STATISTICAL ANALYSIS PLAN

A Phase 3, Randomized, Double Blinded, Active Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL, EXPAREL admixed with Bupivacaine HCl vs. Bupivacaine HCl Administered as Combined Sciatic (in popliteal fossa) and Saphenous (in adductor canal) Nerve Blocks for Postsurgical Analgesia in Subjects Undergoing Lower Extremity Surgeries

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TABLE OF CONTENTS

1.	LIST OF ABBREVIATIONS	5
2.	INTRODUCTION	6
3.	STUDY OBJECTIVES	6
3.1.	Primary Objective	6
3.2.	Secondary Objectives	6
4.	STUDY OVERVIEW	7
5.	DEFINITIONS	12
6.	STUDY ASSESSMENTS	15
6.1.	Efficacy Assessment	15
6.1.1.	Pain Intensity Assessment	15
6.1.2.	Opioid Dose Conversion	15
6.1.3.	Subject Satisfaction with Pain Management	16
6.1.4.	Postsurgical Breakthrough Pain Medication	16
6.2.	Pharmacokinetic assessments (Cohort 1 only)	17
6.3.	Pharmacodynamic Assessments (Cohort 1 only)	17
6.3.1.	Assessment of Sensory Block:	17
6.3.2.	Assessment of Motor Block:	18
6.4.	Change in the Study Design and Its Effect on the Statistical Analysis	19
7.	ANALYSIS SETS	19
8.	STUDY ENDPOINTS	19
8.1.	Efficacy Endpoints	19
8.1.1.	Primary Endpoint	20
8.1.2.	Secondary Endpoints	20
8.1.3.	Exploratory Endpoints	20
8.2.	Safety Endpoints	20
8.3.	Pharmacokinetic (PK) Endpoints (Cohort 1 only)	20
8.4.	Pharmacodynamic (PD) Endpoints (Cohort 1 only)	20
9.	METHODS OF STATISTICAL ANALYSIS	21
9.1.	General Principles	21
9.2.	Handling Missing Values	21
9.2.1.	Total Post-Surgical Opioid Consumption	21
9.2.2.	NRS Pain Intensity Scores	21
9.2.3.	Adverse Event or Concomitant Medications Dates or Times	24
9.2.4.	Adverse Event Severity or Relationship to Study Drug	25
9.2.5.	Time to Event	25
9.3.	Subject Disposition	25

9.4.	Description of Demographics and Baseline Characteristics	26
9.4.1.	Demographics	26
9.4.2.	Baseline Characteristics	26
9.4.3.	Medical and Surgical History	27
9.4.4.	Surgery Characteristics	27
9.4.5.	Intraoperative, Prior, and Concomitant Medications	27
9.4.6.	Measurements of Treatment Compliance	28
9.5.	Efficacy Analysis	28
9.5.1.	Primary Efficacy Endpoint	29
9.5.2.	Secondary Efficacy Endpoints	30
9.5.2.1.	Total postsurgical opioid consumption in oral morphine equivalents from 0 to 96 hours post-surgery comparing EXPAREL to 0.25% bupivacaine HCl	30
9.5.2.2.	Time to first postsurgical opioid consumption comparing EXPAREL to 0.25% bupivacaine HCl	31
9.5.2.3.	AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery comparing EXPAREL to EXPAREL admixed with 0.25% bupivacaine HCl	31
9.5.2.4.	Duration of the motor block comparing EXPAREL to EXPAREL admixed with 0.25% bupivacaine HCl (Cohort 1 only)	32
9.5.3.	Subgroup Analysis for the Primary and First Secondary Efficacy Endpoints	32
9.5.4.	Exploratory Endpoints	32
9.6.	Pharmacokinetic Analysis	33
9.6.1.	Pharmacokinetic Parameter Calculation Methods	33
9.6.2.	Pharmacokinetic Concentrations and Variables	35
9.7.	Pharmacodynamic Analysis	36
9.7.1.	Sensory Function	36
9.7.2.	Motor Function	36
9.8.	Safety Assessments	36
9.9.	Interim Analysis	38
10.	SAMPLE SIZE CALCULATIONS	39
11.	REFERENCES	39

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
CRF	Case report form
CSR	Clinical study report
CV	Coefficient of Variation
EMA	European Medicines Agency
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 durg
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	Table, listings and figures
NRS	Numerical rating scale
WHO-DD	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-333 titled "A Phase 3, Randomized, Double Blinded, Active Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL, EXPAREL admixed with 0.25% Bupivacaine HCl vs. 0.25% Bupivacaine HCl Administered as Combined Sciatic (in popliteal fossa) and Saphenous (in adductor canal) Nerve Blocks for Postsurgical Analgesia in Subjects Undergoing Lower Extremity Surgeries".

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-333 issued on 28 July 2020
- Protocol 402-C-333 Amendment 1 issued on 06 November 2020
- Electronic Case Report Form (eCRF) dated 11 November 2020

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. STUDY OBJECTIVES

3.1. Primary Objective

To compare the magnitude of the analgesic effect following a single dose injection of EXPAREL vs. 0.25% bupivacaine hydrochloride (HCl).

3.2. Secondary Objectives

- To compare the total opioid consumption (in oral morphine equivalents) from 0 to 96 hours following a single dose injection of EXPAREL vs. 0.25% bupivacaine HCl
- To compare the time to first opioid consumption following a single dose injection of EXPAREL vs. 0.25% bupivacaine HCl.
- To characterize and compare the magnitude of the duration of motor block following a single dose injection of EXPAREL vs. EXPAREL admixed with 0.25% bupivacaine HCl.
- To further assess the efficacy, safety, and pharmacokinetic (PK) profile of EXPAREL; EXPAREL admixed with 0.25% bupivacaine HCl and/or 0.25% bupivacaine HCl.

4. STUDY OVERVIEW

This is a Phase 3, multicenter, randomized, double blind, active controlled study in approximately 120 subjects undergoing lower extremity surgeries. This study will have 2 cohorts. Both cohorts will enroll in parallel.

Randomization

Cohort 1 will enroll about 60 subjects undergoing bunionectomy to obtain information on PK profile, PD, efficacy and safety. Subjects in this cohort will be randomized (1:1:1) to receive combined sciatic (in popliteal fossa) and saphenous (in the adductor canal) nerve block with EXPAREL, EXPAREL admixed with 0.25% bupivacaine HCl, or 0.25% bupivacaine HCl.

