Cumulative Oliceridine Dose (mg)						
N	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

Note: Percentages are based on the number of patients in each cumulative dose group.
[a] Duration is defined as the difference in total hours from the first dose to the last dose of of study medication.
[b] See section 6.2.3 of the SAP for windowed time point intervals.

Table 14.3.1.2
Exposure to Study Drug by Sex
(Safety Analysis Set)

	Oliceridine <=4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine > 36 mg N=XXX	All Treated Patients N=XXX
Sex: Male	xxx	xxx	xxx	xxx	xxx	xxx
Method of Administration, n(%)						
Bolus	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
PCA	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Exposure to Oliceridine [a] (Hours)						
N	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Number of Patients Exposed by Study Window [b], n(%)						
<T30 Minutes>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<T96 Hours>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Cumulative Oliceridine Dose (mg)						
N	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Sex: Female	xxx	xxx	xxx	xxx	xxx	xxx
...						

Note: Percentages are based on the number of patients in each cumulative dose group.
[a] Duration is defined as the difference in total hours from the first dose to the last dose of of study medication.
[b] See section 6.2.3 of the SAP for windowed time point intervals.

Source: Listing x.x.x
Program Name: s<nnn>xxxx

Use the same template as for Table 14.3.1.2 for the following tables:

Table 14.3.1.3
Exposure to Study Drug by Age Group 1
(Safety Analysis Set)

Table 14.3.1.4
Exposure to Study Drug by Age Group 2
(Safety Analysis Set)

Table 14.3.1.5
Exposure to Study Drug by Race
(Safety Analysis Set)

Table 14.3.1.6
Exposure to Study Drug by Median Baseline NPRS Score (< Median Baseline NPRS Score , >= Median Baseline NPRS Score)
(Safety Analysis Set)

Table 14.3.1.7
Exposure to Study Drug by CYP2D6 Metabolizer Status
(Safety Analysis Set)

Table 14.3.1.8
Exposure to Study Drug by BMI Category
(Safety Analysis Set)

Table 14.3.1.9
Exposure to Study Drug by Initial Setting
(Safety Analysis Set)

Table 14.3.2.1
Summary of Treatment Emergent Adverse Events (TEAE)
(Safety Analysis Set)

	Oliceridine <=4 mg N=XXX n(%)[E]	Oliceridine >4 to 8 mg N=XXX n(%)[E]	Oliceridine >8 to 16 mg N=XXX n(%)[E]	Oliceridine >16 to 36 mg N=XXX n(%)[E]	Oliceridine > 36 mg N=XXX n(%)[E]	All Treated Patients N=XXX n(%)[E]
Patients with at Least 1 TEAE	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
Patient with at Least 1 Serious TEAE	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
Number of Patients Who Had a TEAE with a Fatal Outcome	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
Patients with at Least 1 TEAE Leading to Early Study Medication Discontinuation [a]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
Due to Study Medication-Related TEAE [b]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
Due to Serious TEAE	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
Patients with TEAEs by Maximum Severity						
Mild	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
Moderate	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
Severe[c]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]

Note: E = Number of events.
Percentages are based on the number of patients in each cumulative dose group.
All adverse events were coded using MedDRA version 19.0. TEAEs are defined in section 6.3.3 of the SAP.
[a] AE recorded as having an action taken of drug discontinued.
[b] Includes events recorded as possibly related, probably related, or missing.
[c] Missing severities are assumed to be severe.
[d] Missing relationships are assumed to be probably related.

Source: Listing x.x.x
Program Name: s<nnn>xxxx

Data Extraction: yyyymmdd Output Date: yyyymmddthh:mm

Table 14.3.2.1(*continued*)
Summary of Treatment Emergent Adverse Events (TEAE)
(Safety Analysis Set)

	Oliceridine <=4 mg N=XXX n(%)[E]	Oliceridine >4 to 8 mg N=XXX n(%)[E]	Oliceridine >8 to 16 mg N=XXX n(%)[E]	Oliceridine >16 to 36 mg N=XXX n(%)[E]	Oliceridine > 36 mg N=XXX n(%)[E]	All Treated Patients N=XXX n(%)[E]
Patients with TEAEs by Maximum Relationship [d]						
Not Related	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
Unlikely Related	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
Possibly Related	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
Probably Related	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
Possibly or Probably Related	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]

Note: E = Number of events.
Percentages are based on the number of patients in each cumulative dose group.
All adverse events were coded using MedDRA version 19.0. TEAEs are defined in section 6.3.3 of the SAP.
[a] AE recorded as having an action taken of drug discontinued.
[b] Includes events recorded as possibly related, probably related, or missing.
[c] Missing severities are assumed to be severe.
[d] Missing relationships are assumed to be probably related.

Use the same template as for Table 14.3.2.1 for the following tables:

Table 14.3.2.1.1
Summary of Treatment Emergent Adverse Events (TEAE) by Age Group 1
(Safety Analysis Set)

Table 14.3.2.1.2
Summary of Treatment Emergent Adverse Events (TEAE) by Age Group 2
(Safety Analysis Set)

Table 14.3.2.1.3
Summary of Treatment Emergent Adverse Events (TEAE) by Race
(Safety Analysis Set)

Table 14.3.2.1.4
Summary of Treatment Emergent Adverse Events (TEAE) by Median Baseline NPRS Score (< Median Baseline NPRS Score , >= Median Baseline NPRS Score)
(Safety Analysis Set)

Table 14.3.2.1.5
Summary of Treatment Emergent Adverse Events (TEAE) by CYP2D6 Metabolizer Status
(Safety Analysis Set)

Table 14.3.2.1.6
Summary of Treatment Emergent Adverse Events (TEAE) by BMI Category
(Safety Analysis Set)

Table 14.3.2.1.7
Summary of Treatment Emergent Adverse Events (TEAE) by Initial Setting
(Safety Analysis Set)

Table 14.3.2.2.1
Treatment Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term
(Safety Analysis Set)

System Organ Class Preferred Term	Oliceridine <= 4 mg N=XXX n(%) [E]	Oliceridine >4 to 8 mg N=XXX n(%) [E]	Oliceridine >8 to 16 mg N=XXX n(%) [E]	Oliceridine >16 to 36 mg N=XXX n(%) [E]	Oliceridine >36 mg N=XXX n(%) [E]	All Treated Patients N=XXX n(%) [E]
Patients with at Least 1 TEAE	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
<SOC 1>	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
<Preferred term 1>	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
...	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
<Preferred term n>	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
...						
<SOC n>	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
<Preferred term 1>	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
...	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
<Preferred term n>	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]

Note: E = Number of events.
All adverse event terms were coded using MedDRA dictionary version 19.0.
Percentages are based on the number of patients in each cumulative dose group.
Patients are counted once within each system organ class and each preferred term.
TEAEs are defined in section 6.3.3 of the SAP.

