Pacira Pharmaceuticals, Inc.

DISCLOSURE: REDACTED STATISTICAL ANALYSIS PLAN

Title: A Phase 3, Randomized, Double-Blind, Multicenter, Active-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL Admixed with Bupivacaine HCl vs. Bupivacaine HCl Administered via Adductor Canal Block for Postsurgical Analgesia in Subjects Undergoing Primary Unilateral Total Knee Arthroplasty
NCT Number: NCT05139030
Protocol Number: 402-C-335

Statistical Analysis Plan Version 1.2, Approval Date: 08-Dec-2022

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This may include, but is not limited to, redaction of the following:

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STATISTICAL ANALYSIS PLAN

A Phase 3, Randomized, Double-Blind, Multicenter, Active-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL Admixed with Bupivacaine HCl vs. Bupivacaine HCl Administered via Adductor Canal Block for Postsurgical Analgesia in Subjects Undergoing Primary Unilateral Total Knee Arthroplasty

Protocol No.:	402-C-335
IND No.:	069,198
Study Phase:	3
Study Drug:	EXPAREL (bupivacaine liposome injectable suspension)
Original Protocol Date	23 September 2021
Amendment 1 Date	22 October 2021
Sponsor:	Pacira BioSciences, Inc. 5 Sylvan Way Parsippany, NJ 07054 Tel: CCI [redacted]
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SAP Date/Version	08 December 2022 / Version 1.2

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1. LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic class
BMI	Body mass index
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CP	Conditional Power
CRF	Case report form
CSR	Clinical study report
CV	Coefficient of Variation
FDA	Food and Drug Administration
h	Hour
ICH	International Conference on Harmonization
IV	Intravenous
LN	Natural Log
LSM	Least Squares Mean
MedDRA	Medical dictionary for regulatory affairs
mg	milligram
min	Minutes
N, n	Number of subjects
NRS	Numerical Rating Scale
NSAID	Nonsteroidal anti-inflammatory drug
OMED	Oral morphine equivalent dose in mg
PACU	Postanesthesia care unit
PD	Pharmacodynamics
PK	Pharmacokinetics
PO	Per oral
POD	Postoperative Day
PRN	*pro re nata*, as needed
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of special interest
TLF	Tables, listings and figures
WHODD	World Health Organization Drug Dictionary

2. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analysis and reporting for the clinical study 402-C-335 titled "A Phase 3, Randomized, Double-Blind, Multicenter, Active-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL Admixed with Bupivacaine HCl vs. Bupivacaine HCl Administered via Adductor Canal Block for Postsurgical Analgesia in Subjects Undergoing Primary Unilateral Total Knee Arthroplasty".

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or manuscripts. Post-hoc exploratory analyses not identified in this SAP may be performed to further examine study data. Any post-hoc, unplanned, or exploratory analyses performed will be clearly identified as such in the final CSR.

The following documents were reviewed in preparation of this SAP:

- Protocol 402-C-335 issued on 23 September 2021
- Protocol 402-C-335 Amendment 1 issued on 22 October 2021
- Electronic Case Report Form (eCRF) dated 07 June 2022

The reader of this SAP is encouraged to also read the clinical protocol and other identified documents for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

3. CHANGE TO THE PROTOCOL SPECIFIED METHODS OR TO THE PREVIOUS SIGNED-OFF SAP

No change to the protocol specified terminology or methods.

This version of the SAP removes "Time to offset of sensory block and motor block" from the list of Section 9.4 Pharmacodynamic (PD) Endpoints (Cohort 1 only)" and adds the word "Median" to read "Median time to onset …" and "Median duration of …" to the remaining two endpoints to be consistent with the protocol specified PD endpoints. "Time to offset" was intended to be an intermediate variable for the calculation of duration. It was not intended to be an endpoint.

4. STUDY OBJECTIVES

4.1. Primary Objective

- To compare the magnitude of the postsurgical analgesic effect following a single dose of EXPAREL admixed with bupivacaine hydrochloride (HCl) vs. bupivacaine HCl when

administered via an adductor canal block in subjects undergoing primary unilateral total knee arthroplasty (TKA).

4.2. Secondary Objectives

- To compare the total postsurgical opioid consumption (in oral morphine equivalents) following a single dose of EXPAREL admixed with bupivacaine HCl vs. bupivacaine HCl.
- To compare the time to first opioid consumption post-surgery, following a single dose of EXPAREL admixed with bupivacaine HCl vs. bupivacaine HCl.
- To characterize and compare the magnitude of the duration of sensory and motor block following a single dose of EXPAREL admixed with bupivacaine HCl vs. bupivacaine HCl.
- To assess the safety and pharmacokinetic (PK) profile of EXPAREL admixed with bupivacaine HCl and bupivacaine HCl.

5. STUDY OVERVIEW

This is a Phase 3, multicenter, randomized, double-blind, active-controlled study in approximately 160 subjects undergoing primary unilateral TKA under spinal anesthesia. This study will have 2 cohorts. Both cohorts will enroll in parallel.

Cohort 1 (PK, PD, Efficacy, and Safety)

Cohort 1 will enroll approximately 40 subjects (20 subjects per treatment arm) undergoing primary unilateral TKA under spinal anesthesia to obtain information on PK profile, pharmacodynamics (PD), efficacy and safety. Subjects in this cohort will be randomized (1:1) to receive an adductor canal block with a single dose of either EXPAREL admixed with bupivacaine HCl, or bupivacaine HCl alone.

Cohort 2 (Efficacy and Safety)

Cohort 2 will enroll approximately 120 subjects (60 subjects per treatment arm) undergoing primary unilateral TKA under spinal anesthesia to obtain information on efficacy and safety. Subjects will be randomized (1:1) to receive an adductor canal block with a single dose of either EXPAREL admixed with bupivacaine HCl, or bupivacaine HCl alone.

Treatment

For both Cohorts 1 and 2, subjects randomized to the EXPAREL admixed arm will receive 10 mL (133 mg) EXPAREL admixed with 10 mL (50 mg) 0.5% bupivacaine HCl; subjects randomized to the bupivacaine HCl arm will receive 10 mL (50 mg) 0.5% bupivacaine HCl mixed with 10 mL normal saline. The total dose volume will be consistent (20 mL) for all subjects.

Block Procedure

Subjects may be lightly sedated with 1 to 2 mg of midazolam intravenously (IV) before the nerve block procedure. The study drug (EXPAREL admixed with bupivacaine HCl, or bupivacaine HCl) will be administered under ultrasound guidance 90 min (±30 min) prior to surgery. A confirmatory ultrasound video will be captured with needle in place to ensure accurate block placement. The video will be reviewed by an independent ultrasound adjudication committee to ensure accuracy of study drug administration. The designated study drug administrators (anesthesiologist) will not participate in any other study related assessments after randomization.

Pre-Operative Medication

- All subjects will receive celecoxib 200 mg, orally (PO) within 4 hours prior to surgery.
- All subjects will receive an infiltration between the popliteal artery and capsule of the knee (IPACK) under ultrasound guidance with 15 mL of 0.25% bupivacaine HCl (37.5 mg) immediately following study drug administration (with the same setup as for the nerve block).

Anesthesia and Intraoperative Medication

- All subjects will receive spinal anesthesia immediately prior to surgery with 0.5% bupivacaine HCl (up to 15 mg). No other medication (including opioids) will be mixed with the bupivacaine HCl for spinal anesthesia.
- No dexamethasone, NSAIDs, or ketamine will be permitted.
- All subjects will receive a dose of 1000 mg of IV acetaminophen at the time of surgical incision. IV fentanyl (not to exceed 1 μg/kg unless deemed medically necessary) will be allowed for intraoperative pain control.

Postsurgical Pain Management

An unscheduled pain intensity assessment using the NRS (measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee right now?") must be completed immediately prior to administration of any breakthrough pain medication up to 96 hours post-surgery.

All subjects will receive a second postoperative dose of 1000 mg IV acetaminophen, administered approximately 8 hours after the first dose (approximately 8 hours after incision). The maximum total dose should not exceed 2000 mg. No additional acetaminophen is permitted after the second IV acetaminophen dose.

Immediate-release PO oxycodone will be administered on an as needed (PRN) basis for breakthrough pain through 96 hours post-surgery in a stepwise approach:

- Initial dose of 5 mg oxycodone may be offered.

- If the initial opioid dose is insufficient for pain relief, an additional 5 mg oxycodone may be offered up to a maximum of 10 mg (total dose).
- If a subject is unable to tolerate PO medication (or the PO oxycodone pain relief is insufficient), IV morphine (initiated at 2 mg) or IV hydromorphone (initiated at 0.2 mg) may be administered.

No NSAIDs or other opioids (including tramadol) are allowed for the breakthrough pain management. No acetaminophen (other than the scheduled IV acetaminophen) should be used for breakthrough pain.

Interim Analysis

An adaptive study design will be used in this study. An interim analysis to evaluate the sample size assumptions and evaluate futility will occur when a total of approximately 80 subjects (40 in each arm) combined from either Cohort 1 or Cohort 2 have enrolled and provided complete assessment data for the primary efficacy outcome. The final sample size may be increased based on the conditional power (CP) calculated at the interim analysis. Refer to Interim Analysis Plan for detail.

Figure 1 presents a schematic diagram of the study design. Protocol Time and Events schedule for study procedures are presented in Table 1 and for PK and PD Assessment Schedule are presented in Table 2.