Cohort 2 will enroll about 60 subjects to obtain information on efficacy and safety. Subjects in this cohort will receive combined sciatic (in popliteal fossa) and saphenous (in the adductor canal) nerve block. Subjects will be randomized (1:1:1) to receive EXPAREL, EXPAREL admixed with 0.25% bupivacaine HCl, or 0.25% bupivacaine HCl, by stratifying by each surgery grouping.

Treatment

For both Cohorts 1 and 2, subjects randomized to the EXPAREL arm will receive 20 mL (266 mg) EXPAREL mixed with 20 mL saline; subjects randomized to EXPAREL admix arm will receive 20 mL (266 mg) EXPAREL admixed with 20 mL (50 mg) 0.25% bupivacaine HCl; subjects randomized to the 0.25% bupivacaine HCl arm will receive 40 mL (100 mg) 0.25% bupivacaine HCl.

Block Procedure

Subjects may be lightly sedated with 1 to 2 mg of midazolam intravenously (IV) before the block procedure. The study drug (EXPAREL, EXPAREL admixed with 0.25% bupivacaine HCl, or 0.25% bupivacaine HCl) will be administered under ultrasound guidance 90 min (±30 min) prior to surgery.

Breakthrough Pain Medication

All opioid and other analgesics administered post-surgery through post-operative day 14 (POD14) will be recorded.

For the initial treatment of breakthrough pain, subjects may receive acetaminophen or NSAIDs.

If the initial pain treatment (acetaminophen or NSAIDs) is insufficient for pain relief, immediate release PO oxycodone may 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, 10 mg oxycodone may be offered.

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.

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

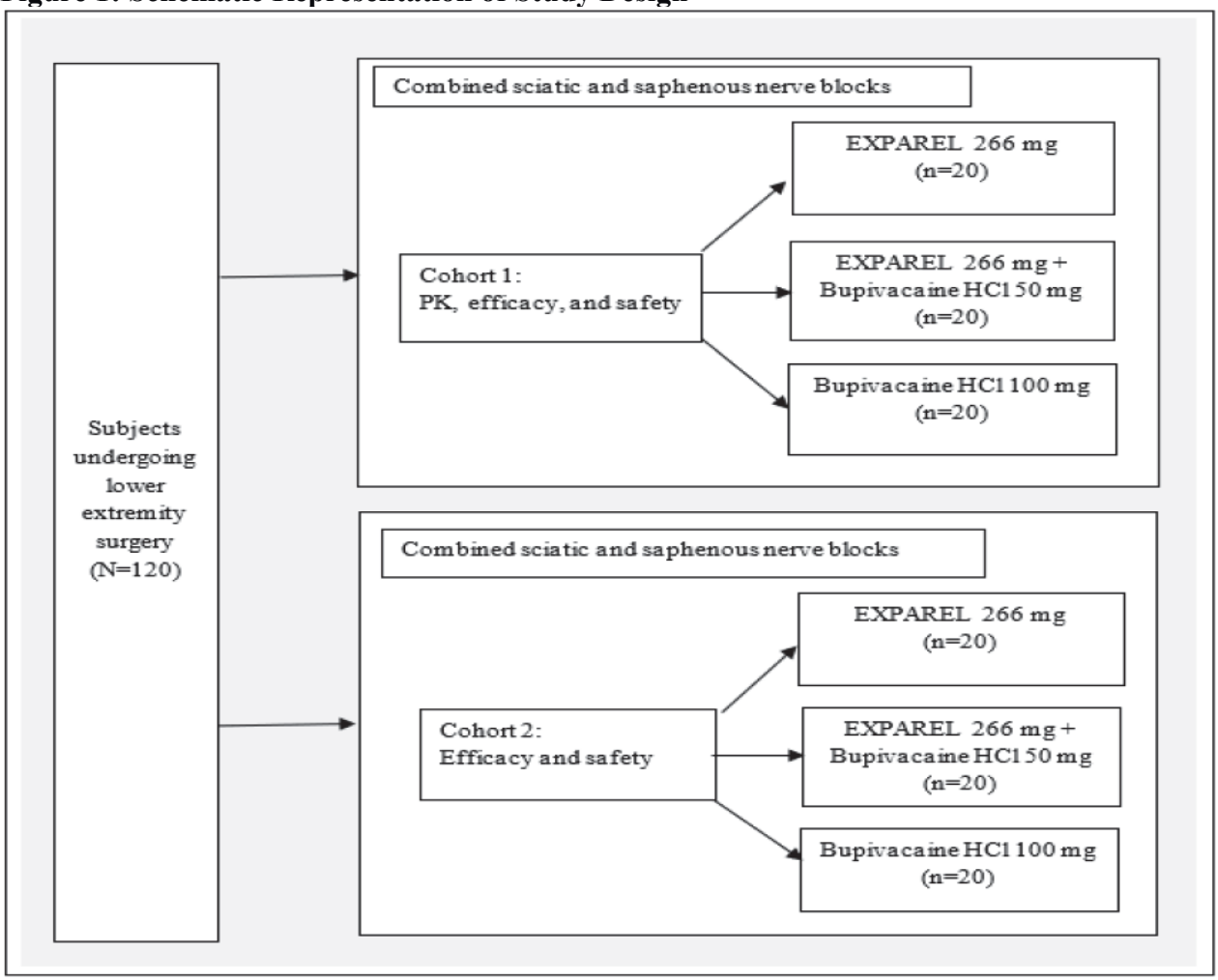

Table 1: Time and Events Schedule of Study Procedures (Screening Through Day 14)

	Screening Visit[1]	Day of Surgery Prior to Nerve Block	OR	PACU	Time from End of Surgery (h)																Health Care Facility Discharge[2]	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																				
Record medical/ surgical history*	X																					
Collect height/weight for BMI calculation*	X																					
Demographics and baseline characteristics*	X																					
Administer Pain Catastrophizing Scale	X																					
Record prior and concomitant medications	X	X		◄	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - ►	
Provide e-diary and explain expectations		X[3]																				
Urine pregnancy test for WOCBP[4]	X	X[3]																				
Record *worst* and *average* pain (NRS) in the last 30 days		X[3]																				
Randomize subject; prepare study drug.		X																				
Record block start/end times[5]		X																				
Record surgery start and end times			X																			
Record intra-op medication administered			X																			
Record PACU time in and out				X																		
Record **scheduled** NRS scores[6,7]				X[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

