Pacira Pharmaceuticals, Inc.

DISCLOSURE: REDACTED STATISTICAL ANALYSIS PLAN

Title: A Phase 3, Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL vs. Bupivacaine HCl Administered as a Sciatic (in the Popliteal Fossa) Nerve Block for Postsurgical Analgesia in Subjects Undergoing Bunionectomy
NCT Number: NCT05157841
Protocol Number: 402-C-334

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

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STATISTICAL ANALYSIS PLAN

A Phase 3, Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL vs. Bupivacaine HCl Administered as a Sciatic (in the Popliteal Fossa) Nerve Block for Postsurgical Analgesia in Subjects Undergoing Bunionectomy

Protocol No.:	402-C-334
IND No.:	069,198
Study Phase:	3
Study Drug:	EXPAREL (bupivacaine liposome injectable suspension)
Original Protocol Date	23 September 2021
Amendment 2 Date	24 February 2022
Sponsor:	Pacira BioSciences, Inc. 5 Sylvan Way Parsippany, NJ 07054 Tel: CCI [redacted]
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SAP Date/Version	08 December / 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
PP	Predictive Power
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-334 titled "A Phase 3, Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL vs. Bupivacaine HCl Administered as a Sciatic (in the Popliteal Fossa) Nerve Block for Postsurgical Analgesia in Subjects Undergoing Bunionectomy".

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-334 issued on 23 September 2021
- Protocol 402-C-334 Amendment 1 issued on 22 October 2021
- Protocol 402-C-334 Amendment 2 issued on 24 February 2022
- Electronic Case Report Form (eCRF) v5.0 dated 13 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 TERMINOLOGY OR SPECIFIED METHODS OR TO THE PREVIOUS SIGNED-OFF SAP

The protocol uses the term "conditional power" to specify how the dose selection is made during the interim analysis. This term is now replaced by "predictive power" to be precise when describing the dose selection method. There is no change in the protocol specified statistical 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 vs. 0.25% bupivacaine hydrochloride (HCl) when administered as a sciatic nerve block in subjects undergoing bunionectomy.

4.2. Secondary Objectives

- To compare the total postsurgical opioid consumption (in oral morphine equivalents) from 0 to 96 hours following a single dose of EXPAREL vs. 0.25% bupivacaine HCl
- To compare the percentage of opioid-free subjects post-surgery through 96 hours following a single dose of EXPAREL vs. 0.25% bupivacaine HCl
- To compare the time to first opioid consumption post-surgery, following a single dose of EXPAREL vs. 0.25% bupivacaine HCl
- To characterize and compare the magnitude of the duration of motor and sensory block following a single dose of EXPAREL vs. 0.25% bupivacaine HCl
- To assess the safety and pharmacokinetic (PK) profile of EXPAREL and 0.25% bupivacaine HCl

5. STUDY OVERVIEW

This is a Phase 3, multicenter, randomized, double-blind, active-controlled study in approximately 180 subjects undergoing bunionectomy. Subjects will receive a combined sciatic (in the popliteal fossa) nerve block with a single dose of either EXPAREL 266 mg, EXPAREL 133 mg, or 0.25% bupivacaine HCl (50 mg). The study will be conducted in two parts (Part A and Part B). Part A will be completed and analyzed before enrollment in Part B is initiated.

Part A (PK, PD, Efficacy, and Safety)

Part A is a 3-arm cohort. It will enroll approximately 60 subjects undergoing bunionectomy to obtain information on pharmacokinetic (PK) profile, pharmacodynamics (PD), efficacy, and safety. Subjects will be randomized (1:1:1) to receive either EXPAREL 266 mg, EXPAREL 133 mg, or 0.25% bupivacaine HCl (50 mg).

Part B (Efficacy and Safety)

Part B is a 2-arm cohort. It will enroll approximately 120 subjects undergoing bunionectomy to evaluate the efficacy and safety of EXPAREL compared with bupivacaine HCl. The dose of the EXPAREL arm will be determined based on the interim analysis of the Part A cohort results.