Source: Listing x.x.x
Program Name: s<nnn>xxxx

Data Extraction: yyyymmdd Output Date: yyyymmddthh:mm

Use the same template as for Table 14.3.2.2.1 for the following tables:

Table 14.3.2.2.1.1
Treatment Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term by CYP2D6 Metabolizer Status
(Safety Analysis Set)

Table 14.3.2.2.1.2
Treatment Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term by BMI Category
(Safety Analysis Set)

Table 14.3.2.2.2
Serious Treatment Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term
(Safety Analysis Set)

Table 14.3.2.2.2.1
Serious Treatment Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term by CYP2D6 Metabolizer Status
(Safety Analysis Set)

Table 14.3.2.2.2.2
Serious Treatment Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term by BMI Category
(Safety Analysis Set)

Table 14.3.2.2.3
Treatment Emergent Adverse Events (TEAE) Resulting in Early Discontinuation by System Organ Class and Preferred Term
(Safety Analysis Set)

Table 14.3.2.2.3.1
Treatment Emergent Adverse Events (TEAE) Resulting in Early Discontinuation by System Organ Class and Preferred Term by CYP2D6 Metabolizer Status
(Safety Analysis Set)

Table 14.3.2.2.3.2
Treatment Emergent Adverse Events (TEAE) Resulting in Early Discontinuation by System Organ Class and Preferred Term by BMI Category
(Safety Analysis Set)

Table 14.3.2.3.1
Treatment Emergent Adverse Events (TEAE) in Decreasing Frequency of Preferred Term
(Safety Analysis Set)

Preferred Term	Oliceridine <= 4 mg N=XXX n(%) [E]	Oliceridine >4 to 8 mg N=XXX n(%) [E]	Oliceridine >8 to 16 mg N=XXX n(%) [E]	Oliceridine >16 to 36 mg N=XXX n(%) [E]	Oliceridine >36 mg N=XXX n(%) [E]	All Treated Patients N=XXX n(%) [E]
Patients with at Least 1 TEAE	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
<Preferred term 1>	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
<Preferred term 2>	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
...						
<Preferred term n>	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]

Note: E = Number of events.
All adverse event terms were coded using MedDRA dictionary version 19.0.
Percentages are based on the number of patients in each cumulative dose group.
Patients are counted once within each preferred term.
TEAEs are defined in section 6.3.3 of the SAP.
Preferred terms are sorted in descending patient level incidence in the All Treated Patients column.

Programmer's Note: Order preferred terms based on the All Treated Patients column. If preferred terms have the same patient count, order by descending event count and then alphabetically.

Use the same template as for Table 14.3.2.3.2 for the following tables:

Table 14.3.2.3.1.1
Treatment Emergent Adverse Events (TEAE) in Decreasing Frequency of Preferred Term by CYP2D6 Metabolizer Status
(Safety Analysis Set)

Table 14.3.2.3.1.2
Treatment Emergent Adverse Events (TEAE) in Decreasing Frequency of Preferred Term by BMI Category
(Safety Analysis Set)

Table 14.3.2.4.1
Treatment Emergent Adverse Events (TEAE) by Cumulative Dose and Cumulative Time
(Safety Analysis Set)

Cumulative Duration of Exposure[a]	Oliceridine <= 4 mg N=XXX n(%) [E]	Oliceridine >4 to 8 mg N=XXX n(%) [E]	Oliceridine >8 to 16 mg N=XXX n(%) [E]	Oliceridine >16 to 36 mg N=XXX n(%) [E]	Oliceridine >36 mg N=XXX n(%) [E]	All Treated Patients N=XXX n(%) [E]
Patients with at Least 1 TEAE	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
<T30 Minutes>	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
<T2 Hours>	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
....	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]

Note: E = Number of events.
Percentages are based on the number of patients in each cumulative dose group and cumulative duration of exposure windowed time point. The denominators for each cell can be referenced in table 14.3.1.1.
See section 6.2.3 of the SAP for windowed time point intervals.
TEAEs are defined in section 6.3.3 of the SAP.
[a] Duration is defined as the difference in total hours from the first dose to the last dose of of study medication.

Use the same template as for Table 14.3.2.4.1 for the following tables:

Table 14.3.2.4.2
Serious Treatment Emergent Adverse Events (TEAE) by Preferred Term and Duration of Exposure
(Safety Analysis Set)

Table 14.3.2.4.3
Treatment Emergent Adverse Events (TEAE) Resulting in Early Discontinuation by Preferred Term and Duration of Exposure
(Safety Analysis Set)

Table 14.3.2.5.1
Treatment Emergent Adverse Events (TEAE) by Cumulative Dose and Cumulative Time by Preferred Term
(Safety Analysis Set)

Preferred Term [a] Cumulative Duration of Exposure[b]	Oliceridine <= 4 mg N=XXX n(%) [E]	Oliceridine >4 to 8 mg N=XXX n(%) [E]	Oliceridine >8 to 16 mg N=XXX n(%) [E]	Oliceridine >16 to 36 mg N=XXX n(%) [E]	Oliceridine >36 mg N=XXX n(%) [E]	All Treated Patients N=XXX n(%) [E]
<Preferred term 1>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<T30 Minutes>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<T2 Hours>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
....						
<Preferred term 2>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
....						
....						
<Preferred term n>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
....						

Note: E = Number of events.
Percentages are based on the number of patients in each cumulative dose group and cumulative duration of exposure windowed time point. The denominators for each cell can be referenced in table 14.3.1.1.
Patients are counted once within each preferred term.
See section 6.2.3 of the SAP for windowed time point intervals.
TEAEs are defined in section 6.3.3 of the SAP.
[a] All adverse event terms were coded using MedDRA dictionary version 19.0.
[b] Duration is defined as the difference in total hours from the first dose to the last dose of of study medication.

Table 14.3.2.6.1
Summary of Most Common Treatment Emergent Adverse Events (>=5% of All Treated Patients) by Decreasing Frequency of Preferred Term
(Safety Analysis Set)

Preferred Term[a]	Oliceridine <= 4 mg N=XXX n(%) [E]	Oliceridine >4 to 8 mg N=XXX n(%) [E]	Oliceridine >8 to 16 mg N=XXX n(%) [E]	Oliceridine >16 to 36 mg N=XXX n(%) [E]	Oliceridine >36 mg N=XXX n(%) [E]	All Treated Patients N=XXX n(%) [E]
Patients with at Least 1 TEAE	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
<Preferred term 1>	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]
...						
<Preferred term n>	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]	xxx (xxx.x) [xxx]

Note: E = Number of events.
Percentages are based on the number of patients in each cumulative dose group.
Patients are counted once within each preferred term.
TEAEs are defined in section 6.3.3 of the SAP.
Preferred terms are sorted in descending patient level incidence in the All Treated Patients column.
[a] All adverse event terms were coded using MedDRA dictionary version 19.0.