	Screening Visit[1]	Day of Surgery Prior to Nerve Block	OR	PACU	Time from End of Surgery (h)																Health Care Facility Discharge[2]	PO D 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		
Subject records *worst* and *average* NRS scores daily at 21:00 (±3 h) POD 1-14[6,7]								◄	-	-	-	-	-	-	-	-	-	-	-	-	-	►
Record **unscheduled** NRS immediately prior to breakthrough pain medication[7,8,9]				◄	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	►		
Record date, time, dose of breakthrough pain medication[8,9]				◄	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	►
Record day and time of HCF admission and discharge[1]		X																			X	
Record AEs/SAEs	◄	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	►
Remind subject to return e-diary																						X
Subject to record subject satisfaction questionnaire																				X		

Abbreviations: AE=adverse event; BMI=Body Mass Index; D=day; ED=Emergency Department; 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 30 days before scheduled surgery day

1. Subjects may be screened on the same day as health care facility admission/surgery or up to 30 days prior to surgery but eligibility should be re-confirmed on day of surgery and ample time must be allowed for the informed consent process. 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. Subjects in Cohort 1 and Cohort 2 will be discharged after 168 h and 96 h assessments, respectively. At discharge, subject should be re-instructed on duties with the e-diary.
3. Provision of e-diary to subject, urine pregnancy test, and score of worst and average pain score over the previous 30 days to be assessed prior to study drug administration. The diary may be activated during the screening period in order to perform set-up and training, but no data entry may occur in the e-diary before the day of surgery.
4. Pregnancy test should be re-confirmed on the day of surgery prior to study drug administration.
5. Block to be administered 90 min (±30 min) prior to surgery.
6. To assess pain intensity at rest, the subject should rest quietly in a supine or seated position that does not exacerbate his or her postsurgical pain for 5-10 minutes before entering the pain score using the NRS. This assessment should not be completed immediately following physical activity.

7. Pain scores (24 h recall) once daily (i.e., worst/average pain) will be collected at 21:00 (±3 hours) from POD 1 to POD 14. Pain scores (current pain) will be collected 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.
8. Breakthrough pain medication will be provided on a PRN basis in relation to the breakthrough pain intensity. Opioids should not be the first choice for pain relief, unless clinically indicated in the opinion of the Investigator, and should not be given on a schedule.
9. For the initial treatment of post-surgical pain, subjects may receive acetaminophen or NSAIDs without exceeding the maximum daily dose. If the initial pain treatment (acetaminophen or NSAIDs) is insufficient for pain relief, immediate release PO oxycodone may be offered in a stepwise approach: initial dose of 5 mg oxycodone will be offered; if the initial opioid dose is insufficient for pain relief, 10 mg oxycodone may be offered. 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.

Table 2: Pharmacokinetic and Pharmacodynamic Assessment Schedule (Cohort 1 bunionectomy 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	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess and record sensory and motor function[b,c]	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. Once offset of sensory and motor block are determined (in two consecutive evaluations), no subsequent assessments will be conducted. Sensory and motor are assessed independently.
c. When subject is in surgery, no sensory or motor block assessments be conducted.

5. DEFINITIONS

Start and End of Block

See Sections 6.3.1 and 6.3.2 for onset and offset of sensory block and motor block, respectively.

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 evaluation, Time 0 is defined as the date and time of the end of the study drug administration. For NRS pain collection and opioid consumption, 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.

Surgical Type

It is expected this study will enroll patients for bunionectomy, 1st metatarsophalangeal fusion, specific forefoot surgeries, midfoot fusion, hindfoot fusion, and total ankle arthroplasty. Due to overwhelmingly large number of bunionectomy patients enrolled as of this date, patients will be subgrouped into bunionectomy and non-bunionectomy for the purpose of by-subgroup summaries.

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.

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

Table below provides the time window for the NRS pain score for analysis. 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 equidistance the later will be chosen.

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

Scheduled Time of Collection	Time Window for Acceptable Actual Time of Collection
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 Window for Sensory and Motor Block Tests

Table below provides the time window for the sensory block and motor block summaries by timepoint (Sections 9.7.1 and 9.7.1).

Table 4. Time Window for the 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 on the same route and unit. The conversion factor is listed in Table 5.

Time Window for Opioid Pain Medication

This window (see Section 9.2.2 Table 6) captures the opioid analgesic effect from start of the opioid administration to the end of the opioid effect.

6. STUDY ASSESSMENTS

6.1. Efficacy Assessment

6.1.1. Pain Intensity Assessment

- Pain intensity scores measured using NRS as "How much pain are you experiencing right now?" * will be assessed as follows:
  - Upon arrival in the Post-Anesthesia Care Unit (PACU)
  - At 15-minute intervals in the PACU
  - At to PACU discharge
  - Every 6 hours from the end of surgery to 96 hours postsurgery as follows: 6 h, 12 h, 18 h, 24 h, 30 h, 36 h, 42 h, 48 h, 54 h, 60 h, 66 h, 72 h, 78 h, 84 h, 90 h, and 96 h.
  - Prior to administration of any pain medication until 96 hours post-surgery
- Pain intensity using the NRS once daily at 21:00 (±3 h) from POD 1 to POD 14 measured as "What was your **worst** pain in the last 24 hours?"
- Pain intensity using the NRS once daily at 21:00 (±3 h) from POD 1 to POD 14 measured as "What was your **average** pain 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.

6.1.2. Opioid Dose Conversion

Opioids dose will be converted to oral morphine equivalent dose (OMED mg) using the conversion factor in Table 5 for all summaries. Total opioid dose is the sum of all opioids in OMED taken during the time interval of interest.

Table 5. Conversion Factors to IV and 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

Table 5. Conversion Factors to IV and Oral Morphine Equivalent Dose from Other Opioids			
Medication	**Unit**	**Route**	**Oral Morphine Conversion (Multiplication) Factor**
Hydrocodone combination product - Vicodin, Norco, Lorcet, Lortab, hydrocodone-acetaminophen, Ketobemidone	mg	PO	1
Codeine combination product - Tylenol 3, acetaminophen-coedine, Paracetamol Forte, Tylenol 4	mg	PO	0.15
Ultram, Tramadol, Tramacol 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/Nallouphine (Nubain/Manfine)	mg	IV, IM, SC	3
PO = oral, IV = intravenous, IM = Intramuscular, SC = subcutaneous.			