Adaptive Study Design

An unblinded interim analysis will be conducted by an independent party after completion of the Part A enrollment and assessment for the primary efficacy outcome. The predictive power (PP) of success at the end of the study for the primary efficacy outcomes comparing each of the two EXPAREL arms (EXPAREL 266 arm and EXPAREL 133 arm) to the bupivacaine HCl arm will be calculated:

1. If the PP of one EXPAREL arm is less than 30% and the other EXPAREL arm is greater than or equal to 30%, then
    - The EXPAREL arm with PP less than 30% will be dropped in Part B.
2. If both EXPAREL arms have a PP greater than or equal to 30%, then
    - If the PP of the 266 mg EXPAREL arm is more than 10% greater than the PP of the 133 mg EXPAREL arm, then the 266 mg EXPAREL arm will be kept and the 133 mg EXPAREL arm will be dropped. Otherwise, the 133 mg EXPAREL arm will be kept and the 266 mg EXPAREL arm will be dropped in Part B.
3. If the PPs of both treatment arms are less than 30%, then
    - The study will stop for futility.

Final Analysis

The final analysis will include subjects from both Part A and Part B cohorts.

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 266 mg, EXPAREL 133 mg, or 0.25% bupivacaine HCl (50 mg) will be administered under ultrasound guidance 90 min (±30 min) prior to surgery. A confirmatory ultrasound video will be taken during hydrodissection and infiltration of the study drug, with the 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.
- Midazolam (versed) 1 to 2 mg and Ondansetron are allowed.
- Gabapentinoids are not allowed.

Anesthesia and Intraoperative Medication

- All subjects in Part A and Part B will receive a Mayo field block with 20 mL of 0.5% bupivacaine HCl after study drug administration (i.e., in the operating room immediately prior to surgical incision). The Mayo field block will be performed by the surgeon.
- All subjects will receive a dose of 1000 mg of IV acetaminophen at the time of surgical incision.
- IV fentanyl will be allowed for intraoperative pain control (at a dose not to exceed 1 μg/kg unless deemed medically necessary).

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 foot 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.

Study design is presented as a schematic diagram in Figure 1. Protocol schedule of events and procedures are presented in Table 1. PK and PD assessment schedule are presented in Table 2.

Figure 1. Schematic Representation of Study Design

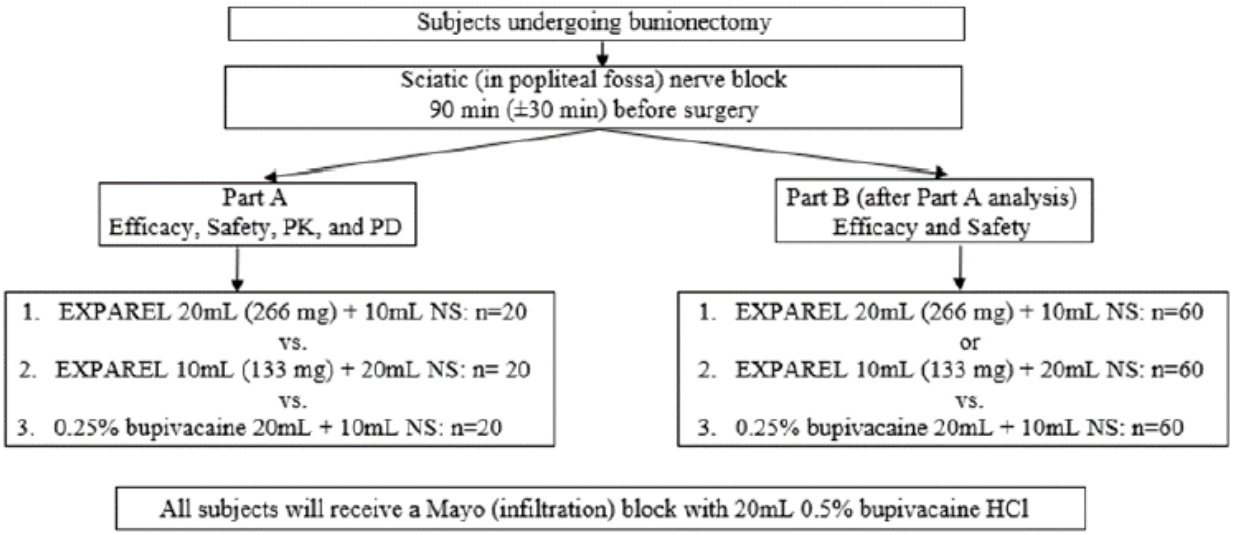

Table 1. Time and Events Schedule of Study Procedures (Screening Through POD 14)

	Screen-ing Visit[1]	Day of Surgery (Prior to Surgery)	OR	PACU	Time from End of Surgery (h)																120-168 ±3[2]	Health Care Facility Dis-charge[3]	POD 14 Call ±3 days
					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			
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 pre-op and post-op scheduled medications[7]		X	◄	----	----	►|																	
Capture ultrasound video for nerve block and send to sponsor		X																					
Administer Mayo field block			X																				
Record block start/end times[8]		X	X																				
Record surgery start and end times			X																				
Record intra-op medication administered			X																				
Record PACU time in and out				X																			