Programmer's Note: Order preferred terms based on the All Treated Patients column. If preferred terms have the same patient count, order by descending event count and then alphabetically.

Table 14.3.2.7.1
Treatment Emergent Adverse (TEAE) by Maximum Severity, System Organ Class and Preferred Term
(Safety Analysis Set)

System Organ Class Preferred Term[a] Severity	Oliceridine <= 4 mg N=XXX n(%) [E]	Oliceridine >4 to 8 mg N=XXX n(%) [E]	Oliceridine >8 to 16 mg N=XXX n(%) [E]	Oliceridine >16 to 36 mg N=XXX n(%) [E]	Oliceridine >36 mg N=XXX n(%) [E]	All Treated Patients N=XXX n(%) [E]
Patients with at Least 1 TEAE	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Mild	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Moderate	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Severe	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
<SOC 1>	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Mild	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Moderate	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Severe	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
<Preferred Term 1>	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Mild	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Moderate	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Severe	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
...						

Note: E = Number of events.
Percentages are based on the number of patients in each cumulative dose group.
Patients are counted once within each system organ class and preferred term.
TEAEs are defined in section 6.3.3 of the SAP.
If a patient had more than one occurrence of the same event, the highest severity is summarized. Missing severities are assumed to be severe.
[a] All adverse event terms were coded using MedDRA dictionary version 19.0.

Programmer's Note: Order system organ class alphabetically and preferred term alphabetically withing each system organ class. Repeat SOC on each page if it wraps on to multiple pages.

Table 14.3.2.8.1
Treatment Emergent Adverse (TEAE) by Maximum Relationship, System Organ Class and Preferred Term
(Safety Analysis Set)

System Organ Class Preferred Term[a] Relationship	Oliceridine <= 4 mg N=XXX n(%) [E]	Oliceridine >4 to 8 mg N=XXX n(%) [E]	Oliceridine >8 to 16 mg N=XXX n(%) [E]	Oliceridine >16 to 36 mg N=XXX n(%) [E]	Oliceridine >36 mg N=XXX n(%) [E]	All Treated Patients N=XXX n(%) [E]
Patients with at Least 1 TEAE	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Not Related	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Unlikely Related	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Possibly Related	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Probably Related	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Possibly or Probably Related [b]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
<SOC 1>	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Not Related	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Unlikely Related	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Possibly Related	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Probably Related	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Possibly or Probably Related [b]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
<Preferred Term 1>	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Not Related	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Unlikely Related	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Possibly Related	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Probably Related	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
Possibly or Probably Related [b]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]	xxx (xxx.x)[xxx]
...						

Note: E = Number of events.

Source: Listing x.x.x
Program Name: s<nnn>xxxx

Percentages are based on the number of patients in each cumulative dose group.
Patients are counted once within each system organ class and preferred term.
TEAEs are defined in section 6.3.3 of the SAP.
[a] All adverse event terms were coded using MedDRA dictionary version 19.0.
[b] Missing relationships are assumed to be probably related.

Programmer's Note: Order system organ class alphabetically and preferred term alphabetically withing each system organ class. Repeat SOC on each page if it wraps on to multiple pages.

Table 14.3.3.1
Change from Baseline in Clinical Laboratory Results: Hematology
(Safety Analysis Set)

Parameter (unit) Windowed Time Point[a]	Baseline/ Observed/ Change from Baseline	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX
<Parameter x (unit)>							
Baseline[b]							
n	Observed	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
<T30 Minutes>							
n	Baseline[c]	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
n	Observed	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
n	Change	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
...							

Note: Percentages are based on the number of patients in each cumulative dose group.
[a] See section 6.2.3 of the SAP for windowed time point intervals.
[b] Baseline is the last non-missing value prior to the patient receiving the first dose of oliceridine.

Parameter (unit) Windowed Time Point[a]	Baseline/ Observed/ Change from Baseline	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX

[c] Only patients with both a baseline value and a windowed time point value are summarized at a given windowed time point.

Programmer's Note: Repeat Parameter (unit) in each page if it wraps on to multiple pages.

Use the same template as for Table 14.3.3.1 for the following tables:

Table 14.3.3.2
Summary of Clinical Laboratory Results: Chemistry
(Safety Analysis Set)

Table 14.3.3.1.1
Clinical Laboratory Hematology Results for Shifts from Baseline
(Safety Analysis Set)

Parameter (unit) Windowed Time Point[a]	Cumulative dose group	Baseline [b]	Post Baseline Low n (%)	Post Baseline Normal n (%)	Post Baseline High n (%)	Post Baseline Total n (%)	Post Baseline Missing
<Parameter 1 (unit)>	Oliceridine <= 4 mg (N=XXX)						
Worst Post Baseline		Low	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx
		Normal	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx
		High	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx
		Total	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx
		Missing	xxx	xxx	xxx	xxx	xxx
<T30 Minutes>		Low	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx
		Normal	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx
		High	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx
		Total	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx
		Missing	xxx	xxx	xxx	xxx	xxx
...							
<Time Point n>		Low	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx
		Normal	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx
		High	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx
		Total	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx
		Missing	xxx	xxx	xxx	xxx	xxx

Note: Low = below normal reference range; Normal = within normal reference range; High = above normal reference range.
Percentages are based on the number of patients with a non-missing baseline and post-baseline windowed time point value within each windowed time point, parameter and cumulative dose group.
Worst post-baseline is calculated as the most extreme absolute change from baseline value.
[a] See section 6.2.3 of the SAP for windowed time point intervals.
[b] Baseline is the last non-missing value prior to the patient receiving the first dose of oliceridine.

Use the same template as for Table 14.3.4.1.3 for the following tables:

Table 14.3.3.2.1
Clinical Laboratory Chemistry Results for Shifts from Baseline
(Safety Analysis Set)

Table 14.3.3.1.2
Clinically Significant Clinical Laboratory Hematology Results
(Safety Analysis Set)

Parameter (unit) Windowed Time Point [a] Interpretation	Oliceridine <= 4 mg N=XXX n(%)	Oliceridine >4 to 8 mg N=XXX n(%)	Oliceridine >8 to 16 mg N=XXX n(%)	Oliceridine >16 to 36 mg N=XXX n(%)	Oliceridine >36 mg N=XXX n(%)	All Treated Patients N=XXX n(%)
Patients with at Least 1 Clinically Significant Hematology Result	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<Parameter 1 (unit)>						
Baseline[b]	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Normal	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Abnormal, NCS	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Abnormal, CSig	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Worst Post-Baseline Value	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Normal	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Abnormal, NCS	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Abnormal, CSig	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<T30 Minutes>	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Normal	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Abnormal, NCS	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Abnormal, CSig	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...						