6.1.3. 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 eleven-point Likert scale from zero (extremely dissatisfied) to 10 (extremely satisfied).

6.1.4. Postsurgical Breakthrough Pain Medication

All opioid and other analgesics (pain medications) administered post-surgery through POD 14 will be recorded. Analgesics will be administered based on the pain assessment as outlined below.

- For the initial treatment of post-surgical pain, subjects may receive either acetaminophen or NSAIDs without exceeding the maximum daily dose.
- If the initial pain treatment (acetaminophen or NSAIDs) is insufficient for pain relief, immediate release PO oxycodone may 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, 10 mg oxycodone may be offered.

- 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.

Post discharge, the subject will be provided with a prescription for oxycodone 5 mg. The subject may take acetaminophen, NSAIDs, or the prescribed oxycodone and will be given instructions on which medication to take PRN based on their pain intensity.

6.2. Pharmacokinetic assessments (Cohort 1 only)

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

6.3. Pharmacodynamic Assessments (Cohort 1 only)

Time of onset/offset is collected on the corresponding "PD Assessment – Onset/Offset Sensory/Motor Block" eCRF.

6.3.1. Assessment of Sensory Block:

Sensory function for the sciatic and saphenous nerve will be assessed independently using a wooden tongue depressor and ice. This assessment will evaluate light touch and cold sensation.

Sensory function assessment will include the following four locations:

1. Saphenous proximal - Medial aspect of the lower leg (3-4 cm below the knee)
2. Saphenous distal - Medial aspect of the lower leg (3-4 cm above ankle)
3. Sciatic proximal - Lateral aspect of the lower leg (3-4 cm above ankle)
4. Sciatic distal - Sole of the foot

The tongue depressor application and ice will be performed at predose, 15 min, 30 min, 45 min, 1 h, 2 h, 8 h, 12 h, 24 h, 30 h, 48 h, 60 h, 72 h, 84 h, 96 h, 120 h, 144 h, and 168 h hours from the end of the nerve block procedure, or until full sensory function has returned to baseline (pre-block) levels in two consecutive evaluations. 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.

Onset of sensory block (sciatic and saphenous nerve tracked independently) will be defined as the earliest timepoint with loss of EITHER light touch sensation OR cold sensation in EITHER proximal OR distal locations at any time. If onset time is not achieved, it will be considered censored at the last onset assessment time prior to surgery. **Offset of sensory block** (sciatic and saphenous nerve tracked independently) will be defined as recovery of BOTH light touch

sensation AND cold sensation in BOTH proximal and distal locations on two consecutive recovery assessments (excluding Not Done assessment). After offset of all sensory assessments are noted (on 2 consecutive assessments for all 4 locations), 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. If the patient's sensory block is recovered at the last assessment time (scheduled at 168 h or unscheduled post-168 h) without the second consecutive assessment to confirm, the sensory block is considered recovered at this last time point. **Duration of sensory block** will be defined as the time between onset and offset of the sensory blocks for each nerve individually. 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 9.5.2.4 for how the censoring is handled in the 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.

6.3.2. Assessment of Motor Block:

Motor function (onset and offset of motor block) will be assessed using the 2-point scale on the side of the block. This will be used to determine the onset and duration of motor blockade.

Motor function will be assessed using a 2-point scale. The motor function test will be performed at predose, 15 min, 30 min, 45 min, 1 h, 2 h, 8 h, 12 h, 24 h, 30 h, 48 h, 60 h, 72 h, 84 h, 96 h, 120 h, 144 h, and 168 h from end of block procedure, or until full motor function has returned to pre-dose levels in two consecutive evaluations. 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.

Onset of motor block will be defined as the earliest timepoint with 2-point score of 1- Partial or no foot movement as opposed to 0- Complete foot movement. If subject does not experience loss of motor, their onset will be censored at their last available motor assessment time point prior to surgery. **Offset of motor block** will be defined as resolution of motor block at foot, first time point of the two consecutive recovery assessments (score 0- complete foot movement) (excluding Not Done assessment). 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 (on 2 consecutive assessments), no subsequent assessments will be required. If the patient's motor block is recovered at the last assessment time (scheduled at 168 h or unscheduled post-168 h) without the second consecutive assessment to confirm, the motor block is considered recovered at this last time point. **Duration of motor block** will be 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.

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

Protocol version 1.0 (dated 28 July 2020) specified sensory function assessment by light touch. Six subjects enrolled under this version. Protocol Amendment 1 (dated 6 November 2020) adds cold sensation in the sensory function assessment. As such, six (6) subjects enrolled under Protocol v1.0 did not have cold sensation assessment. These 6 subjects will be excluded from the sensory block evaluation.

7. ANALYSIS SETS

The following study analysis sets are planned:

Safety Analysis Set - The safety analysis set will include all subjects who receive study drug. All analyses based on the safety 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. 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 excludes Subject (101-1013) who received non-randomized study drug and Subject (101-1167) who passed the screening, completed the study but later discovered the subject actually failed the screening (ie, met the screening exclusion criteria).

Pharmacokinetic Concentration (PKC) Analysis Set – This set will include all subjects in Cohort 1 who received study drug and have at least one post dose plasma concentration sample. PK concentration analysis will be based on the actual treatment subject 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. For example, Subjects 104-1020 and 103-1076 discontinued the PK sampling after 30-hour and 48-hour time points, respectively. They will be excluded from the PK Parameter analysis set. The final inclusion in the PK analysis set will be defined in the PK report. PK analysis will be based on the actual treatment subject received.

Pharmacodynamics (PD) Analysis Set - The PD analysis set will include all subjects in Cohort 1 who receive study drug and provide sufficient data to allow for calculation of PD parameters required for analysis. For example, the first 6 enrolled subjects who had light touch but no cold test will be excluded from the sensory block analysis. PD analysis will be based on the randomized treatment group.

8. STUDY ENDPOINTS

8.1. Efficacy Endpoints

8.1.1. 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 comparing EXPAREL to 0.25% bupivacaine HCl.