					Time from End of Surgery (h)																	
	Screening 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
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	X	
Record scheduled ***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 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; PO=by mouth/orally administered; 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 day the 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 Part A subjects only: A 12-lead EKG will be performed, and Vital sign will be measured and recorded at additional time points 120 (±3h), 144 (±3h), and at 168 (±3h).
3. Subjects in Part A and Part B will be discharged after 168 h and 96 h assessments, respectively.
4. Eligibility, prior medications, 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 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. Record all pre-operative and post-operative scheduled analgesic medication (celecoxib and acetaminophen).
8. Block to be administered 90 min (±30 min) prior to surgery.
9. The NRS pain intensity assessment should not be completed after any physical activity, including the motor block assessment. 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 h 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 Part A 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 (Part A 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 the 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 ankle 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 signs, 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 the 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 Windows 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 Section 10.2.2 Table 6.

Time Window for Opioid Pain Medication

This window (see Section 10.2.2 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 below provides the time window 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
0.25-hour	From 0-hour to 0.25-hour (inclusive)
1-hour	From 0.25-hour (exclusive) to 1.5-hour (inclusive)
2-hour	From 1.5-hour (exclusive) to 3-hour (inclusive)
6-hour	From 3-hour (exclusive) to 9-hour (inclusive)
12, 18, …q6h, …, 96-hour	From time point - 3 hour (exclusive) to time point + 3 hour (inclusive)
120-hour (Cohort 1 only)	From 99-hour (exclusive) to 132-hour (inclusive)
144-hour (Cohort 1 only)	From 132-hour (exclusive) to 156-hour (inclusive)
168-hour (Cohort 1 only)	From 156-hour (exclusive) to 180-hour (inclusive)

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 foot 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 foot 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 foot 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 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 (Part A only)

Blood samples for PK assessment will be obtained from subjects enrolled in Part A. 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 (Part A 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 – Lateral aspect of the lower leg (3-4 cm above ankle)
2. Distal – Sole of the foot

The intent of applying the tongue depressor to the contralateral foot is to establish a reference sensation to compare to the test area. The subject is to determine if the sensation on the contralateral foot 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 areas. 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 voluntary active movement of the foot. 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 partial or no foot movement. 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 complete foot movement. 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 Part A and Part B, and 120, 144, and 168 hours for Part A subjects.

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

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.

Pharmacokinetic Concentration (PKC) Analysis Set – This set will include all subjects enrolled in Part A 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 Part A 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 Part A 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. Opioid-free status from 0 to 96 hours post-surgery
3. Time to first opioid consumption post-surgery
4. Worst and average NRS pain intensity scores at 24, 48, 72, and 96 hours post-surgery

9.1.3. Exploratory Endpoints

[redacted]

[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 (Part A 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
- Apparent terminal elimination half-life ($t_{1/2el}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (V_d)

9.4. Pharmacodynamic (PD) Endpoints (Part A 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 Part, 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).

This study is comprised of two parts. Part A will enroll subjects into 3 treatment groups (EXPAREL 133 mg, EXPAREL 266 mg, and bupivacaine). Upon interim analysis when Part A is completed, one of the EXPAREL dose group will be dropped and the other EXPAREL dose group will be selected for the Part B cohort. The final CSR tables will pool subjects from both Part A and Part B cohorts. The summary statistics will be presented for the bupivacaine, the EXPAREL 133 mg, and the EXPAREL 266 mg groups, as well as the EXPAREL 133 and 266 mg combined group (for disposition, baseline characteristics and safety only). The statistical analysis for efficacy will only apply to the bupivacaine group and the selected EXPAREL dose group pooled from both parts.

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 if the subject is unable to tolerate oral oxycodone. 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 scores 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. Subjects from Part A and Part B will be pooled and presented.

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 all 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 all 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 all 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 all 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 Pooling Part A and Part B subjects. Simple summary statistics (e.g., mean, standard deviation, median, minimum, and maximum) will be presented for all 3 treatment groups. However, the statistical analysis (e.g., least square means, standard errors, the associated 95% confidence intervals, and the p-values) will be performed only for the select EXPAREL dose group for Part B and the bupivacaine group.