Note: NCS = Not clinically significant; CSig = Clinically significant.
Clinical significance is based on the investigator interpretation as recorded.
Percentages are based on the number of patients with a non-missing baseline and post-baseline windowed time point value within each windowed time point, parameter and cumulative dose group.
Worst post-baseline is calculated as the most extreme absolute change from baseline value.

Source: Listing x.x.x
Program Name: s<nnn>xxxx

Data Extraction: yyyymmdd Output Date: yyyymmddthh:mm

[a] See section 6.2.3 of the SAP for windowed time point intervals.
[b] Baseline is the last non-missing value prior to the patient receiving the first dose of oliceridine.

Programmer's Note: Continue with all parameters and all windowed time points even if all counts are 0.

Use the same template as for Table 14.3.3.1.2 for the following tables:

Table 14.3.3.2.2
Clinically Significant Clinical Laboratory Chemistry Results
(Safety Analysis Set)

Table 14.3.4.1
Select Hepatic Laboratory Findings on Treatment
(Safety Analysis Set)

Windowed Time Point [a] Test Result	Oliceridine <= 4 mg N=XXX n(%)	Oliceridine >4 to 8 mg N=XXX n(%)	Oliceridine >8 to 16 mg N=XXX n(%)	Oliceridine >16 to 36 mg N=XXX n(%)	Oliceridine >36 mg N=XXX n(%)	All Treated Patients N=XXX n(%)
Patients with at Least 1 Hepatic Laboratory Finding						
AST >=3 X ULN	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
ALT >=3 X ULN	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
AST or ALT >=3 X ULN	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
AST >=5 X ULN	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
ALT >=5 X ULN	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
AST or ALT >=5 X ULN	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
BILI >=2 X ULN	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<T30 Minutes>						
AST >=3 X ULN	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
ALT >=3 X ULN	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
AST or ALT >=3 X ULN	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...						

Note: ALT = Alanine Aminotransferase; AST = Asparate Aminotransferase; BILI = Total Bilirubin; ULN = Upper Limit of Normal.
Percentages are based on the number of patients with a non-missing windowed time point value within each windowed time point and cumulative dose group.
[a] See section 6.2.3 of the SAP for windowed time point intervals.

Programmer's Note: Continue with all windowed time points and criteria rows, even if all counts are 0..

Table 14.3.5.1
Change from Baseline in Vital Signs
(Safety Analysis Set)

Parameter (unit) Windowed Time Point[a]	Baseline/ Observed/ Change from Baseline	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX
<Parameter x (unit)>							
Baseline[b]							
n	Observed	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
<T30 Minutes>							
n	Baseline[c]	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
n	Observed	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
n	Change	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
...							

[a] See section 6.2.3 of the SAP for windowed time point intervals.
[b] Baseline is the last non-missing value prior to the patient receiving the first dose of oliceridine.
[c] Only patients with both a baseline value and a windowed time point value are summarized at a given windowed time point. *Programmer's Note: Repeat Parameter (unit) in each page if it wraps on to multiple pages.*

Table 14.3.5.2
Change from Baseline in Oxygen Saturation (%)
(Safety Analysis Set)

Windowed Time Point[a]	Baseline/ Observed/ Change from Baseline	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX
Baseline[b]							
n	Observed	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
<T30 Minutes>							
n	Baseline[c]	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
n	Observed	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
n	Change	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
...							

[a] See section 6.2.3 of the SAP for windowed time point intervals.
[b] Baseline is the last non-missing value prior to the patient receiving the first dose of oliceridine.
[c] Only patients with both a baseline value and a windowed time point value are summarized at a given windowed time point.

Table 14.3.5.1.1
Potentially Clinically Significant Vital Signs
(Safety Analysis Set)

PCSA Criterion	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX
Systolic Blood Pressure <= 80 mmHg	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
Systolic Blood Pressure >= 180 mmHg	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
Systolic Blood Pressure change from baseline > 25% increase	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
Systolic Blood Pressure change from baseline > 25% decrease	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
Diastolic Blood Pressure <= 40 mmHg	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
Diastolic Blood Pressure >= 110 mmHg	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)

Note: Percentages are based on the number of patients in each cumulative dose group.

Table 14.3.5.1.1 *(continued)*
Potentially Clinically Significant Vital Signs
(Safety Analysis Set)

PCSA Criterion	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX
Diastolic Blood Pressure change from baseline > 25% increase	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
Diastolic Blood Pressure change from baseline > 25% decrease	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
Pulse Rate <= 40 bpm	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
Pulse Rate >= 120 bpm	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
Pulse Rate change from baseline > 15 bpm increase	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)
Pulse Rate change from baseline > 15 bpm Decrease	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)

Note: Percentages are based on the number of patients in each cumulative dose group.

Table 14.3.5.1.1 *(continued)*
Potentially Clinically Significant Vital Signs
(Safety Analysis Set)

PCSA Criterion	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX
Oxygen Saturation < 90%	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)	xxx (xxx.x%)

Note: Percentages are based on the number of patients in each cumulative dose group.

Table 14.3.6.1
Moline-Roberts Pharmacologic Sedation Scale (MRPSS) Total Score at Each Time Point
(Safety Analysis Set)

Windowed Time Point [a] Sedation	Oliceridine <= 4 mg N=XXX n(%)	Oliceridine >4 to 8 mg N=XXX n(%)	Oliceridine >8 to 16 mg N=XXX n(%)	Oliceridine >16 to 36 mg N=XXX n(%)	Oliceridine >36 mg N=XXX n(%)	All Treated Patients N=XXX n(%)
<Baseline [b]>						
1. None to Minimal	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
2. Anxiolysis	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
3. Moderate Sedation	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
4. Moderate Sedation	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
5. Deep Sedation	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
6. General Anesthesia	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<T30 Minutes>						
1. None to Minimal	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
2. Anxiolysis	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
3. Moderate Sedation	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
4. Moderate Sedation	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
5. Deep Sedation	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
6. General Anesthesia	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)

. . .

Note: Percentages are based on the number of patients in each cumulative dose group.
Somnolence/sedation was measured with the Moline-Roberts Pharmacologic Sedation Scale (MRPSS).
[a] See section 6.2.3 of the SAP for windowed time point intervals.
[b] Baseline is the last non-missing value prior to the patient receiving the first dose of oliceridine.