8.1.2. Secondary Endpoints

1. Total postsurgical opioid consumption in oral morphine equivalents from 0 to 96 hours post-surgery comparing EXPAREL to 0.25% bupivacaine HCl
2. Time to first postsurgical opioid consumption comparing EXPAREL to 0.25% bupivacaine HCl
3. AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery comparing EXPAREL to EXPAREL admixed with 0.25% bupivacaine HCl
4. Duration of the motor block comparing EXPAREL to EXPAREL admixed with 0.25% bupivacaine HCl (Cohort 1 only)
5. Proportion of opioid-free subjects through 24, 48, 72, and 96 hours from end of surgery

8.1.3. Exploratory Endpoints

1. Subject satisfaction as measured by International Pain Outcome (IPO) at 96 hours
2. AUC of "average" pain scores from POD1 through POD4 and POD1 through POD14
3. AUC of "worst" pain scores from POD1 through POD4 and POD1 through POD14
4. Current pain intensity scores post-surgery through 96 hours

8.2. Safety Endpoints

Safety endpoints will include the incidence of treatment-emergent AEs and SAEs from the start of block procedure through POD14.

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

The following model-predicted PK endpoints will be determined.

- Area under the plasma concentration-versus-time curve (AUC). Specifically $\mathbf{AUC_{0\text{-}last}}$ and $\mathbf{AUC_{0\text{-}\infty}}$
- Maximum plasma concentration (C_{max}) and time of C_{max} (T_{max}). Specifically Early and Late C_{max} and T_{max}
- The apparent terminal elimination half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution ($V_{d/F}$)

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

- Time to onset of sensory block and motor block

- Duration of the sensory block and motor block

9. METHODS OF STATISTICAL ANALYSIS

9.1. 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 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 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).

9.2. Handling Missing Values

9.2.1. Total Post-Surgical Opioid Consumption

For the calculation of the total postsurgical opioid consumption 0-96 hours, both opioid pain medication before hospital discharge and opioid pain medication in the daily diary after discharge will be included. If opioid is taken on the start of study drug administration day but time is missing, time will be imputed as end time of surgery plus (+1) 1 minute. If opioid is taken after the day of study drug administration and time is missing, it will be imputed as 00:00.

For the calculation of the total dose through 96 hours, if a subject's last follow-up time is 96-x hours, then the opioid that was taken between 96-2x 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.

9.2.2. NRS Pain Intensity Scores

Pain scores obtained during the opioid medication window will be replaced with the worst observation carried forward (wWOCF). For this study, the prescribed opioid pain medication

is oxycodone. However, morphine, hydromorphone, or other opioids may be used. The durations of the analgesic effect for various opioids are listed in Table 6.

Table 6: 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-coedine, Paracetamol Forte, Tylenol 4	PO	6 hours
Ultram, Tramadol, Tramacol 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 score 0-96 post-surgery, after applying the visit windows (Section 5 Table 3) and wWOCF to all scheduled/unscheduled pain scores, remaining missing data at each scheduled time point (6 h, 12 h , 18 h, 24 h, 30 h, 36 h, 42 h, 48 h, 54 h, 60 h, 66 h, 72 h , 78 h, 84 h, 90 h, and 96 h) will be imputed using the Rubin's (1987) multiple imputation procedure. This procedure replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute. The procedures of wWOCF and multiple imputation are described in the order as follows.

A. For subjects who take an opioid pain medication, their NRS scores recorded within the window of controlled type of opioid medication (see Table 6) 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. The NRS score at the time of opioid pain medication

administration will be included in this calculation. Note (1) the NRS score in the window that is higher than the worst value to be carried forward, this "higher" value will not be overwritten. Instead, the worst value will be replaced by this "higher" value and continue carrying forward until the end of the window. (2) if the scheduled NRS score within the window is missing, it will be imputed with this worst value.

B. After the wWOCF imputation described above, if there are still missing NRS scores at scheduled time points, they will be imputed using the multiple imputation procedures using the Markov Chain Monte Carlo (MCMC) method (Schafer 1997). This imputation will be carried out within each treatment group using SAS PROC MI. Thirty imputations will be conducted. To minimize the effect of data skewness on the imputation result, the NRS score is log-transformed [y=log(x+0.5), where y is the transformed score, x is the raw NRS score, and constant 0.5 is added to avoid log(0)] prior to the imputation and back-transformed after the imputation. In order to achieve the stationary distribution and to avoid dependency within samples generated by MCMC method, the number of iterations for the burn-in period will be set to 2000 and the number of iterations between two consecutive samples will be set to 1000.

   For the imputed NRS scores, the associated time will be assigned with the exact scheduled time, eg, 48.0 h.

   To better simulate the observed NRS pain score, all imputed scores will be rounded to become a number between 0.0 and 10.0 with 1 decimal place.

C. The AUC at various time intervals will be derived as described in Section 9.5.1 from the imputed NRS scores. For each subject, there will be 50 sets of AUC from the 50 imputed data sets.

D. The endpoints derived in Step C will be analyzed as described in Section 9.5.1 for each imputed data set.

E. Rubin's (1987) synthesizing procedure will be applied to synthesize analysis results from the 50 imputed data sets. SAS PROC MIANALYZE will be used for this analysis. The least squares mean (LSM) and standard error (SE) for each treatment group, and the LSM, SE, 95% CI and p-value for the between treatment difference in AUC will be computed from this analysis.

The SAS pseudo-code for multiple imputations and analysis is as follows.

```
** Step (b) uses MCMC method to create fully imputed data sets
** Note the value for the random seed is fixed to be 156799 so that the results are
reproducible, MIN=0 and MAX=10 are to bound the imputed VAS score within 0-10,
ROUND=0.1 is to round the imputed NRS score with 1 decimal place. The Box-Cox
transformation is to reduce the skewness of the data distribution **

proc mi data=adef seed=156799 nimpute=50 out=output_step1 min=0
max=10 round=0.1 minmaxiter=10000;
```

```
      by treatment;
      mcmc chain=multiple impute=full initial=em prior=jeffreys
      nbiter=2000 niter=1000;
      var t6 t12 t18 t24 t30 t36 t42 t48 t54 t60 t66 t72 t78 t84 t90
      t96 ;
      transform boxcox (t6 t12 t18 t24 t30 t36 t42 t48 t54 t60 t66
      t72 t78 t84 t90 t96 / c=0.5 lambda=0) ;* this is log(t+0.5)
      transformation ;
run;
```