Figure 1. Schematic Representation of Study Design

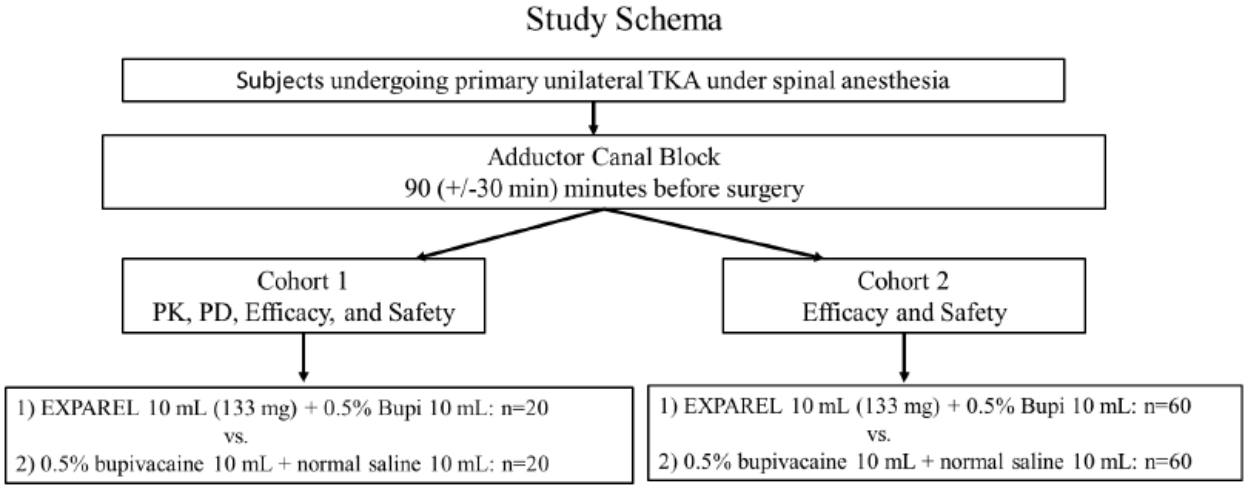


Table 1. Time and Events Schedule of Study Procedures (Screening Through POD 14)

					Time from End of Surgery (h)																		
	Screen-ing Visit[1]	Day of Surgery (Prior to Surgery)	OR	PACU	6 ±2	12 ±2	18 ±2	24 ±2	30 ±2	36 ±2	42 ±2	48 ±2	54 ±2	60 ±2	66 ±2	72 ±2	78 ±3	84 ±3	90 ±3	96 ±3	120-168 ±3[2]	Health Care Facility Discharge[3]	POD 14 Call ±3 days
Obtain ICF*	X																						
Assess/confirm eligibility*	X	X[4]																					
Record medical/ surgical history*[5]	X																						
Collect height/weight for BMI calculation*	X																						
Demographics and baseline characteristics*	X																						
Record prior and concomitant Medications[5]	X	X[4]	◄	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	►
Urine pregnancy test for WOCBP	X	X[4]																					
Urine drug screen		X[4]																					
Perform 12-lead EKG[6]	X							X				X				X				X	X		
Review Pain Rating Guide		X[4]																					
Record *worst* and *average* pain (NRS) in the last 30 days		X[4]																					
Randomize subject; prepare study drug		X																					
Record block start/ end times[7]		X																					
Capture ultrasound video for the nerve block and send to Sponsor		X																					
Record IPACK start/end times		X																					
Record surgery start and end times			X																				

					Time from End of Surgery (h)																	
	Screen-ing Visit[1]	Day of Surgery (Prior to Surgery)	OR	PACU	6 ±2	12 ±2	18 ±2	24 ±2	30 ±2	36 ±2	42 ±2	48 ±2	54 ±2	60 ±2	66 ±2	72 ±2	78 ±3	84 ±3	90 ±3	96 ±3	120-168 ±3[2]	Health Care Facility Dis-charge[3]	POD 14 call ±3 days
Record intra-op medication administered			X																			
Record Pre-op and post-op scheduled analgesic medication[8]		X	◄	- - -	- - -	►																
Record PACU time in and out				X																		
Record **scheduled** NRS scores[9,10]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Measure and record vital signs[11]		X[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record *worst* and *average* NRS scores (24-hour recall)[9,10]								X				X				X				X		
Record **unscheduled** NRS immediately prior to breakthrough pain medication[12]				◄	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	►		
Record breakthrough pain medication[12]				◄	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	►		
Record day and time of HCF admission and discharge		X																			X	
Record AEs/SAEs[13]	◄	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	►	
Perform unscheduled neurological assessment[14]		◄	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	►	
Subject's satisfaction questionnaire (IPO)																			X			

Abbreviations: AE=adverse event; BMI=Body Mass Index; h=hour(s); HCF=health care facility; ICF=informed consent form; IPO=International Pain Outcome; min=minute(s); NRS=numeric rating scale; NSAID=nonsteroidal anti-inflammatory drug; OR=Operating Room; PACU=Post-Anesthesia Care Unit; POD=Post-operative Day; SAE=serious adverse event; WOCBP=women of childbearing potential.

* No more than 45 days before scheduled surgery day

1. Subjects may be screened on the same day as health care facility admission/surgery (with ample time for the informed consent process) or up to 45 days prior to surgery, but eligibility will be re-confirmed on the day of surgery prior to randomization. Screening procedures that are standard of care at the institution may be completed prior to written informed consent. Any screening procedures that are not SOC must be completed after written informed consent is obtained.
2. For Cohort 1 subjects only: A 12-lead EKG will be performed, and vital signs will be measured and recorded at additional time points: 120 (±3h), 144 (±3h), and at 168 (±3h).
3. Subjects in Cohort 1 and Cohort 2 will be discharged after 168 h and 96 h assessments, respectively.
4. Eligibility criteria, prior medication, urine pregnancy test, and urine drug screen to be assessed prior to randomization; review of Pain Rating Guide and worst and average pain scores over the previous 30 days to be assessed prior to study drug administration.
5. Relevant medical/surgical history within the last 5 years (including all ongoing history, regardless of start date) should be recorded, with the exception of history that is relevant to the TKA surgery, in which case all years should be recorded. Prior medications taken within 30 days of randomization (including all ongoing medications, regardless of start date) will be recorded.
6. A baseline 12-lead EKG must be performed at screening visit. A 12-lead EKG must be performed if a subject experiences an AESI or an SAE (see footnote 15)
7. Block to be administered 90 min (±30 min) prior to surgery.
8. Record all pre-operative and post-operative scheduled analgesic medication (celecoxib and acetaminophen)
9. The NRS pain intensity assessment should not be completed after any physical activity, including the motor block assessment (for Cohort 1 subjects). If that is not possible, to assess pain intensity at rest, the subject should rest quietly in a supine or seated position that does not exacerbate subject's postsurgical pain for 5-10 minutes before assessing the pain score using the NRS. If a subject is asleep, the subject will not be awakened to assess pain. If the subject awakens within the assessment window, a pain score will be collected then.
10. Pain scores (24 hr recall) once daily (i.e., worst/average pain) will be collected at 24 (±2 h), 48 (±2 h), 72 (±2 h), and 96 (±3 h) post-surgery. Pain scores (current pain) will be collected by the study staff beginning at PACU admission (±5 min); q15 min in PACU (±5 min); at PACU discharge (±5 min) ; then q6h (±2 h) from end of surgery to 72 hours post-surgery and q6h (±3 h) from 78-96 hours post-surgery.
11. Vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation and blood pressure) will be measured after the subject has rested in a supine position for at least 5 minutes. Vital signs will be measured before study drug administration, upon arrival in the PACU (±5 min), at PACU discharge (±5 min), then q6h (±2 h) from end of surgery to 72 hours post-surgery and q6h (±3 h) from 78-96 hours post-surgery, and at hospital discharge. Additionally, for Cohort 1 subjects: 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h). Vital signs must be measured and recorded if a subject experiences an AESI or an SAE (see footnote 15)
12. Oxycodone will be administered on an as needed (PRN) basis for breakthrough pain through 96 hours post-surgery; opioids should not be given on a pre-determined schedule. Immediate release oral (PO) oxycodone will be administered in a stepwise approach:
    - Initial dose of 5 mg oxycodone may be offered.
    - If the initial opioid dose is insufficient for pain relief, an additional 5 mg oxycodone may be offered up to a maximum of 10 mg (total dose).

    If a subject is unable to tolerate PO medication (or the PO oxycodone pain relief is insufficient), IV morphine (initiated at 2 mg) or hydromorphone (initiated at 0.2 mg) may be administered.
13. Document all AEs with an onset after the subject is randomized and SAEs with an onset after the subject signs the ICF.
14. An unscheduled neurological assessment will be conducted once daily if a subject experiences an AESI or an SAE, until resolution of symptoms (see footnote 15).
15. In case an AE of special interest (AESI) or serious AE (SAE) occurs during the study, if the investigator or medical monitor considers that the event may be related to study treatment or suggests the possible occurrence of local anesthetic systemic toxicity (LAST; with or without the need for treatment [e.g., intralipids]), an unscheduled PK blood sample, 12-lead EKG, and vital signs must be collected. Neurological assessments will be conducted according to the study site's standard of care at least once daily until resolution of symptoms.