Table 14.3.7.1
Change from Baseline in Electrocardiogram Results
(Safety Analysis Set)

Parameter (unit) Windowed Time Point [a]	Baseline/ Observed/ Change from Baseline	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX
<Parameter x (unit)>							
Baseline [b]							
n	Observed	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing		xxx	xxx	xxx	xxx	xxx	xxx
<T30 Minutes>							
n	Baseline [c]	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing		xxx	xxx	xxx	xxx	xxx	xxx
n	Observed	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing		xxx	xxx	xxx	xxx	xxx	xxx
n	Change	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)		xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max		xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing		xxx	xxx	xxx	xxx	xxx	xxx
. . .							

Note: Percentages are based on the number of patients in each cumulative dose group.

[a] See section 6.2.3 of the SAP for windowed time point intervals.
[b] Baseline is the last non-missing value prior to the patient receiving the first dose of oliceridine.
[c] Only patients with both a baseline value and a windowed time point value are summarized at a given windowed time point.

Programmer's Note: Repeat Parameter (unit) in each page if it wraps on to multiple pages.

Table 14.3.7.1.1
Selected QTcF Thresholds
(Safety Analysis Set)

Windowed Time Point [a]	Oliceridine <= 4 mg N=XXX n(%)	Oliceridine >4 to 8 mg N=XXX n(%)	Oliceridine >8 to 16 mg N=XXX n(%)	Oliceridine >16 to 36 mg N=XXX n(%)	Oliceridine >36 mg N=XXX n(%)	All Treated Patients N=XXX n(%)
Overall	xxx	xxx	xxx	xxx	xxx	xxx
Change from Baseline of > 30 msec	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Change from Baseline of > 60 msec	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Increase to > 500 msec	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<T30 Minutes>	xxx	xxx	xxx	xxx	xxx	xxx
Change from Baseline of > 30 msec	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Change from Baseline of > 60 msec	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Increase to > 500 msec	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...						

Note: Percentages are based on the number of patients in each cumulative dose group.
Baseline is the last non-missing value prior to the patient receiving the first dose of oliceridine.
[a] See section 6.2.3 of the SAP for windowed time point intervals.

Programmer's Note: Display all ECG windowed time points after overall.

Table 14.3.7.1.2
Summary of Electrocardiogram (ECG) Findings
(Safety Analysis Set)

Windowed Time Point [a] Finding	Oliceridine <= 4 mg N=XXX n(%)	Oliceridine >4 to 8 mg N=XXX n(%)	Oliceridine >8 to 16 mg N=XXX n(%)	Oliceridine >16 to 36 mg N=XXX n(%)	Oliceridine >36 mg N=XXX n(%)	All Treated Patients N=XXX n(%)
Patients with at Least 1 Clinically Significant ECG Result	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Baseline [b]						
Normal	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Abnormal, NCS	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Abnormal, CSig	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
<T30 Minutes>						
Normal	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Abnormal, NCS	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Abnormal, CSig	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
Missing	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)	xxx (xxx.x)
...						

Note: NCS = Not clinically significant; CSig = Clinically significant.
Clinical significance is based on the investigator interpretation as recorded.
Percentages are based on the number of patients in each cumulative dose group.
[a] See section 6.2.3 of the SAP for windowed time point intervals.
[b] Baseline is the last non-missing value prior to the patient receiving the first dose of oliceridine.

Table 14.3.8.1
Summary of Subjective Opioid Withdrawal Scale (SOWS) Total Score
(Safety Analysis Set)

	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX
N	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing	xxx	xxx	xxx	xxx	xxx	xxx

Note: Total score is derived by summing the individual symptom intensities. If no more than half of the symptoms are missing, imputation with the mean score of the non-missing questions is used to calculate total score. If more than half of the symptoms are missing the total score is also set to missing.

Table 14.3.9.1
Summary of Plasma Concentrations
(Safety Analysis Set)

Windowed Time Point[a]	Oliceridine <= 4 mg N=XXX	Oliceridine >4 to 8 mg N=XXX	Oliceridine >8 to 16 mg N=XXX	Oliceridine >16 to 36 mg N=XXX	Oliceridine >36 mg N=XXX	All Treated Patients N=XXX
T30 Minutes						
N	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing	xxx	xxx	xxx	xxx	xxx	xxx
T1.5 Hours						
N	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Missing	xxx	xxx	xxx	xxx	xxx	xxx

Note: Unscheduled PK samples will be displayed in the listing.
[a] See section 6.2.3 of the SAP for windowed time point intervals.

Listing 16.2.1.1
Patient Disposition
(Enrolled Analysis Set)

Patient ID	Sex/Age/ Cumulative Dose Group	Date/Time of First Dose of Oliceridine	Date/Time of End of Treatment (Cumulative Duration of Exposure [b])	Date of Study Completion/ Discontinuation[a]	Primary Reason for Termination (Other)

[a] Date/time of study completion/discontinuation is the date collected at the end of study instead of the of the date/time last dose received.
[b] Duration is defined as the difference in total hours from the first dose to the last dose of of study medication.

Listing 16.2.1.2
Inclusion/Exclusion Criteria
(Enrolled Analysis Set)

Patient ID	Sex/Age/ Cumulative Dose Group	Met all Eligibility Criteria?	Criteria not Met

Note: Patients may fail screening for more than one reason.

Listing 16.2.1.3
Protocol Deviations
(Enrolled Analysis Set)

Cumulative Dose Group: Oliceridine <= 4 mg

Patient ID/Sex/Age	Deviation Type	Deviation Text Detail	Deviation Criticality	IRB Reportable?/Report Date

Note: IRB = Institutional Review Board.

Listing 16.2.2.1
Demographics and Baseline Characteristics
(Enrolled Analysis Set)

Cumulative Dose Group: Oliceridine <= 4 mg

Patient ID/Sex/Age	Race/ Specify	Ethnicity	Informed Consent Date	Baseline Height (cm)/ Weight (kg)/ BMI (kg/m^2)	ASA Physical Status Classificiation [a]	ESI Classification	CYP2D6 Phenotype (EM vs PM)

Note: BMI = Body mass index; ASA = American Society of Anesthesiologists; ESI = Emergency Severity Index;
EM = Extensive metabolizer; PM = Poor metabolizer.
[a] ASA Physical Status is defined as follows: I - Normal healthy patient; II - Patient with mild systemic disease; III - Patient with severe systemic disease; IV - Patient with severe systemic disease that is a constant threat to life; V – Moribund patient who is not expected to survive without the operation; VI – Declared brain-dead patient whose organs are being removed for donor purposes.
[b] Extensive Metabolizer patients include those with a predictive phenotype of Ultra Metabolizer or Extensive Metabolizer; Poor Metabolizer patients include those with a predictive phenotype of Intermediate Metabolizer or Poor Metabolizer.