** Step (c) calculates AUC for each subject in the imputed data set (with _IMPUTATION_ =1 to 50) **;

** Step (d) analyzes AUC using ANCOVA model for each imputed data set and derives LSM, SE for each treatment group and LSM, SE, and 95% CI for the between treatment difference **;

```
ods output Diffs=diff LSMeans=lsm ;
proc genmod data=auc1;
      by _imputation_;
      class trtpn siteid;
      model aval=trtpn siteid age height / dist= normal
      link=identity;
      lsmeans trtpn / diff cl alpha=0.05 ilink;
      ods output LSMeans=lsm;
      ods output Diffs=diff;
run;
```

** Step (e) synthesizes LSMs and SEs derived from the 50 imputed data sets ** ;

```
ods output ParameterEstimates=lsmdif ;
proc mianalyze data=diff alpha=0.05 ;
      modeleffects estimate ;
      stderr stderr ;
run ;

ods output ParameterEstimates=lsmeans ;
proc mianalyze data=lsm alpha=0.05 ;
      by trtpn ;
      modeleffects estimate ;
      stderr stderr ;
run ;
```

9.2.3. Adverse Event or Concomitant Medications Dates or Times

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 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 9.2.3 provides rules for the determination of prior or concomitant status.

9.2.4. 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.

9.2.5. 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 6.3.1 and 6.3.2 when the onset time or the offset time of sensory or motor block is not captured.

9.3. Subject Disposition

Subject disposition summaries will include the number (and %) of subjects by treatment group.

- Screened,
    - Screen failure
    - Enrolled (ie, randomized)
- Randomized

  - Randomized not treated
  - Randomized treated
- In the Safety analysis set
- In the Efficacy analysis set
- In the Pharmacokinetic analysis set
- In the Pharmacodynamics analysis set
- Protocol
  - Enrolled under each amendment
- Completed the study as planned
- Discontinued from the study
  - Reasons for discontinuation from the study

Percentages will be reported for the screen failures and enrolled using the number of subjects screened as the denominator; other percentages will use the number of subjects randomized and treated as denominator. All data will be presented as randomized, although analysis for Safety set (see Section 9.8) will be based on the actual treatment patients received.

9.4. Description of Demographics and Baseline Characteristics

9.4.1. Demographics

The summary of demographic data will present:

- Age (years) – descriptive statistics
- Sex – n (%)
- Ethnicity – n (%)
- Race – n (%)

Age is calculated at the date the subject signed the informed consent form. It is presented as the number of years rounding down to the nearest integer.

The demographic summary will present the data for each treatment group. Summaries will be provided for each (efficacy, safety, PK and PD) analysis set separately.

9.4.2. Baseline Characteristics

The summary of baseline characteristic data will present:

- American Society of Anesthesiologists (ASA) Classification – n (%)
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)
- **Average** and **Worst** pain intensity scores on the numeric rating scale (NRS) in the last 30 days

- Pain Catastrophizing Scale Total Score

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.

The Pain Catastrophizing Scale Total Score is the summation of the 13 questions.

Baseline characteristics summaries will present the data for each treatment group. Summaries will be provided for each (efficacy, safety, PK and PD) analysis set separately.

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

9.4.3. Medical and Surgical History

Subject medical and surgical history will be provided in a by treatment group and subject data listing.

9.4.4. Surgery Characteristics

Surgery characteristics including duration of surgery will be summarized using descriptive statistics. Summaries will be provided for each (efficacy and safety) analysis set.

Duration of surgery is calculated as the difference between the end of surgery and start of surgery times and reported in hours.

9.4.5. Intraoperative, Prior, and Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO Drug Dictionary Global September 2020 C3 Format) 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, 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 is Prior medication.
  - Otherwise, it is concomitant medication.
- If the medication stop date is completely missing, it is concomitant medication.

All medications will be summarized separately by category using n (%) of subjects for each treatment group and across treatment groups by ATC3 term and PT for the safety analysis set. Subjects may have more than one medication per ATC3 and PT. At each level of subject summarization, a subject will be counted once if one or more medications are reported by the same subject at that level.

All medications will be included in the data listing.

9.4.6. Measurements of Treatment Compliance

Study drug is administered by the site personnel; therefore, compliance is assumed.

9.5. Efficacy Analysis

For Primary and Secondary Efficacy Analyses, descriptive statistics that are appropriate for the efficacy variable will also be shown by surgical type, but no statistical analyses will be performed within a surgery type. All efficacy analyses will be performed using the Efficacy analysis set.

Unless specified otherwise, all confidence interval will be 2-sided with 95% confidence. All statistical comparison will be 2-sided at alpha=0.05 level. The leading statistical comparison is between EXPAREL and 0.25% bupivacaine HCl for the primary and first two secondary endpoints and between EXPAREL and EXPAREL admixed with 0.25% bupivacaine HCl for the third and fourth secondary endpoints, though all 3 pairwise comparisons (EXPAREL vs 0.25% bupivacaine HCl, EXPAREL vs EXPAREL admixed with 0.25% bupivacaine HCl, and EXPAREL admixed with 0.25% bupivacaine HCl vs 0.25% bupivacaine HCl) will be presented.

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. See also Section 8.1 for detail.

1. Primary endpoint: EXPAREL vs 0.25% bupivacaine HCl
2. First secondary endpoint: EXPAREL vs 0.25% bupivacaine HCl
3. Second secondary endpoint: EXPAREL vs 0.25% bupivacaine HCl
4. Third secondary endpoint: EXPAREL vs EXPAREL admixed with 0.25% bupivacaine HCl

5. Fourth secondary endpoint: EXPAREL vs EXPAREL admixed with 0.25% bupivacaine HCl

9.5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is AUC of the NRS pain intensity scores from 0 to 96 hours post-operation using Efficacy Analysis Set. The NRS pain intensity score is collected from the assessment "How much pain are you experiencing right now?" The worst and average daily pain scores are not included in the AUC calculation.

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 9.2.2). 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 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. It is the first time NRS score is collected.

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.

$AUC_{0\text{-}96}$ for pain intensity from 0 to 96 hours will be summarized by treatment group, by surgery type and overall.