Table 2. Pharmacokinetic and Pharmacodynamic Assessment Schedule (Cohort 1 subjects only)

		Post-study Drug Administration[a]															
		Day of Study Drug Administration to Post-operative Day 4 (POD 4)													POD 5	POD 6	POD 7
Time Window	**Up to 15 mins before blocks**	**15m**	**30m**	**45m**	**1h**	**2h**	**8h**	**12h**	**24h**	**30h**	**48h**	**60h**	**72h**	**84h**	**96h**	**120h**	**144h**	**168h**
		±5m	**±5m**	**±5m**	**±15m**	**±30m**	**±30m**	**±30m**	**±1h**	**±1h**	**±1h**	**±2h**	**±2h**	**±2h**	**±3h**	**±3h**	**±3h**	**±3h**
Collect PK blood sample; Record date and time of blood sample[b]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess and record sensory and motor function[c,d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: h=hour; m=minute; PK=pharmacokinetic

a. All timepoints are from end of block administration.
b. An unscheduled PK sample must be collected if a subject experiences an AESI or an SAE (see footnote 15 in Table 1)
c. Once the offset of light touch sensation is recorded and documented in both locations, no further scheduled sensory assessments are required. Once the offset of motor block is recorded and documented, no further scheduled motor assessments are required. Pharmacodynamic assessments must be performed by blinded, trained, licensed medical staff (e.g., Physician, Registered Nurse, Physician Assistant) and documented on the investigator's study delegation log. A limited number of study staff should perform the sensory/motor assessments.
d. When subject is in surgery, no sensory or motor function assessments will be conducted.

6. DEFINITIONS

Start and End of the Nerve Block Procedure

The start and end of study drug administration is indicative of the start and end of nerve block procedure.

Sensory and Motor block

Sensory block is evaluated by subject's light touch sensation at proximal and distal locations and comparing the sensation between the treated leg and untreated leg. Motor block is evaluated by subject's level of knee movement. See Sections 7.3.1 and 7.3.2 for detail.

Study Day

Study Day is calculated as the date of event minus the date of end of study drug administration plus one (1), if the date of event is on or after the date of end of study drug administration. If the date of event is before the end of study drug administration, study day is the date of event minus the date of study drug administration.

Time 0

For PK, PD, and safety evaluations, Time 0 is defined as the date and time of the end of the study drug administration.

For NRS pain collection, opioid consumption, vital sign, and EKG assessments, Time 0 is defined as the date and time of the end of the surgery.

Baseline

Baseline is defined as the last available measurement prior to start of study drug administration.

Treatment-Emergent Adverse Events (TEAEs)

TEAEs are those with onset date and time on or after the start date and time of study drug administration.

Beginning of Surgery

The beginning of surgery is defined as the time of the first incision.

End of Surgery

The end of surgery is defined as the time recorded in the surgical record.

Postsurgical

Postsurgical is defined as after the end of surgery. Postsurgical Day 1 is the day of surgery.

Time Window for Numeric Rating Scale (NRS) for Scheduled Pain Score Collection

Table 3 below provides the time windows for the NRS pain score for analysis by time point. If multiple scheduled or unscheduled assessments occur within the same window, the assessment closest to the scheduled time will be chosen. If the assessments are equidistant the later assessment will be chosen.

Table 3. Time Windows for NRS Pain Score Collected at Scheduled Time Points Post-Surgery

Scheduled Time of Collection	Time Window for Acceptable Actual Time of Collection
PACU	First collection in PACU prior to the 6-hour time point
6-hour	From PACU arrival to 9-hour
12-hour	From >9-hour to 15-hour
18-hour	From >15-hour to 21-hour
24-hour	From >21-hour to 27-hour
30-hour	From >27-hour to 33-hour
36-hour	From >33-hour to 39-hour
42-hour	From >39-hour to 45-hour
48-hour	From >45-hour to 51-hour
54-hour	From >51-hour to 57-hour
60-hour	From >57-hour to 63-hour
66-hour	From >63-hour to 69-hour
72-hour	From >69-hour to 75-hour
78-hour	From >75-hour to 81-hour
84-hour	From >81-hour to 87-hour
90-hour	From >87-hour to 93-hour
96-hour	From >93-hour to 99-hour

Time Windows for Sensory and Motor Block Tests

Table 4 below provides the time windows for the sensory block and motor block summaries by timepoint (Sections 10.7).

Table 4. Time Window for Sensory and Motor Block Tests at Scheduled Time Points Post-Study Drug Administration

Scheduled Time of Collection	Time Window for Acceptable Actual Time of Collection
Predose	Predose
15-min	From end of study drug administration to 22.5-min
30-min	From >22.5-min to 37.5-min
45-min	From >37.5-min to 52.5-min
1-hour	From >52.5-min to 1.5-hour
2-hour	From >1.5-hour to 5-hour
8-hour	From >5-hour to 10-hour
12-hour	From >10-hour to 18-hour
24-hour	From >18-hour to 27-hour
30-hour	From >27-hour to 39-hour
48-hour	From >39-hour to 54-hour
60-hour	From >54-hour to 66-hour
72-hour	From >66-hour to 78-hour
84-hour	From >78-hour to 90-hour
96-hour	From >90-hour to 108-hour
120-hour	From >108-hour to 132-hour
144-hour	From >132-hour to 156-hour
168-hour	From 156-hour to 180-hour

Oral Morphine Equivalent Dose (OMED)

This is an OMED converted from opioid dose subjects take during the study. This conversion enables the comparison of the analgesic effects of different opioid medications by the same route and in the same units. The conversion factors are listed in Table 6.

Time Window for Opioid Pain Medication

This window (see Table 8) captures the opioid analgesic effect from start of the opioid administration to the end of the opioid effect.

Time Windows for Vital Signs

Table 5 below provides the time windows for vital signs for analysis by time point. If multiple scheduled or unscheduled assessments occur within the same window, the assessment closest to the scheduled time will be chosen. If the assessments are equidistant the later assessment will be chosen.

Table 5. Time Windows for Vital Signs Collected for Scheduled Time Points Post-Surgery

Scheduled Time of Collection	Time Window for Acceptable Actual Time of Collection
Baseline	Prior to study drug administration
1-hour	Immediately after surgery to ≤1.5-hour
2-hour	>1.5-hour to ≤3-hour
6-hour	>3-hour to ≤9-hour
12, 18, …q6h, …, 96-hour	> time point - 3 hour to ≤ time point + 3 hour
120-hour	>99-hour to ≤132-hour
144-hour	>132-hour to ≤156-hour
168-hour	>156-hour to ≤180-hour

7. STUDY ASSESSMENTS

7.1. Efficacy Assessment

7.1.1. Pain Intensity Assessment

- Pain intensity scores measured using NRS as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee right now?" will be assessed as follows*:
  - Upon arrival in the Post-Anesthesia Care Unit (PACU)
  - Every 15 minutes interval in the PACU
  - At PACU discharge
  - Every 6 hours from the end of surgery to 96 hours post-surgery as follows: 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, and 96 hours
  - Prior to administration of any pain medication until 96 hours post-surgery
- Pain intensity using the NRS at 24, 48, 72, and 96 hours post-surgery measured as "What was your **worst** pain in your operative knee in the last 24 hours?"
- Pain intensity using the NRS at 24, 48, 72, and 96 hours post-surgery measured as "What was your **average** pain in your operative knee in the last 24 hours?"

* If subject is asleep, the subject will not be awakened to assess pain. If the subject awakens within the time window, a pain score will be collected then.

7.1.2. Opioid Dose Conversion

Opioid dose will be converted to oral morphine equivalent dose (OMED mg) using the conversion factor in Table 6 for all summaries. Total opioid dose is the sum of all opioids in OMED taken during the time interval of interest.

Table 6. Conversion Factors to Oral Morphine Equivalent Dose from Other Opioids

Medication	Unit	Route	Oral Morphine Conversion (Multiplication) Factor
Oxycodone, Oxycocet, Percocet, acetaminophen-oxycodone	mg	PO	1.5
Morphine	mg	IV, IM, SC	3
Morphine	mg	PO	1
Hydromorphone (Dilaudid)	mg	IV, IM, SC	20
Hydromorphone (Dilaudid)	mg	PO	4
Fentanyl	mg	IV, PO, IM	300
Hydrocodone combination product - Vicodin, Norco, Lorcet, Lortab, hydrocodone-acetaminophen, Ketobemidone	mg	PO	1
Codeine combination product - Tylenol 3, acetaminophen-codeine, Paracetamol Forte, Tylenol 4	mg	PO	0.15
Ultram, Tramadol, Tramadol hydrochloride	mg	PO, IM	0.25
Demerol, Meperidine, Pethidine	mg	IV, SC	0.3
Demerol, Meperidine, Pethidine	mg	PO	0.1
Ketobemidone, Oxycodone	mg	IV	3
Nalbuphine (Nubain/Manfine)	mg	IV, IM, SC	3

PO = oral, IV = intravenous, IM = Intramuscular, SC = subcutaneous.

7.1.3. Subject Satisfaction with Pain Management

The subject's satisfaction with pain management will be collected at 96 hours post-surgery using 1 question from the International Pain Outcome (IPO). Subjects will be asked to circle a number

that best describes how satisfied they are with the results of their pain treatment since surgery on an 11-point Likert scale from 0 (extremely dissatisfied) to 10 (extremely satisfied).