Unless specified otherwise, all confidence intervals will be 2-sided with 95% confidence. All hypothesis tests will be between the select EXPAREL dose group for Part B and the bupivacaine HCl group. All statistical comparisons will be 1-sided tests at an alpha level of 0.025.

10.5.1. Adjustments for 2-Stage Design and Multiplicity

Adjustment due to interim dose selection and 2-stage design (Chaturvedi et al 2014):

To control for the inflation in the overall Type-I error rate due to EXPAREL dose selection in the interim analysis, a closed testing procedure will be carried out for the hypotheses described below:

$$H_o^{(1)}: \theta_1 = 0$$
$$H_o^{(2)}: \theta_2 = 0$$
$$H_o^{(1,2)}: \theta_1 = \theta_2 = 0$$

where θ_i is the mean difference between EXPAREL dose group *i* and the bupivacaine control group. Without loss of generality, suppose dose group 1 is selected at the interim analysis. To declare statistical significance for dose group 1, both $H_o^{(1)}$ and $H_o^{(1,2)}$ will have to be rejected at level α. Applying the Simes testing procedure, the intersection hypothesis p-value at the interim analysis is derived as

$$p^{(1,2)} = min\ (2p^{(1)}, p^{(2)})$$

where $p^{(1)}$ and $p^{(2)}$ are the p-values for EXPAREL dose group 1 and dose group 2 at the interim analysis. It is assumed $p^{(1)} < p^{(2)}$ because $p^{(1)}$ is selected for Part B.

The inverse normal combination function (also known as the method of inverse normal p-values [MINP]),

$$C(p,q) = 1 - \emptyset\left[\sqrt{\frac{n_1}{n_1+n_2}}\emptyset^{-1}(1-p) + \sqrt{\frac{n_2}{n_1+n_2}}\emptyset^{-1}(1-q)\right]$$

will be used to combine the p-value from Part A and Part B to derive the final p-value, where $n_1 = 20$ and $n_2 = 60$ are the sample sizes and p and q are the p-values of Part A and Part B.

The final p-value, adjusting for multiplicity and 2-stage design, for the select EXPAREL dose group 1 is derived as follows

$$\text{p-value} = max\{C(p^{(1)}, q^{(1)}), C(p^{(1,2)}, q^{(1)})\}.$$

Note this MINP method will only apply to the primary efficacy endpoint.

Adjustment for multiplicity:

To control for the overall Type-I error rate for the multiple comparisons, 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 consumption 0-96 hours post-surgery)
3. Second secondary endpoint (opioid-free through 96 hours)
4. Third 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 foot 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 (at the dose selected for Part B) dose group and the bupivacaine HCl group. The superiority of EXPAREL to bupivacaine HCl 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 is not superior to bupivacaine HCl with respect to AUC of NRS pain intensity scores from 0 to 96 hours.
>
> H_a: EXPAREL is superior to bupivacaine HCl 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 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 – 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 NRS_{0-96} (EXPAREL– bupivacaine HCl only) is ≤0.025, then the superiority of EXPAREL to bupivacaine HCl is achieved.

To test for significant differences between the select EXPAREL dose group and the bupivacaine HCl group, an analysis of covariance (ANCOVA) model with main effect of treatment and covariate of 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;
      model aval=trtpn age / dist= normal link=identity;
      lsmestimate trtpn 'Group x vs Group 3' 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,

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

Because this is a 2-stage design with dose selection after Part A is completed, to prevent the inflation in the Type-I error rate, the ANCOVA model will be performed for Part A and Part B separately. The Simes multiple comparison procedure will be applied to the comparisons of the two EXPAREL dose groups to the bupivacaine group for Part A, and the inverse normal p-value method will be used to derive the final p-value for the select EXPAREL dose group compared to the bupivacaine group by combining the p-values from Part A and Part B (Section 10.5.1).

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 select EXPAREL and bupivacaine HCl 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 total opioid consumption. The LS means for the select EXPAREL and bupivacaine HCl groups, LS mean difference between the select EXPAREL 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 calculations 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. Opioid-free status through 96 hours Post-surgery

The percentage of opioid-free subjects through 96 hours post-surgery or PACU discharge, whichever is earlier, will be analyzed using the logistic regression model with treatment as main effect, and site and age as covariates. The percentage of opioid-free subjects from the model, odds ratio of select EXPAREL dose group over the bupivacaine HCl group and 95% CI for the odds ratio and p-value will be presented. The primary analysis will be performed based on the Efficacy Analysis Set.