Listing 16.2.2.2
Prior and Concomitant Medications
(Enrolled Analysis Set)

Cumulative Dose Group: Oliceridine <= 4 mg

Patient ID/Sex/Age	Base Preferred Name/ ATC Class/ Medication	Start Date/Time	Stop Date/Time or Ongoing	P/C	Dose and Unit	Route (Other)	Frequency	Indication	Given for AE?/ AE #

Note: AE = Adverse Event; ATC = Anatomic Theraputic Chemical; P = Prior Medication; C = Concomitant Medication;

Programmer's Note: Sort by Start date/time. For missing date/times sort alphabetically

Listing 16.2.2.3
Reason for Receiving Oliceridine
(Safety Analysis Set)

Cumulative Dose Group: Oliceridine <= 4 mg

Patient ID/Sex/Age	Initial Setting	Condition	ICD-10 Code/ICD Description	Specialty

Listing 16.2.2.4
Medical History
(Enrolled Analysis Set)

Patient ID	Sex/Age/ Cumulative Dose Group	Medical History	System Organ Class	Preferred Term	Start Date	Stop Date or Ongoing

Listing 16.2.3.1
Study Drug Administration
(Safety Analysis Set)

Cumulative Dose Group: Oliceridine <= 4 mg

Patient ID/Sex/Age	Method of Administration	Start Date/Time	Windowed Time Point [a]	Dose Received	Cumulative Dose

Note: Asterisk (*) denotes the last dose received.
[a] See section 6.2.3 of the SAP for windowed time point intervals.

Listing 16.2.4.1
Numeric Pain Rating Scale (NPRS) Scores
(Safety Analysis Set)

Cumulative Dose Group: Oliceridine <= 4 mg

Patient ID/Sex/Age	Assessment Date/Time	Windowed Time Point[a]	Numeric Pain Rating Scale (NPRS) Score

Note: Asterisk (*) denotes the value used in descriptive summary statistics.
[a] See section 6.2.3 of the SAP for windowed time point intervals.

Listing 16.2.5.1
Adverse Events
(Enrolled Analysis Set)

Patient ID/Sex/Age/Cumulative Dose Group: 1001/Male/30/ Oliceridine <= 4 mg

System Organ Class/ Preferred Term [a]/ Verbatim Term	AE #	Start Date/Time/ End Date/Time (or Ongoing)	Intenity/ Relationship	Concomitant medication given?/CM #	Action Taken	Outcome	Serious?/ Reason for Serious	Additional Information

Note: All adverse events were coded using MedDRA version 19.0. TEAEs are defined in section 6.3.3 of the SAP.

Listing 16.2.6.1
Vital Signs
(Safety Analysis Set)

Cumulative Dose Group: Oliceridine <= 4 mg

Patient ID/Sex/Age	Collection Date/Time	Windowed Time Point [a]	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	Oral Temperature (C)	Pulse Oximetry (SpO2 %)

Note: Asterisk (*) denotes the value used in descriptive summary statistics.
[a] See section 6.2.3 of the SAP for windowed time point intervals.

Listing 16.2.7.1
Laboratory Results: Chemistry
(Safety Analysis Set)

Cumulative Dose Group: Oliceridine <= 4 mg

Patient ID/Sex/Age	Lab Collection Date/Time	Windowed Time Point [a]	Lab Test (Unit)	Lab Value	Overall Interpretation

Note: N = Normal; NCS = Not Clinically Significant; Csig = Clinically Significant;
Asterisk (*) denotes the value used in descriptive summary statistics.
The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding is clinically significant.
[a] See section 6.2.3 of the SAP for windowed time point intervals.

Use the same template as for Listing 16.2.7.1 for the following listings:

Listing 16.2.7.2
Laboratory Results: Hematology
(Safety Analysis Set)

Listing 16.2.8
12 Lead Electrocardiogram Results
(Safety Analysis Set)

Patient ID/Sex/Age/Cumulative Dose Group: 1001/Male/30/ Oliceridine <= 4 mg

Assessment Date/Time	Windowed Time Point[a]	Heart Rate (beats/min)	PR Interval (msec)	RR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTcF Interval (msec)	Interpretation	Abnormal, Sepcify

Note: Csig = Clinically Significant; NCS = Not Clinically Significant.
Asterisk (*) denotes the value used in descriptive summary statistics.

Listing 16.2.9
Subjective Opioid Withdrawal Scale (SOWS)
(Safety Analysis Set)

Cumulative Dose Group: Oliceridine <= 4 mg

Patient ID/Sex/Age	Assessment Date/Time	Symptom	Intensity Rating [a]

[a] 0 = Not at all; 1 = A little; 2 = Moderately; 3 = Quite a bit; 4 = Extremely.

Listing 16.2.10
Physical Examination
(Safety Analysis Set)

Cumulative Dose Group: Oliceridine <= 4 mg

Patient ID/Sex/Age	Assessment Date/Time	Changes From Previous Visit?

Listing 16.2.11
Moline-Roberts Pharmacologic Sedation Scale Score
(Safety Analysis Set)

Cumulative Dose Group: Oliceridine <= 4 mg

Patient ID/Sex/Age	Assessment Date/Time	Windowed Time Point [a]	Total Score

Note: Asterisk (*) denotes the value used in descriptive summary statistics.
[a] See section 6.2.3 of the SAP for windowed time point intervals.

Listing 16.2.12.x
Patient Profiles for Patients with Durations Over 96 Hours
(Safety Analysis Set)

Patient ID/Sex/Age/Cumulative Dose Group: xxxxx

Method of Administration	Cumulative Oliceridine Dose (mg)	Cumulative Duration of Exposure [a] (Hours)	Completed the Study?[b]	Reason for Early Termination
xx	xx	xx		

Base Preferred Name/ ATC Class/ Medication	Start Date/Time	Stop Date/Time or Ongoing	P/C	Dose and Unit	Route (Other)	Frequency	Indication	Given for AE?/ AE #