7.2. Pharmacokinetic assessments (Cohort 1 only)

Blood samples for PK assessment will be obtained from subjects enrolled in Cohort 1. A total of 17 PK samples will be collected for each subject. These samples will be obtained at pre-dose/baseline (up to 15 min before block), 30 min, 45 min, and 1, 2, 8, 12, 24, 30, 48, 60, 72, 84, 96, 120, 144, and 168 hours from end of block procedure.

7.3. Pharmacodynamic Assessments (Cohort 1 only)

PD assessments will be performed by a limited number of blinded, trained, licensed medical staff.

7.3.1. Assessment of Sensory Block:

Sensory assessment for light touch will be performed at pre-dose, 15, 30, and 45 minutes, and 1, 2, 8, 12, 24, 30, 48, 60, 72, 84, 96, 120, 144, and 168 hours from the end of the nerve block procedures, or until full sensory function has returned to baseline (pre-dose) levels. Each light touch area of assessment will be rated independently. Additional unscheduled assessments may be performed, particularly around the surgery, if no onset of block is noted on the last scheduled assessment prior to surgery.

For each sensory assessment, both locations mentioned below will be assessed for light touch. If on the 168 hours assessment there is a sensory deficit, the incident will be recorded as an AE. The physician will assess the subject for other etiologies that may explain the persistent sensory deficit. If the sensory deficit persists at the 168-hour assessment, the subject is to return for unscheduled visit(s) at the Investigator's discretion until the sensory function has returned.

Sensory function assessment will include the following two locations:

1. Proximal - Medial aspect of the lower leg (3-4 cm below the knee)
2. Distal - Medial aspect of the lower leg (3-4 cm above ankle)

The intent of applying the tongue depressor to the contralateral leg is to establish a reference sensation to compare to the test area. The subject is to determine if the sensation on the contralateral leg is the same as the test area (“Yes” = the same = sensory not blocked) or if there is a decreased sensation or not the same sensation (“No” = not the same = sensory blocked).

The test may be repeated in case of ambiguous or inconsistent responses until the examiner is satisfied with the accuracy of the assessment. The assessments will be conducted single-blinded (i.e., the subject will be instructed to close their eyes). Once the offset of sensory block (return of light touch sensation in both test areas in a single assessment) is recorded, no further scheduled sensory assessments are required.

Onset of sensory block is defined as the earliest timepoint with loss of light touch sensation in the distal test area. If onset time is not achieved, it will be considered censored at the last onset assessment time prior to surgery.

Offset of sensory block is defined as the first timepoint of return of light touch sensation along the distribution of the target nerve distal to the site of the block. After offset of sensory assessments are noted (light touch sensation in BOTH proximal and distal test areas in a single assessment), no subsequent assessments will be conducted. If offset time is not achieved, it will be considered censored at the last offset assessment time after surgery.

Duration of sensory block is defined as the time between onset and offset of the sensory blocks. If onset is not achieved, duration will be calculated from the surgery start time through the offset time, left censored. If both onset and offset are not achieved, duration will be calculated from the surgery start time through the last offset assessment time, interval censored. See Section 10.5.5.1 for how the censoring is handled in analysis. If post-dose onset assessments are completely missing, time to onset will be set to missing. If either onset or offset assessments are completely missing, duration of sensory block will be set to missing.

7.3.2. Assessment of Motor Block

Motor function (onset and offset of motor block) will be assessed by active movement of the knee (knee extension). This will be used to determine the onset and duration of motor blockade.

The motor function test will be performed at pre-dose, 15, 30, and 45 minutes, 1, 2, 8, 12, 24, 30, 48, 60, 72, 84, 96, 120, 144, and 168 hours from the end of the nerve block procedure, or until full motor function has returned to baseline (pre-dose) levels. Additional unscheduled assessments may be performed, particularly around the surgery if no onset of block is noted on the last scheduled assessment prior to surgery. Once the offset of motor block is recorded, no further scheduled motor assessments are required.

Onset of motor block is defined as the earliest timepoint with no knee extension. If subject does not experience loss of motor function, their onset will be censored at their last available motor assessment time point prior to surgery.

Offset of motor block is defined as resolution of motor block with knee extension. If offset time is not achieved, it will be considered censored at the last offset assessment time after surgery. After offset of motor block is noted, no subsequent assessments will be required.

Duration of motor block is defined as time between onset and offset of motor block. The censoring and missing data rule for the duration of sensory block also applies to the duration of motor block.

7.4. Safety Assessments

Adverse events and concomitant medications will be collected from signing the informed consent form (ICF) through end of study. In case an AE of special interest (AESI) or serious AE (SAE) occurs during the study, if the investigator or medical monitor considers that the event may be related to study treatment or suggests the possible occurrence of local anesthetic systemic toxicity (LAST; with or without the need for treatment [e.g., intralipids]), an unscheduled PK blood sample, 12-lead EKG, and vital signs will be collected. Unscheduled neurological assessments will be conducted according to the investigator site's standard of care until resolution.

Vital signs will be collected at baseline, upon arrival in PACU, at PACU discharge, and every 6 hours post-surgery through 96 hours, and at hospital discharge for both Cohort 1 and Cohort 2, and at 120, 144, and 168 hours for Cohort 1 subjects.

12-lead EKG assessments will be performed at screening, and at 24, 48, 72, and 96 hours post-surgery for subjects in both Cohort 1 and Cohort 2, and additionally at 120, 144, and 168 hours post-surgery for subjects in Cohort 1.

7.5. Change in the Study Design and Its Effect on the Statistical Analysis

None.

8. ANALYSIS SETS

The following study analysis data sets are planned:

Safety Analysis Set - The safety analysis set will include all randomized subjects who receive study drug. All analyses based on the Safety Analysis Set will be by actual treatment received.

Efficacy Analysis Set - The efficacy analysis set will include all subjects in the safety analysis set who undergo the planned surgery and have at least one post-study drug administration NRS pain assessment. All analyses based on the Efficacy Analysis Set will be by randomized treatment regardless of treatment actually received. This analysis set will be used for all efficacy analysis.

Sensitivity Analysis Set – This is a subset of Efficacy Analysis Set. This set will exclude Subject (XXX-XXXX) who received non-randomized study drug. Additional subjects may be excluded for the same reason if found after this SAP is signed off.

Pharmacokinetic Concentration (PKC) Analysis Set – This set will include all subjects enrolled in Cohort 1 who receive study drug and have at least one post-dose plasma concentration sample. All analyses based on the PKC Analysis Set will be based on the actual treatment received.

Pharmacokinetic Parameter (PKP) Analysis Set - The PK analysis set will include all subjects in Cohort 1 who receive study drug and provide sufficient samples to enable calculation of PK

parameters. The final inclusion in the PK analysis set will be defined in the PK report. All analyses based on the PKP Analysis Set will be based on the actual treatment received.

Pharmacodynamics (PD) Analysis Set - The PD analysis set will include all subjects in Cohort 1 and in the efficacy analysis set who provide sufficient data to allow for calculation of PD parameters required for analysis. All analyses based on the PD Analysis Set will be based on the randomized treatment group.

9. STUDY ENDPOINTS

9.1. Efficacy Endpoints

9.1.1. Primary Endpoint

The primary endpoint is the area under the curve (AUC) of the NRS pain intensity scores from 0 to 96 hours post-surgery.

9.1.2. Secondary Endpoints

1. Total postsurgical opioid consumption in oral morphine equivalents dose (OMED) from 0 to 96 hours post-surgery
2. Time to first opioid consumption post-surgery
3. Worst and average NRS pain intensity scores at 24, 48, 72, and 96 hours post-surgery

9.1.3. Exploratory Endpoints

[redacted]

9.2. Safety Endpoints

Safety endpoints will include the incidence of treatment-emergent AEs and SAEs from start of the nerve block procedure through POD14, change from baseline in vital signs over time, and abnormal post-baseline EKG findings.

9.3. Pharmacokinetic (PK) Endpoints (Cohort 1 only)

The following PK endpoints will be determined.

- Area under the plasma concentration-versus-time curve (AUC), specifically $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$
- Maximum plasma concentration (C_{max}) and time of C_{max} (T_{max}) for subjects treated with bupivacaine HCl and early and late C_{max} and T_{max} for subjects treated with EXPAREL admixed with bupivacaine HCl
- Apparent terminal elimination half-life ($t_{1/2el}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V_d)

9.4. Pharmacodynamic (PD) Endpoints (Cohort 1 only)

- Median time to onset of sensory block and motor block
- Median duration of the sensory block and motor block

10. METHODS OF STATISTICAL ANALYSIS

10.1. General Principles

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). All analyses and tabulations will be performed using SAS® Version 9.4 or later. Continuous variables will be summarized using descriptive statistics [sample size (n), mean, standard deviation (SD), minimum, median, and maximum]. Categorical variables will be tabulated with number (n) and percentage (%) of unique subjects. Unless otherwise noted, percentages will be calculated using the number of subjects in the respective treatment group and analysis set as the denominator and presented with only those categories appearing in the data.

Individual subject data will be provided in listings. All listings will be sorted by cohort, treatment, site, subject, and, if applicable, collection date and time.

The statistical methods presented in this document supersedes the statistical analysis methods described in the clinical protocol. Significant deviations/changes from the planned analyses described in this SAP will be identified, with justification, in the appropriate section of the clinical study report (CSR).