Tests for the superiority of treatment effect of EXPAREL versus 0.25% bupivacaine HCl will be based on the following null hypotheses and alternative hypotheses using the Efficacy analysis set and multiple imputation method:

> H_O: EXPAREL is not different from 0.25% bupivacaine HCl with respect to AUC for pain intensity
>
> H_A: EXPAREL is superior to 0.25% bupivacaine HCl with respect to AUC for pain intensity

A two-sided hypothesis test will be performed at 5% level of significance comparing EXPAREL and 0.25% bupivacaine HCl as follows:

- If the upper bound of the 2-sided 95% confidence interval for the least square (LS) means for the difference of $AUC_{0\text{-}96}$ (EXPAREL) – $AUC_{0\text{-}96}$ (0.25% bupivacaine HCl) is ≥0, then superiority of EXPAREL to 0.25% bupivacaine HCl is not achieved.

- If the upper bound is <0 then declare that the superiority of EXPAREL to 0.25% bupivacaine HCl is achieved.

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,

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

To test for significant differences between EXPAREL and 0.25% bupivacaine HCl, an analysis of covariance (ANCOVA) model with main effects of treatment (EXPAREL, EXPAREL+0.25% bupivacaine HCl, and 0.25% bupivacaine HCl), and covariates of investigator site (categorical), age and height 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 p-value will be presented.

Due to multiple imputations for the missing pain scores (Section 9.2.2), 50 sets of $AUC_{0\text{-}96}$ will be generated for each subject. The average of these 50 sets of AUCs are the basis of the summary statistics. No Rubin's synthesizing method will be applied for the computations of these statistics. For the hypothesis tests and the least square mean computations, the synthesizing method will be used to account for the between imputation variability.

In addition to the above-described primary efficacy analysis, a 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, where AUC is calculated using all NRS pain score collected 0 – 96 h without imputation, and the time span is last NRS time minus the first NRS time for the AUC calculation.

Another sensitivity analysis will be carried out in the same way as the primary analysis but excluding the subject (101-1013) who received non-randomized study drug and the subject (101-1167) who passed the screening, completed the study but later discovered the subject actually met the exclusion criteria at the screening time.

9.5.2. Secondary Efficacy Endpoints

9.5.2.1. Total postsurgical opioid consumption in oral morphine equivalents from 0 to 96 hours post-surgery comparing EXPAREL to 0.25% bupivacaine HCl

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

To test for significant difference between EXPAREL and 0.25% bupivacaine HCl, an analysis of covariance (ANCOVA) model with treatment as main effect and investigator site (categorical), age, and height as covariates will be applied to the natural log-transformed total dose. The LS means for EXPAREL and 0.25% bupivacaine HCl, LS mean difference between

EXPAREL and 0.25% bupivacaine HCl, two-sided 95% CI for the LS mean difference, and the two-sided p-value 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 for the ANCOVA analysis using log-transformation.

In addition to the presentation for the between group difference, the percent reduction in total opioid consumption will also be presented similar to Section 9.5.1.

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

A sample SAS code is as follows.

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

Another sensitivity analysis will be carried out in the same way as for the primary analysis using ANCOVA but excluding two subjects described in Section 9.5.1.

9.5.2.2. Time to first postsurgical opioid consumption comparing EXPAREL to 0.25% bupivacaine HCl

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 have an opioid usage 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.

Time to first opioid usage will be analyzed by the Kaplan-Meier survival analysis. Median time and the log-rank test comparing EXPAREL and 0.25% bupivacaine HCl will be presented. The log-rank test will be stratified by the age and height group (Section 9.5.3). Cox proportional hazards regression with treatment (EXPAREL, EXPAREL admixed with 0.25% bupivacaine, and 0.25% bupivacaine HCl) as factors and categorical investigator site, continuous age and height as covariates will also be performed. 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.

9.5.2.3. AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery comparing EXPAREL to EXPAREL admixed with 0.25% bupivacaine HCl

To examine differences between EXPAREL and EXPAREL admixed with 0.25% bupivacaine HCl, the same ANCOVA model as for the primary efficacy endpoint will be used. The LS mean difference between EXPAREL and EXPAREL admixed with 0.25% bupivacaine HCl groups, and two-sided 95% CI for the LS mean difference will be presented.

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

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

9.5.2.4. Duration of the motor block comparing EXPAREL to EXPAREL admixed with 0.25% bupivacaine HCl (Cohort 1 only)

Duration of motor block will be analyzed by the Kaplan-Meier survival analysis. Although duration can be captured as left, right, or interval censored (Section 6.3.1), all these censored durations will be considered right censored for the programming purpose, because all these censoring implies that the actual duration is longer than the observed censored duration. Median time and the stratified log-rank test comparing EXPAREL and EXPAREL admixed with 0.25% bupivacaine HCl will be presented.

In addition to the presentation of the median, the ratio of EXPAREL to 0.25% bupivacaine HCl in motor duration median will be presented. The ratio is derived as follows,

$$\text{Ratio} = (\text{Median}_{\text{EXPAREL}}/\text{Median}_{\text{EXP+Bup}})$$

9.5.3. Subgroup Analysis for the Primary and First Secondary Efficacy Endpoints

The analysis of the primary and the first secondary endpoints will be repeated for select subgroups such as

- Age (<45, and ≥45),
- Sex
- Race (White and Non-White),
- BMI (<25, 25 to <30, and ≥30+ kg/m^2)
- Height (<165 cm, and ≥165 cm)
- Site
- Surgical Type

9.5.4. Exploratory Endpoints

Assessment of subject satisfaction with pain control using International Pain Outcome (IPO) at 96 hours will be summarized by treatment group.

Current pain intensity collected 0 to 96 hours post surgery will be summarized by treatment group and analyzed for between treatment difference using ANCOVA at each scheduled time point. See Section 9.5.1 for model specification. This analysis will use wWOCF-imputed pain intensity data set (see Section 9.2.2A).

"Average" and "worst" pain score over the last 24 hours will be summarized by treatment group daily from POD1 through POD14. They will also be analyzed each day using ANCOVA (see Section 9.5.1).

AUC of "average" and "worst" pain scores will be calculated for each subject from POD1 through POD4 and through POD14 using the ranctangular area method as follows.

$$AUC_{0-4} = \sum_{i=\text{POD1}}^{POD4} p_i \text{ and } AUC_{0-14} = \sum_{i=\text{POD1}}^{POD14} p_i$$

The ranctangular method is chosen because the pain score here is already a summary of the last 24 hours pain by the patient.