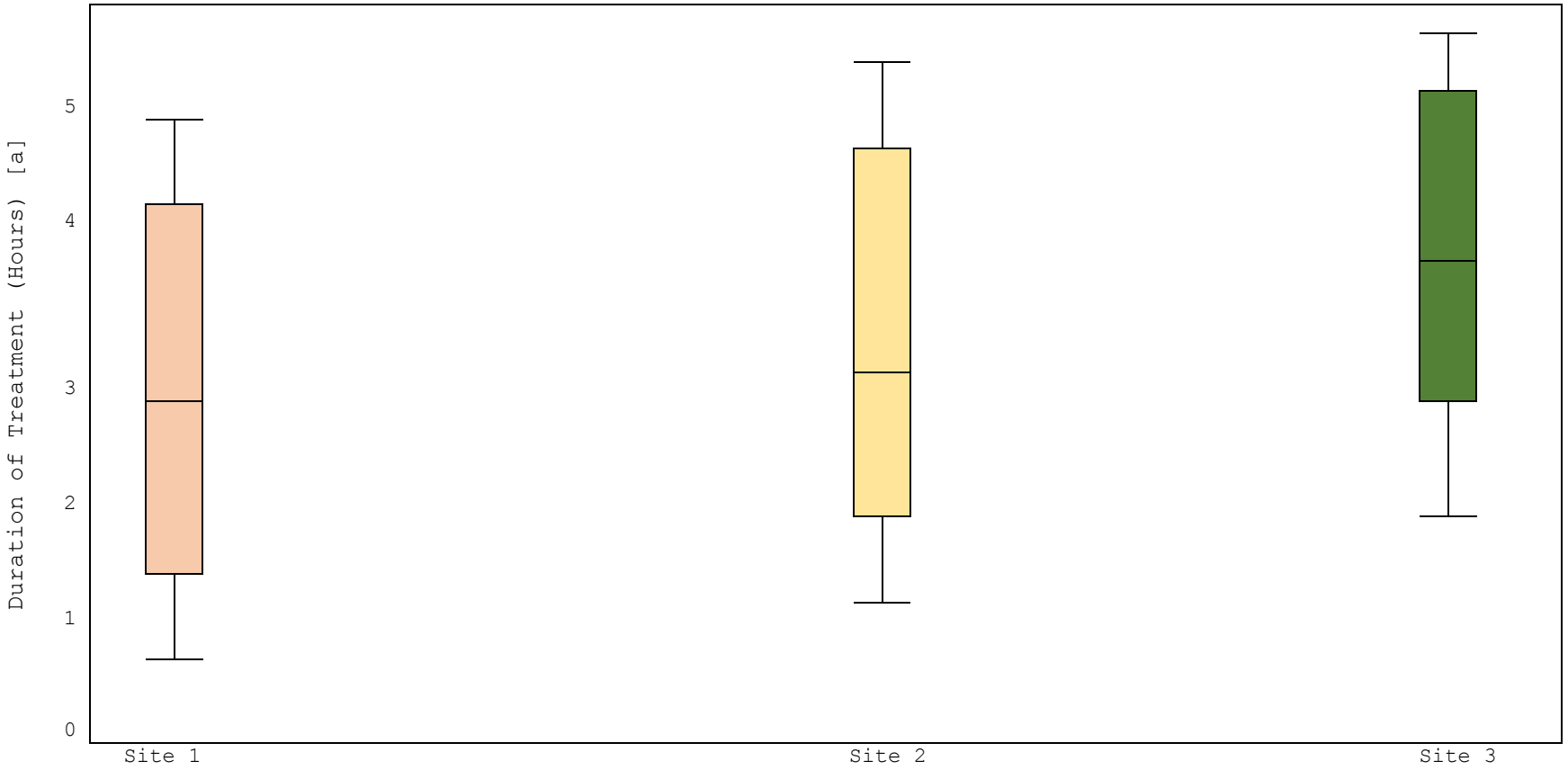
System Organ Class/ Preferred Term [a]/ Verbatim Term	AE #	Start Date/Time/ End Date/Time (or Ongoing)	Intensity/ Relationship	Action Taken	Outcome	Serious?/ Reason for Seriousness

Note: AE = Adverse Event; ATC = Anatomic Theraputic Chemical; P = Prior Medication; C = Concomitant Medication;
All adverse events were coded using MedDRA version 19.0.
[a] Duration is defined as the difference in total hours from the first dose to the last dose of of study medication.
[b] Because the duration of treatment for each patient in this study will be determined by the clinical need for parenteral opioid therapy, a patient will be considered to be a completer if no early termination reason is indicated.

Source: Listing x.x.x
Program Name: s<nnn>xxxx

Data Extraction: yyyymmdd Output Date: yyyymmddthh:mm

Figure 1.1
Duration of Treatment by Site
(Safety Analysis Set)



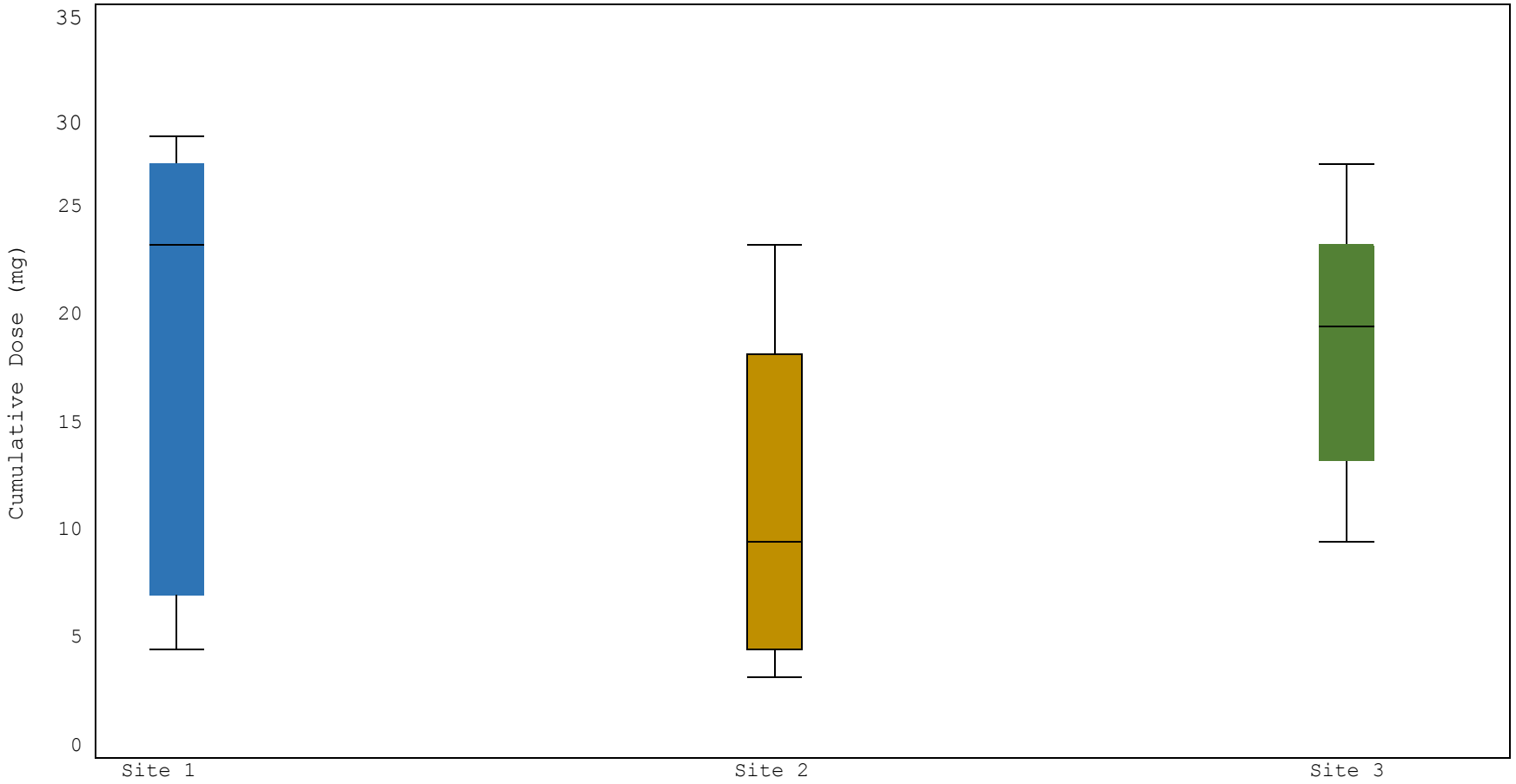
[a] Duration is defined as the difference in total hours from the start of the first dose of study medication to end-time for the last dose of study drug administration.