When investigator site is used as a stratification variable or as a categorical covariate, sites with fewer than 8 subjects in the efficacy analysis set will be pooled with other sites for analysis. US Census Bureau geographic regions (see Table 7) will be used for the pooling. Sites meeting the criteria for pooling will be pooled with other small sites within their states. If the resulting pooled site within the state still doesn't have at least 8 subjects, it will be pooled with the site

within the division with the smallest enrollment that doesn't meet the pooling criteria. If all sites within a division are pooled and the resulting pooled site still doesn't have at least 8 subjects, the pooled divisional site will be pooled with other small sites within the region. If the pooled regional site still does not have at least 8 subjects, it will be pooled with the site with the smallest enrollment from the neighboring regions.

Table 7. US Census Regions and Divisions

Region	Division	State
Midwest	East North Central	Illinois, Indiana, Michigan, Ohio, Wisconsin
	West North Central	Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota
Northeast	Middle Atlantic	New Jersey, New York, Pennsylvania
	New England	Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont
South	East South Central	Alabama, Kentucky, Mississippi, Tennessee
	South Atlantic	Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia
	West South Central	Arkansas, Louisiana, Oklahoma, Texas
West	Mountain	Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming
	Pacific	Alaska, California, Hawaii, Oregon, Washington

10.2. Handling Missing Values

10.2.1. Total Post-Surgical Opioid Consumption

For the calculation of the total postsurgical opioid consumption from 0 to 96 hours, opioid pain medication recorded on the Breakthrough Pain Medication eCRF page will be used. If an opioid is taken on the start of study drug administration day but the time is missing, the time will be imputed as end time of surgery plus (+1) 1 minute. If an opioid is taken after the day of study drug administration and time is missing, the time will be imputed as 00:00.

For the calculation of the total dose through 96 hours, if a subject's last follow-up time in the health care facility is 96-*x* hours, then the opioid taken between 96-2*x* hour to 96-*x* hour will be used to project the amount from the last follow-up time to 96 hours, where time of last follow-up will be defined as the latter of (1) the last NRS pain assessment, (2) the start time of the last opioid pain medication, (3) time of the subject completion of the 96-hour satisfaction questionnaire, and (4) time of last sensory and motor block assessment.

10.2.2. NRS Pain Intensity Scores

Pain scores obtained during the opioid medication window will be replaced with the windowed-worst observation carried forward (wWOCF). For this study, the prescribed opioid pain medication for breakthrough pain is oxycodone. However, morphine, hydromorphone, or other

opioids may be used. The durations of the analgesic effect for various opioids are listed in Table 8.

Table 8. Opioid Pain Medication Window

Medication	Route	Window Used to Replace NRS
Oxycodone, Oxycocet, Percocet, acetaminophen-oxycodone, Oxycontin	PO, IM, IV, SC	6 hours
Morphine	IV, PO, SC	4 hours
Hydromorphone (Dilaudid), Hydromorphone hydrochloride	IV	2 hours
Hydromorphone (Dilaudid), Hydromorphone hydrochloride	PO, IM, SC	4 hours
Hydrocodone	PO	6 hours
Fentanyl	IV, PO, IM	6 hours
Hydrocodone combination product - Vicodin, Norco, Lorcet, Lortab, hydrocodone-acetaminophen	PO	6 hours
Codeine combination product - Tylenol 3, acetaminophen-codeine, Paracetamol Forte, Tylenol 4	PO	6 hours
Ultram, Tramadol, Tramadol hydrochloride	PO	6 hours

PO = oral, IV = intravenous, IM = Intramuscular, SC = subcutaneous.

If other opioid pain medications not listed above are given, the window will be determined prior to the database lock and unblinding. If a combination opioid product is given, the window will be determined by the opioid part of the medication.

For the primary efficacy endpoint of AUC of NRS pain intensity score from 0 to 96 post-surgery, after applying the visit windows (Section 6 Table 3) and wWOCF to all scheduled/unscheduled pain scores, remaining missing data at each scheduled time point (6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72 , 78, 84, 90, and 96 hours) will be interpolated by the two data points before and after the missing data points. (Note for Study 402-C-333, out of 3,738 data points collected or missing for 0-100 hours post-surgery, only 72 (1.9%) data points were actually missing [ref ADEF1] for Study 402-C-333). The procedures of wWOCF and interpolation are described as follows.

A. For subjects who take an opioid pain medication, their NRS scores recorded within the window of opioid medication (see Table 8) will be replaced by the 'worst' observation. The 'worst' observation will be the highest NRS score from the end of previous opioid window (excluding the exact end of the window) or the end of surgery whichever is later, inclusive of the unscheduled NRS score taken at the time of opioid pain medication administration. If the scheduled NRS score taken in the window is higher

than the 'worst' observation to be carried forward, the 'worst' observation will be replaced by this higher value which will be carried forward until the end of the window. If the scheduled NRS score within the window is missing, it will be imputed with the 'worst' observation.

B. After the wWOCF imputation described above, if there are still missing NRS scores at scheduled time points, they will be interpolated as follows,

$$p_i = (p_{i+1} - p_{i-1})\frac{t_i - t_{i-1}}{t_{i+1} - t_{i-1}} + p_{i-1},$$

where p_i is the missing pain score at time point t_i, p_{i-1} and p_{i+1} are the two collected or wWOCF imputed pain scores at time t_{i-1} and t_{i+1}. The interpolated value will retain one decimal place in the database.

10.2.3. Adverse Event or Concomitant Medication Date or Time

For AEs with missing or partially missing start date/time, the following imputation rules will be applied for the determination of treatment-emergent status:

If an AE has a partial onset date and time, the collected or imputed start and stop dates and times will be used to determine treatment emergence (e.g., an AE with stop date and time before the start date and time of study treatment is not treatment-emergent).

- If the year is unknown, then the onset date will be assigned the date and time of first dose of study treatment.
- If the year is known to be different from the year of the first dose, then missing month and day will be imputed as the first month and first day of the month.
- If the year is known to be the year of the first dose,
    a) If the month is unknown or is the same as the month of the first dose, then the missing month and day will be imputed by the month and day of the first dose.
    b) If the month is known to be different from the month of the first dose, then the missing day is imputed as 01 (first day of the month).
- If the time is unknown, then:
    a) If the date (day, month, and year) matches the date of the administration of study drug, then the time of the study treatment will be used to impute the missing time.
    b) Otherwise, '00:00' will be assigned.

For medications with missing or partially missing dates, Section 10.4.5 provides rules for the determination of prior or concomitant status.

10.2.4. Adverse Event Severity or Relationship to Study Drug

If severity of an AE is not reported, then for tables of AEs by severity, the event will be classified as 'Severe' and will be footnoted for the table to indicate this imputation. If relationship to study drug is not reported for an AE, then for tables of study-drug related AEs, the event will be assigned the relationship of 'definite'. Tables presenting related AEs will include all AEs with relationships of 'possible,' 'probable,' or 'definite' as assessed by the investigator.

10.2.5. Time to Event

For calculating time to an event when only the hour is reported, the minutes will be set to zero. The censoring method is described in Sections 7.3.1 and 7.3.2 when the onset time or the offset time of sensory or motor block is not captured.

10.3. Subject Disposition

Subject disposition summaries will include the number and percentage of subjects by treatment group for the following categories:

- Screened
  - Screen failure
  - Enrolled (i.e., randomized)
- Randomized
  - Randomized not treated
  - Randomized treated
- In the Safety Analysis Set
- In the Efficacy Analysis Set
- In the Pharmacokinetic Concentration and Parameter (PKC and PKP) Analysis Set
- In the Pharmacodynamics (PD) Analysis Set
- Protocol
  - Enrolled under each amendment
- Completed the study as planned
- Discontinued from the study
  - Reasons for discontinuation from the study

The number and percentage of screen failures will be reported using the number of subjects screened as the denominator. Percentages based on the Efficacy Analysis Set will use the number of subjects randomized and treated as denominator with data grouped by randomized assignment. Percentages for the Safety, PKC, and PKP Analysis Sets (see Section 10.8) will be use the number of subjects treated as the denominator with data grouped by actual treatment received.

In addition to the summary for the overall study, subject disposition will also be summarized by investigator site.

10.4. Description of Demographics and Baseline Characteristics

Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for continuous variables. The number (n) and percentage (%) of subjects will be tabulated for categorical variables.

10.4.1. Demographics

The summary of demographic data will present:

- Age (years) – continuous and categorical (<45, 45 to <65, and ≥65 years), n (%)
- Sex – n (%)
- Ethnicity – n (%)
- Race – n (%)

Age will be calculated based on the date the subject signed the informed consent form (ICF).

The demographics will be summarized by treatment group and for both treatment groups combined. Summaries will be provided for each analysis set separately. The demographics will also be summarized by the pooled investigator site.

10.4.2. Baseline Characteristics

The summary of baseline characteristic data will present:

- American Society of Anesthesiologists (ASA) Classification – n (%)
- Height (cm) – continuous
- Weight (kg) - continuous
- Body Mass Index (BMI) (kg/m^2) – continuous and categorical (<25, 25 to <30, and ≥30 kg/m^2)
- Average pain intensity scores on the NRS in the last 30 days of baseline
- Worst pain intensity scores on the NRS in the last 30 days of baseline

Weight in pounds will be converted to kilograms using the conversion factor of 2.2046 pounds to 1 kilogram. Height in inches will be converted to centimeters using the conversion factor of 2.54 centimeters to 1 inch.