For patients with monotone missing, (ie, once missing, all the following days are missing), the last observation carried forward (LOCF) will be applied to impute the missing daily scores. For patients with intermittent missing, the missing daily scores are imputed as follows.

$$p_x = (p_y + p_z)\frac{x-y}{z-y},$$

where x is the day with missing pain score, y and z are the days with non-missing pain scores closest to but before and after Day x, respectively. As an example, suppose Day 2 and Day 3 are missing, but Day 1 and Day 4 are collected, Day 2 and Day 3 pain scores are imputed as follows.

$$p_2 = (p_1 + p_4)\frac{2-1}{4-1} = 1/3(p_1 + p_4),\ p_3 = (p_1 + p_4)\frac{3-1}{4-1} = 2/3(p_1 + p_4).$$

For subjects with missing score for the first a few days, the first observation will be carried backward for the missing daily scores. AUC of "average" and "worst" pain scores will be summarized by treatment group. The between group difference will be analyzed using ANCOVA similar to the sensitivity analysis for the primary efficacy endpoint (Section 9.5.1).

A listing of admission and discharge to the surgical facilitate and PACU, postsurgical and pain medications will be provided.

9.6. Pharmacokinetic Analysis

9.6.1. 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 analysis of the parameters.
- There will be no imputation of missing concentration data.

For the summaries of concentrations and for the NCA analysis of the 0.25% 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}) will be obtained directly from the concentration-time data.
    - Early C_{max} – occurring between dosing (0 h) 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.
    - Early T_{max} – the time corresponding to Early C_{max}.
    - Late T_{max} – the time corresponding to Late 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 (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.

- 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 $Dose/AUC_{0-\infty}$, where Dose = 266 mg for subjects receiving EXPAREL, 44 mg (50 mg × 0.886 [salt to free base conversion]) for subjects receiving 50 mg 0.25% bupivacaine, and 87 mg for subjects receive 100 mg 0.25% bupivacaine.
- Apparent volume of distribution (V_d/F) will be estimated as $(CL/F)/\lambda_z$.

9.6.2. Pharmacokinetic Concentrations and Variables

The analysis of the PK parameter will be based on the PK analysis set. The analysis of the PK concentration will be based on the Safety 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} will include: n, arithmetic mean, SD, geometric mean, %CV, median, minimum and maximum values. Descriptive statistics for T_{max} (early and late) 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, placed on the same page. 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 global C_{max} for the respective subjects, these concentration values and PK parameters from subjects with these values will be excluded from descriptive statistic summaries.

9.7. Pharmacodynamic Analysis

9.7.1. Sensory Function

Separately for sciatic and saphenous nerve, 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 9.5.2.2. See Section 9.5.2.4 for how to handle censoring time.

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

Additionally, mean PK concentration and % subjects with motor block "on" will be overlaid and plotted over time to show the dynamic relationship between the two for each of the 3 treatment groups.

9.7.2. 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 9.5.2.2. Cumulative subject incidence plot (1 – [minus] Kaplan-Meier curves) will also be presented.

The number (and %) of subjects with complete motor function and partial/no motor function will be tabulated by treatment group and timepoint. Missing assessment will be imputed by LOCF.

Additionally, PD plot similar to the one described in Section 9.7.1 will be created for the sciatic distal and saphenous distal sensory nerves.

9.8. Safety Assessments

Adverse events (AEs) and Serious AEs (SAEs) will be recorded from the time of informed consent through POD14.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 23.1). 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 POD 14±3 days.

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 %) 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 will be counted once in each of the above categories.

The subject incidence of all TEAEs will be tabulated by the number (and %) 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 purpose, 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. A summary of subjects reporting at least one TEAE during the study will also be presented.

- TEAEs by PT (Preferred Term) sorted by the decreasing order of subject incidence in the group combining EXPAREL and EXPAREL admixed with 0.25% bupivacaine HCl
- TEAEs by SOC (System Organ Class) 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 of special interest (TEAESI) by SOC and PT
- Non-Serious TEAE of special interest (TEAESI) by SOC and PT

A subject data listing will be provided for all adverse events. 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 subjects who die on study, experience SAEs, have TEAEs leading to study discontinuation, or AEs of special interest. A listing of the mapping of the SOC and PT to verbatim terms will be presented.

AE of special interest will be extracted based on the MedDRA terms below.

- 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

9.9. Interim Analysis

An unblinded efficacy interim analysis conducted by an independent committee will occur when approximately 60 subjects (20 in each arm) have been randomized, treated, and provided their primary efficacy outcome. An interim analysis will be conducted to evaluate and compare the clinical efficacy between EXAPREL only and 0.25% bupivacaine HCl only. Primary purpose of this interim analysis is to evaluate the sample size assumptions and evaluate futility. Full details on the planned or additional interim analysis will be covered in a separate prospective interim analysis plan.

10. SAMPLE SIZE CALCULATIONS

The sample size was calculated based on the primary efficacy endpoint of the AUC of the NRS pain intensity scores from 0 through 96 hours post-surgery comparing EXPAREL to 0.25% bupivacaine HCl.

The sample size for Cohort 1 was based on the number of subjects necessary to characterize the PK following administration.

Cohort 1 and Cohort 2 subjects will be combined within treatment groups for the efficacy and safety analyses; therefore, the overall sample size was based on the primary efficacy endpoint of the AUC of the NRS pain intensity scores from 0 through 96 hours post-surgery. Assuming a 2-sided 0.05 alpha, common standard deviation (SD) of 170 a sample size of 40 subjects for EXPAREL and 40 subjects for 0.25% bupivacaine HCl should have at least 90% power to detect a true difference of 150-units in the AUCs. Therefore, since Cohort 1 will have 60 subjects (20 EXAPREL, 20 EXPAREL admixed with 0.25% bupivacaine HCl and 20 0.25% bupivacaine HCl), Cohort 2 will need to enroll 60 subjects (20 EXAPREL, 20 EXPAREL admixed with 0.25% bupivacaine HCl and 20 0.25% bupivacaine HCl) to meet the total requirements.

11. REFERENCES

Rubin, DB. (1987). Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons.

Schafer, JL. (1997). Analysis of Incomplete Multivariate Data. New York: Chapman & Hall.