Programmer's Note: Limit to 10 sites per page.

Source: Listing x.x.x
Program Name: s<nnn>xxxx

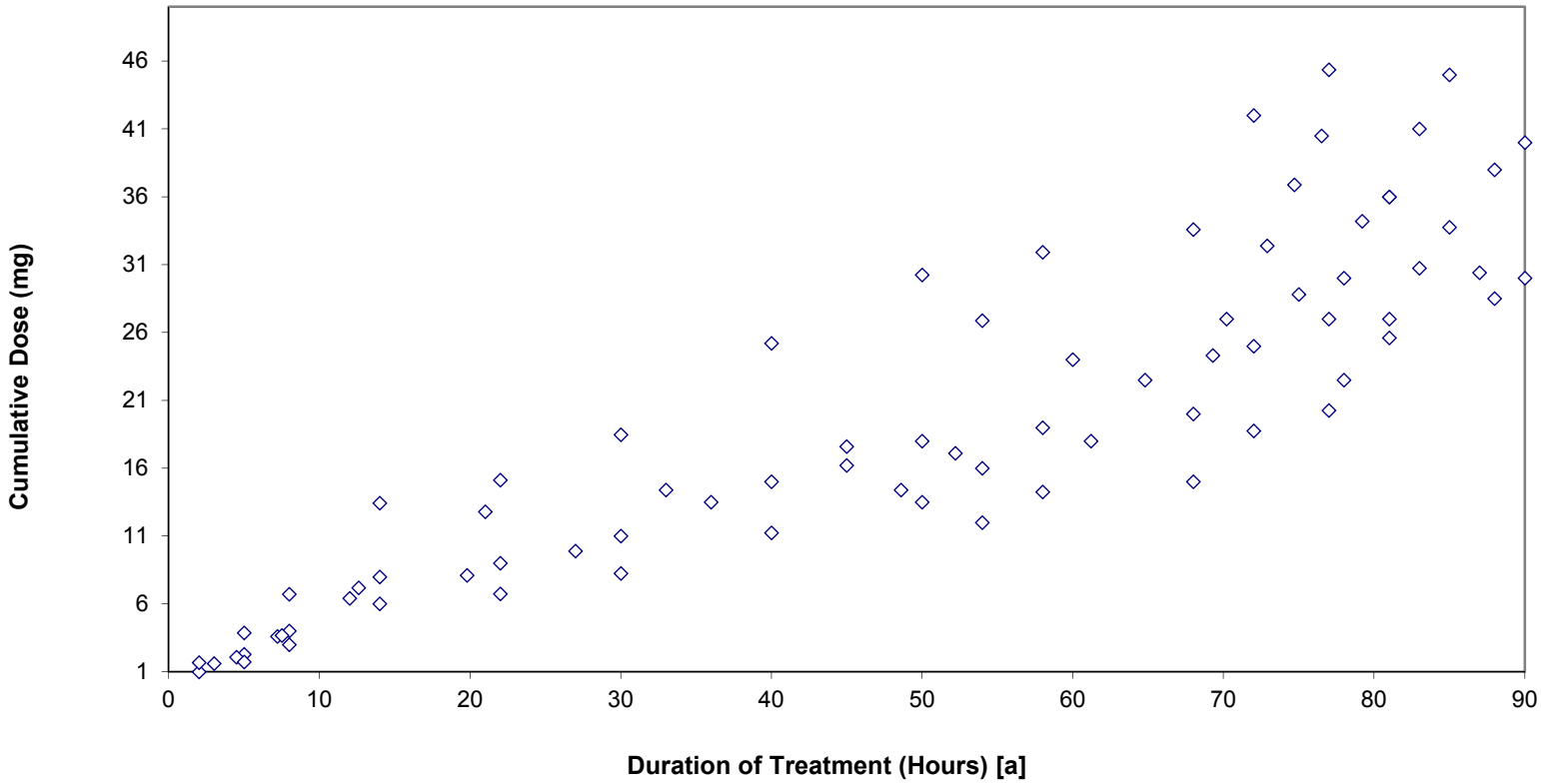
Data Extraction: yyyymmdd Output Date: yyyymmddthh:mm

Figure 1.2
Cumulative Dose by Site
(Safety Analysis Set)



Programmer's Note: Limit to 10 sites per page.

Figure 2.1
Cumulative Dose by Duration of Treatment
(Safety Analysis Set)



Note: Each dot in the graph represents a patient.
[a] Duration is defined as the difference in total hours from the start of the first dose of study medication to end-time for the last dose of study drug administration.

Source: Listing x.x.x
Program Name: s<nnn>xxxx

Data Extraction: yyyymmdd Output Date: yyyymmddthh:mm

Use the same template as for Figure 2.1 for the following Figures:

Figure 2.1.1
Cumulative Dose by Duration of Treatment for Patients With at Least 1 TEAE
(Safety Analysis Set)

Figure 2.1.2
Cumulative Dose by Duration of Treatment for Patients With at Least 1 Related TEAE
(Safety Analysis Set)

Figure 2.1.3
Cumulative Dose by Duration of Treatment for Patients With at Least 1 TEAE Leading to Early Discontinuation
(Safety Analysis Set)

Figure 2.1.4
Cumulative Dose by Duration of Treatment for Patients With at Least 1 SAE
(Safety Analysis Set)