Sample SAS code for logistic regression model follows.

```
ODS OUTPUT OddsRatios=or Diffs=diff(keep=probz) LSMeans=lsm ;
PROC LOGISTIC ;
  CLASS siteid trtpn / PARAM=glm ;
  MODEL avalc(EVENT="Y")=trtpn siteid age ;
  LSMEANS trtpn / DIFF ILINK ;
  ODDSRATIO trtpn ;
RUN ;
```

10.5.3.3. 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 the select EXPAREL group over the bupivacaine HCl group will be presented. Time to first opioid usage will also be analyzed by the Kaplan-Meier survival method for all treatment groups. Summary statistics for time to first postsurgical opioid consumption will be presented for all groups and the log-rank test comparing the select EXPAREL group and the bupivacaine HCl group 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-value will be reported for the Cox regression and two-sided p-value will be reported for the log-rank test.

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 X vs Grp 3' 1 -1 / UPPER ;
RUN ;
```

10.5.3.4. 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 (see Section 10.5.2).

10.5.3.5. Current pain intensity scores post-surgery through 96 hours

Current pain intensity collected 0 to 96 hours post-surgery will be summarized by treatment group in the Efficacy Analysis Set and analyzed for the treatment difference using ANCOVA at each scheduled time point. See Section 10.5.2 for model specification. This analysis will use the wWOCF-imputed pain intensity data set (see Section 10.2.2A).

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 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

$$[redacted]$$

[redacted]

[redacted]

$$[redacted]$$

[redacted]

[redacted]

CCI [redacted]

10.6. Pharmacokinetic Analysis

PK samples are collected from Part A subjects. Summary statistics for all 3 treatment gorups and analysis comparing the two EXPAREL groups against the bupivacaine HCl group will be presented.

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 dose groups, a 2-peak PK profile is expected based on the previous study results. Therefore, the following values will calcualted:
    - 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.

- Time to maximum concentration (T_{max}) is the time at which C_{max} is observed.
  - For EXPAREL
    - Early T_{max} – the time corresponding to Early C_{max}.
    - Late T_{max} – the time corresponding to Late C_{max}.
  - For bupivacaine HCl
    - T_{max} – time corresponding to C_{max}
- 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 (C_t).
  - 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 $(C_t/\lambda_z)/AUC_{0-\infty}$ 100%.
- Apparent clearance CL/F will be estimated as Dose/$AUC_{0-\infty}$, where Dose = 221.7 mg (100 mg [Mayo field block] × 0.8867 [salt to free base conversion for bupivacaine HCl] + 133 mg) and 354.7 mg (100 mg [Mayo field block] × 0.8867 + 266 mg) for subjects receiving EXPAREL 133 mg and 266 mg, respectively, and 44 mg (50 mg × 0.886) for subjects receiving 50 mg bupivacaine HCl.
- Apparent volume of distribution (V_d/F) will be estimated as $(CL/F)/\lambda_z$.

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-treated subject, these concentration values and PK parameters from such subjects with these values will be excluded from descriptive summaries.

10.7. Pharmacodynamic Analysis

PD data are collected from Part A subjects. Summary statistics for all three treatment gorups and analysis comparing the two EXPAREL groups against the bupivacaine HCl group will be presented.

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 10.5.5.1 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 of 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 Section 10.5.3.2. See Section 10.5.5.1 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

Safety data pooling from both Part A and Part B will be presented for all three treatment groups.

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 all subjects enrolled in Part A (approximately 20 in each of the 3 treatment arms) 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 select one of the two EXPAREL arms for Part B of the study and evaluate futility. Full details on the planned interim analysis will be covered in a prospective interim analysis plan (IAP).

11. SAMPLE SIZE CALCULATIONS

Assuming one of the EXPAREL arm will continue from Part A into Part B for the final analysis, the total sample size for Part A and B was calculated based on the primary outcome measure of AUC of NRS pain intensity scores from 0 to 96 hours. A sample size of 80 subjects per study arm (1:1 random allocation, 80 select EXPAREL dose group, and 80 Bupivacaine HCl group) provides at least 85% power to detect a treatment difference of 110 units in the AUC (SD=230) comparing EXPAREL arm with Bupivacaine HCl arm at one sided 0.025 significance level.

12. REFERENCES

Chaturvedi PR, Antonijevic Z, and Mehta C (2014). “Chapter 20. Practical Considerations for a Two-Stage Confirmatory Adaptive Clinical Trial Design and Its Implementation: ADVENT Trial.” In: He W, Pinheiro J, Kuznestsova PM (eds) Practical Considerations for Adaptive Trial Design and Implementation. Springer.