Baseline characteristics will be summarized by treatment group and for both treatment groups combined. Summaries will be provided for each analysis set separately. The baseline characteristics will also be summarized by pooled investigator site.

10.4.3. Medical and Surgical History

The prevalence (frequency and percentage) of medical and surgical histories will be tabulated by MedDRA (v25.0) System Organ Class (SOC) and Preferred Term (PT) for each treatment group and for both groups combined. All medical and surgical histories will be included in the data listing.

10.4.4. Surgery Characteristics

Surgery characteristics including duration of surgery, use of intraoperative medication (Y/N), and AE/SAE report during surgery (Y/N) will be summarized using descriptive statistics. Summaries will be provided for each (efficacy and safety) analysis set.

The duration of surgery will be calculated as the difference between the end of surgery and start of surgery times.

A listing of admission and discharge to the health care facility and PACU will be provided.

10.4.5. Intraoperative, Prior, and Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO Drug Dictionary Global B3 March 2022) and will be classified according to the Anatomical Therapeutic Chemical classification term (ATC) and Preferred Term (PT).

Intraoperative medications are defined as medications given as part of the surgical procedure. These may include anesthesia, local anesthetics, opioids, or other medications collected on the Intraoperative Medication CRF Page.

Prior and concomitant medications are medications collected on the Prior/Concomitant Medication eCRF page. Prior medications are defined as medications with a stop date and time prior to the start of study drug administration. Concomitant medications are defined as medications taken after the start of study drug administration (i.e., started prior to the start of study drug administration and continued after or started after the start of study drug administration).

For the determination of the prior and concomitant status, these rules will be followed for incomplete dates.

- If the medication stop date is partially missing,
    - If the year and month indicate the stop date is before study drug administration, it will be considered a prior medication.
    - Otherwise, it will be considered concomitant medication.
- If the medication stop date is completely missing, it will be considered a concomitant medication.

The frequency and percentage of subjects with prior medication use and concomitant medication use will be tabulated by WHODD ATC (Level 3) and PT for each treatment group and for both groups combined.

All medications will be included in the data listing.

10.4.6. Protocol Deviations

Protocol deviations will be classified into, but not limited to, improper ICF procedure, ineligibility for inclusion/exclusion criteria, efficacy assessments, breakthrough pain medication dispensing procedure, study noncompliance, restricted medication, PK/PD assessments, and study drug error. The frequency and percentage of subjects with important protocol deviations will be tabulated by treatment group.

Additionally, the protocol deviations will also be summarized by investigator site.

10.4.7. Measurements of Treatment Compliance

Study drug is administered by a party other than the subject. However, any deviation from administration of study drug, as randomized, will be captured and summarized as a protocol deviation.

10.5. Efficacy Analysis

All efficacy analyses will be performed using the Efficacy Analysis Set.

Unless specified otherwise, all confidence intervals will be 2-sided with 95% confidence and statistical comparisons will be 1-sided tests at an alpha level of 0.025.

10.5.1. Multiplicity Adjustment

There is no type-I error inflation due to sample size re-estimation (see Interim Analysis Plan for details). To control for the overall Type-I error rate for the multiple comparisons due to multiple endpoints, the statistical tests will be conducted in the hierarchical order as follows.

1. Primary endpoint (AUC of NRS pain 0-96 hours post-surgery).
2. First secondary endpoint (Total postsurgical opioid dose 0-96 hours).
3. Second secondary endpoint (Time to first postsurgical opioid).

At any step if the statistical test becomes non-significant, all the subsequent tests will be deemed non-significant.

10.5.2. Primary Efficacy Endpoint

The primary efficacy endpoint is AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery. The NRS pain intensity score is collected from the assessment, “on a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you

experiencing in your operative knee right now?" The worst and average daily pain scores are not included in the AUC calculation.

For each subject, the AUC curve is derived using the trapezoidal rule (see formula below) on the pain scores adjusted for opioid pain medication using the observed and imputed values (see Section 10.2.2). AUC will start with the first pain assessment obtained after surgery (arrival at PACU) and use all subsequent pain assessments up to 96 hours post-surgery. Pain scores collected prior to the opioid medication administration or unscheduled assessments are also included in the AUC calculation. Exact assessment time will be used in deriving AUC.

$$AUC = \left\{ \sum_{i=2}^{n} (p_i + p_{(i-1)})(t_i - t_{(i-1)}) \right\} / 2$$

where p_i is the NRS pain score at time i and t_i is the time, in hours, from end of surgery. Note t_1 is pain score collected upon PACU arrival.

In calculating $AUC_{0\text{-}96}$, if the exact 96-hour pain score is not collected, it will be interpolated using the two nearest before and after data points. If the last 96-hour assessment is before 96.0 hours, then the exact 96-hour pain score for the AUC calculation will use this last observation carried forward. If the last assessment is after 96-hour but before 100-hour, then the exact 96-hour pain score will be interpolated using this last assessment and the assessment before 96-hour. If the first assessment at PACU arrival time is not collected, the pain score at PACU arrival will use the first assessment after PACU arrival carried backward. The PACU arrival time will be imputed with the median arrival time of all subjects. Generally, when the pain score is not collected at the exact time point for $AUC_{x\text{-}y}$ calculation, the pain score at the exact time point will be interpolated by the two nearest data points before and after the exact time point.

The AUC of NRS pain intensity scores from 0 to 96 hours will be summarized by treatment group.

The primary analysis of the primary efficacy endpoint will compare the EXPAREL admixed with bupivacaine HCl group and the bupivacaine HCl group. The superiority of EXPAREL admixed to bupivacaine HCl only will be evaluated based on the following null hypothesis and alternative hypothesis using the Efficacy Analysis Set with the wWOCF/interpolation method:

> H_0: EXPAREL admixed is not superior to bupivacaine HCl only with respect to AUC of NRS pain intensity scores from 0 to 96 hours.
>
> H_a: EXPAREL admixed is superior to bupivacaine HCl only with respect to AUC of NRS pain intensity scores from 0 to 96 hours.

A one-sided hypothesis test will be performed at α=0.025 level of significance comparing EXPAREL admix and bupivacaine HCl as follows:

- If the one-sided p-value for the least square (LS) mean treatment difference in AUC NRS_{0-96} (EXPAREL admixed – bupivacaine HCl only) is >0.025, then the superiority of EXPAREL admixed to bupivacaine HCl only is not achieved.
- If the p-value for the LS mean treatment difference in AUC NRS0-96 (EXPAREL admixed – bupivacaine HCl only) is ≤0.025, then the superiority of EXPAREL admix to bupivacaine HCl only is achieved.

To test for significant differences between the EXPAREL admixed and bupivacaine HCl only treatment groups, an analysis of covariance (ANCOVA) model with main effect of treatment and covariates of pooled investigator site (categorical) and age (continuous) will be used. The LS means for each treatment group, LS mean difference between the two treatment groups, two-sided 95% CI for the LS mean difference, and one-sided p-value will be presented. The primary analysis will be performed based on the Efficacy Analysis Set.

Sample SAS code for ANCOVA follows.

```
Ods output Diffs=diff LSMEstimates=lsme;
proc genmod data=auc;
      class trtpn (ref=3) siteid ;
      model aval=trtpn age siteid / dist= normal link=identity;
      lsmestimate trtpn 'Group 1 vs Group 2' 1 -1
            / cl lower alpha=0.025 ilink;
run;
```

In addition to the presentation for the between group difference, the percent reduction in AUC will also be presented. The % reduction is derived as follows,

$$\% \text{ Reduction} = \{\text{LS Means}_{Bup} - \text{LS Means}_{EXPAREL}\}/\text{LS Means}_{Bup} \times 100\%.$$

As a sensitivity analysis, the above described procedure will be repeated using the Sensitivity Analysis Set. A separate sensitivity analysis using the same ANCOVA model for Efficacy Analysis Set will be performed on the average NRS pain score derived from AUC/time span ("/" stands for "divided by"), where AUC is calculated using all NRS pain score collected 0 – 96 hours without imputation, and the time span is last NRS time minus the first NRS time for the AUC calculation.

Additional sensitivity analysis evaluating the consistency of the treatment effect will be carried out for AUC over various time intervals (0-24, 0-48, 0-72, 24-48, 24-72, 24-96, 48-72, 48-96, and 72-96 hours).

10.5.3. Secondary Efficacy Endpoints

10.5.3.1. Total postsurgical opioid consumption in oral morphine equivalents from 0 to 96 hours post-surgery

Total postsurgical opioid consumption (OMED mg) will be summarized by treatment group. The summary will include the number of subjects receiving postsurgical opioids, geometric mean consumption, coefficient of variation (CV%), median, minimum, and maximum.

To test for a significant difference between the EXPAREL admixed and bupivacaine HCl only groups, an ANCOVA model with treatment as main effect and pooled investigator site (categorical) and age (continuous) as covariates will be applied to the natural log-transformed opioid consumption. The LS means for EXPAREL admixed and bupivacaine HCl groups, LS mean difference between the EXPAREL admixed and bupivacaine HCl groups, two-sided 95% CI for the LS mean difference, and the one-sided p-value will be reported. LS means, the LS mean difference, and their associated CIs will be reported after back transformation (ie, taking exponential) to the original OMED scale. If a subject does not have postsurgical opioid consumption, a 3.75 mg OMED will be assigned before the log-transformation. The primary analysis will be performed based on the Efficacy Analysis Set.

The percent reduction in total opioid consumption between groups will also be presented using the analogous calculation as outlined in Section 10.5.2.

As sensitivity analysis, this endpoint will also be analyzed using the site-stratified Cochran-Mantel-Haenszel (CMH) test for the row mean score difference with modified ridit scores.

Sample SAS code follows.

```
PROC FREQ ;
     TABLES siteid*trtp*omed / CMH SCORE=modridit ;
RUN ;
```

Additional sensitivity analysis evaluating the consistency of the treatment effect will be carried out for opioid consumption over various time intervals (0-24, 0-48, 0-72, 24-48, 24-72, 24-96, 48-72, 48-96, and 72-96 hours). To facilitate the log-transformation analysis, 0 mg OMED for a time interval will be replaced with 3.75 mg / 96 hour * the length of the interval.

10.5.3.2. Time to first postsurgical opioid consumption

Time to first opioid consumption will be calculated in hours as the date and time of the first opioid medication taken post-surgery minus the date and time of end of surgery. If a subject does not use an opioid post-surgery, the time to first opioid consumption will be censored at the date of End of Study. For this derivation, the opioid consumption recorded on both Breakthrough Pain Medications and Prior/Concomitant Medications CRF pages will be considered.

The primary analysis for time to first postsurgical opioid consumption will be a Cox proportional hazards regression with treatment as the factor and categorical pooled investigator

site and continuous age as covariates. The hazard ratio (risk ratio) of requiring opioid medication of EXPAREL admixed over bupivacaine HCl only will be presented. Time to first opioid usage will also be analyzed by the Kaplan-Meier survival method. Summary statistics for time and the log-rank test comparing EXPAREL admix and bupivacaine HCl only will also be presented as a supportive analysis. The log-rank test will be stratified by the pooled site. In addition, the number (and %) of subjects with opioid pain medication post discharge as well as the number (and %) of subjects without opioid pain medication post discharge will be presented for each treatment group. One-sided p-values will be reported for the Cox regression and two-sided p-value will be reported for the log-rank tests.

Sample SAS code for the log-rank test and the proportional hazards regression follows.

```
ODS OUTPUT HOMTESTS=lpval (WHERE=(TEST='Log-Rank')) ;
PROC LIFETEST DATA=ef1 ;
     TIME aval*cnsr(1);
     STRATA siteid / GROUP=trtn;
RUN;

ODS OUTPUT DIFFS=hr LSMEstimates=pval ;
PROC PHREG DATA=ef1 OUTEST=estim ;
     CLASS trtn(REF='2') siteid / PARAM=glm ;
     MODEL aval*cnsr(1) = trtn siteid age;
     LSMEANS trtn / DIFF CL EXP ILINK ;
     LSMESTIMATE trtn 'Grp 1 vs Grp 2' 1 -1/ UPPER ;
RUN ;
```

10.5.3.3. Worst and average NRS pain intensity scores at 24, 48, 72, and 96 hours post-surgery

"Worst" and "average" pain score over the last 24 hours will be summarized by treatment group daily at 24, 48, 72, and 96 hours. For descriptive purposes, "worst" and "average" pain scores will be analyzed each day using ANCOVA with treatment as a factor, site as a categorical covariate and age as a continuous covariate.

10.5.4. Subgroup Analysis

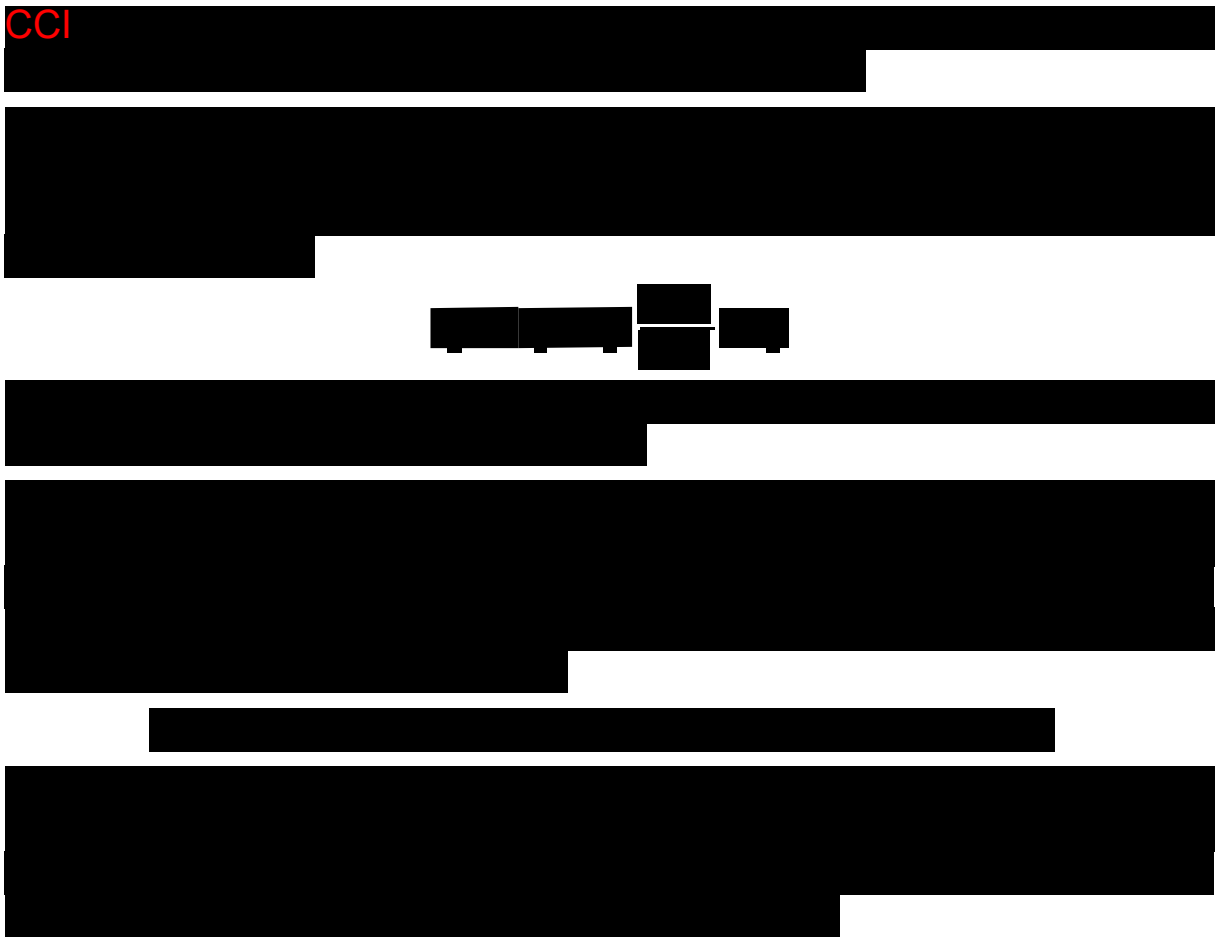
The analysis of the primary and the first secondary endpoints will be repeated for the subgroups defined by the following variables using the Efficacy Analysis Set.

- Pooled investigator site
- Age (<45, 45 to <65, and ≥65 years),
- Sex
- Race (White and Non-White)
- BMI (<25, 25 to <30, and ≥30 kg/m^2)

Because of the small sample sizes, no significance tests will be performed within subgroups.

10.5.5. Exploratory Endpoints

CCI



10.6. Pharmacokinetic Analysis

10.6.1. Pharmacokinetic Parameter Calculation Methods

Pharmacokinetic parameters will be calculated by noncompartmental analysis (NCA) method from concentration-time data following these guidelines:

- Actual sampling times relative to end of study drug administration will be used for all calculations of the PK parameters. If there is any doubt as to the actual time a sample was taken, the scheduled time will be used.
- Concentrations from unscheduled PK blood samples will be included in the calculation of the parameters.
- There will be no imputation of missing concentration data.

For the summaries of concentrations and for the NCA analysis of the bupivacaine plasma concentrations, concentrations below the limit of quantification (BLOQ) will be handled as follows:

- Pre-dose BLOQ values will be set to zero.

- BLOQ values between the dosing time and the first time point above lower limit of quantification (LLOQ) will be set to 0.
- BLOQ values at time points between two measurable concentration values will be set to ½ of LLOQ (lower limit of quantification).
- All remaining BLOQ values will be set to missing.

The PK parameters will be estimated using the non-compartmental method according to the following guidelines:

- The maximum observed plasma concentration (C_{max}) for the bupivacaine HCl group will be obtained directly from the concentration-time data.
- For the EXPAREL admixed group, a 2-peak PK profile is expected because of the combination of the EXPAREL and bupivacaine. Therefore, the following values will be calculated:
    - Early C_{max} – occurring between dosing (0 hour) and *x* hours after dosing if appropriate based on the individual subject and treatment group mean concentration-time plots, where *x* will be determined from the concentration-time plot.
    - Late C_{max} – occurring more than *x* hours after dosing if appropriate based on the individual subject and treatment group mean concentration-time plots.

  where *x* is a subject-specific local minimum turning point in the concentration-time curve.
- For the bupivacaine HCl group, time to maximum concentration (T_{max}) is the time at which C_{max} is observed in the bupviacaine HCl group.
- The apparent terminal elimination rate constant (λ_z) will be estimated at terminal phase by linear regression after log-transformation of the concentrations:
    - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.
    - A minimum number of three data points in the terminal phase will be used in calculating λ_z with the line of regression starting post the late C_{max} data point (C_{max} will not be part of the regression slope) and including the last point above LLOQ value (Ct).
    - An appropriate number of decimal places will be used for λ_z to enable the reported value of terminal half-life ($t_{1/2}$) to be calculated with more precision.
- Rules for excluding subjects from the terminal phase-related parameter calculation:
    1. Adjusted R-square <80%, or

2. Extrapolated AUC >30% of $AUC_{0-\infty}$

- Apparent terminal half-life ($t_{1/2}$) will be calculated as $\ln(2)/\lambda_z$.
- The area under the plasma concentration-time curve from the time of dosing to the time of the last quantifiable concentration (AUC_{0-last}) will be calculated using the linear-up/log down trapezoidal method.
- The area under the plasma concentration-time curve from the time of dosing (zero) to infinity ($AUC_{0-\infty}$) will be calculated as the sum of AUC_{0-last} and residual area C_t/λ_z.
- Extrapolated area under the curve from time of last point above LLOQ (t_{last}) to infinity (AUC_{extr}), expressed as percentage of $AUC_{0-\infty}$ will be calculated as $(Ct/\lambda z)/AUC_{0-\infty} \cdot 100\%$.
- Apparent clearance CL/F will be estimated as $Dose/AUC_{0-\infty}$. Note every subject receives 37.5 mg bupivacaine HCl during IPAC as pre-operative medication. The final Dose in the calculation is 77.6 mg (50 + 37.5 mg) x 0.8867 [salt to free base conversion]) for subjects receiving 50 mg bupivacaine HCl treatment only, and 210.6 mg (133 + [50 + 37.5] x 0.8867) for subjects receiving EXPAREL (133 mg) admixed with bupivacaine HCl (50 mg) treatment.

10.6.2. Pharmacokinetic Concentrations and Variables

The analysis of the PK parameters will be based on the PKP analysis set. The analysis of the PK concentrations will be based on the PKC analysis set.

Bupivacaine plasma concentrations will be listed by treatment, subject, nominal time, and actual time. Concentrations that are BLOQ will be indicated in this listing.

Plasma concentrations will be summarized at each nominal time point seperately for each treatment. The following descriptive statistics will be presented: n, arithmetic mean, SD, geometric mean, %CV, median, minimum, and maximum.

Pharmacokinetic parameters will be summarized by treatment. Descriptive statistics for PK parameters except for T_{max} values will include: n, arithmetic mean, SD, geometric mean, %CV, median, minimum, and maximum values. Descriptive statistics for T_{max} values will include n, median, minimum, and maximum values.

Individual plasma concentration versus actual times will be plotted for each subject in linear and semi-logarithmic scales. Mean plasma concentration at the scheduled time points will be plotted for each treatment in linear and semi-logarithmic scale, with the associated standard errors (for linear scale only) at each scheduled time point.

In the plot for individual subjects, concentrations that are below the limit of quantitation (BLOQ) will be assigned a value of ½ LLOQ if they are collected postdose.

If there are detectable (non-BLOQ) concentration values at pre-dose that are >5% of C_{max} for a bupivacaine HCl-treated subject and the higher of the Early and Late C_{max} values for an EXPAREL admixed-treated subject, these concentration values and PK parameters from such subjects with these values will be excluded from descriptive summaries.

10.7. Pharmacodynamic Analysis

The time windows (Table 4) will be applied in the by-time point summaries and plots for the sensory function and motor function.

10.7.1. Sensory Function

Time to onset of sensory block from end of study drug administration and duration of sensory block will be summarized by the median and quartiles estimated using the Kaplan-Meier method similar to Section 10.5.3.2. See Section 7.3.1 for how to handle censoring time. The Kaplan-Meier plot for time to onset and duration of sensory block will be presented.

The number and percentage of subjects with normal sensation and no sensation will be tabulated by treatment group and timepoint. Because subjects are not required to continue the onset or offset assessment after they have reached the onset or offset respectively, missing scheduled assessment after onset is achieved prior to surgery or after offset is achieved post-surgery will be imputed using the last observation carried forward (LOCF) method.

Additionally, the mean PK concentrations and percentage subjects with sensory block "on" will be overlaid and plotted over time to show the dynamic relationship between the two for each of the treatment groups.

10.7.2. Motor Function

Time to onset of motor block from end of study drug administration and duration of motor block will be summarized by the median and quartiles estimated using the Kaplan-Meier method similar to Section10.5.3.2. See Section 7.3.2 for how to handle censoring time. The Kaplan-Meier plot for time to onset and duration of motor block will be presented.

The number and percentage of subjects with complete motor function and no motor function will be tabulated by treatment group and timepoint. Missing assessment after onset is achieved prior to surgery or after offset is achieved post-surgery will be imputed by LOCF.

Additionally, the mean PK concentrations and percentage of subjects with motor block "on" will be overlaid and plotted over time to show the dynamic relationship between the two for each of the treatment groups.

10.8. Safety Assessments

10.8.1. Adverse Events and Serious Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 25.0). The summary tables will be based on the Safety Analysis Set.

A treatment emergent adverse event (TEAE) is any adverse event with the onset date and time on or after the start date and time of study drug administration and ending with POD14.

All AE summaries will present TEAEs only; AEs that are not treatment-emergent will be included in listings but not summarized.

An overview of all TEAEs will present the number and percentage of unique subjects in the following categories:

- Any TEAE
  - Maximum severity: Mild
  - Maximum severity: Moderate
  - Maximum severity: Severe
- At least one related TEAE
- At least one serious TEAE
- Subjects discontinued due to a TEAE
- Died on study

Subjects may only be counted once in each of the above categories.

The subject incidence of all TEAEs will be tabulated by the number and percentage of subjects reporting the TEAE. Incidence is defined as a subject reporting at least one TEAE within the summary level. Summary levels are 'at least one TEAE', System Organ Class (SOC) and Preferred Term (PT). Subjects will be counted only once within each reporting level in the table. For example if a subject reports a TEAE of headache on two separate occasions, the subject will be counted only once in the headache row of the table. Similarly if a subject reports two separate TEAEs within the same SOC the subject will only be counted once in the summary row for that SOC. For summary purposes, AE relationship to the study drug will be grouped into "Unrelated" for "unrelated" or "unlikely" and "Related" for "possible", "probable", or "definite". For subjects with more than one event coded to the same PT, the subjects will be counted for the categories with the strongest relationship and the greatest severity. Summaries will also be presented for the following categories of events:

- TEAEs by PT sorted by the decreasing order of subject incidence in the group combining EXPAREL doses
- TEAEs by SOC and PT sorted alphabetically
- TEAEs by SOC and PT, and worst severity
- TEAEs by SOC and PT and study drug-relationship

- TEAE of special interest (TEAESI) by SOC and PT
- Serious TEAE by SOC and PT
- Non-Serious TEAE by SOC and PT

A subject data listing will be provided for all AEs. Included in the listing are the reported term, PT, SOC, TEAE flag, study day when AE starts, AE start/stop date and time, relationship to study drug, frequency, severity, action taken with subject, outcome, and seriousness criteria.

Separate data listings will be provided for subject deaths, SAEs, TEAEs leading to study discontinuation, and AEs of special interest. A listing of the mapping of the SOC and PT to verbatim terms will be presented.

AEs of special interest (AESIs) will be extracted based on the MedDRA terms below.

- Falls
- Persistent tingling
- Persistent numbness
- Persistent weakness
- Hypersensitivity
- Seizures
- Tremors
- Dizziness
- Hematoma formation
- Cardiovascular depression
- Dyspnea
- Cardiovascular arrest
- Altered sensorium
- Visual disturbances
- Local anesthetic systemic toxicity

10.8.2. Other Safety Assessments

Vital signs and their change from baseline will be summarized with mean, median and SD at baseline and at each scheduled timepoint (see Table 5 for time windows and Section 7.4 for details).

The frequency and percentage of EKG findings (normal, abnormal/not clinically significant, and abnormal/clinically significant) will be summarized at screening and each scheduled timepoint (Section 7.4).

Both scheduled and unscheduled vital signs and EKG, and unscheduled neurological evaluations will be included in the by-subject data listing.

10.9. Interim Analysis

An unblinded interim analysis will be performed by an independent party when a total of approximately 80 subjects (40 in each arm) combined from Cohort 1 and Cohort 2 have complete assessment data for the primary efficacy outcome. The efficacy will be evaluated and compared between study arms as per the procedures described in Section 5. The purpose of this interim analysis is to evaluate the sample size assumptions and evaluate futility. Full details on the planned interim analysis will be covered in a prospective interim analysis plan (IAP).

11. SAMPLE SIZE CALCULATIONS

The total sample size for Cohort 1 and Cohort 2 was calculated based on the primary outcome measure of AUC of NRS pain intensity scores from 0 to 96 hours. A total sample size of 160 subjects (1:1 randomization, 80 EXPAREL admix: 80 Bupivacaine HCl) provides at least 80% power to detect a treatment difference of 80 units in the AUC (SD=180) comparing the EXPAREL admixed group to the bupivacaine HCl group at the one-sided 0.025 significance level.