STATISTICAL ANALYSIS PLAN

A Multicenter, Randomized, Double-Blind, Controlled Study of EXPAREL for Postsurgical Pain Management in Subjects Undergoing Open Lumbar Spinal Fusion Surgery

Protocol No.:	402-C-409
IND No.:	69,198
Study Phase:	4
Study Drug:	EXPAREL (bupivacaine liposome injectable suspension)
Date/Version:	2 August 2017 (Amendment 2)
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1. SIGNATURE PAGE

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2. TABLE OF CONTENTS

3. LIST OF ACRONYMS/ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
ATC	Anatomical therapeutic class
AUC	Area under the curve
BMI	Body mass index
CRF	Case report form
CSR	Clinical study report
d	days
ECG	Electrocardiogram
EMA	European Medicines Agency
ER	Emergency room
FDA	Food and Drug Administration
FSH	Follical stimulating hormone
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
LIA	Local infiltration analgesia
LOS	Length of stay
MedDRA	Medical dictionary for regulatory affairs
min, m	minutes
MPADSS	Modified Post-Anesthesia Discharge Scoring System
n	Number of subjects
OBAS	Overall Benefit of Analgesia Score
OR	Operating room
PACU	Post-anesthesia care unit
PK	Pharmacokinetic(s)
PT	Preferred Term
NRS	Numeric rating scale
NRS-R	Numeric rating scale at rest
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
VAS	Visual analog scale
WHO-DD	World Health Organization – Drug Dictionary
WOCB	Women of child-bearing potential
yrs	years

INTRODUCTION

This is a Phase 4, Multicenter, Randomized, Double-Blind, Controlled Study of EXPAREL for Postsurgical Pain Management in Subjects Undergoing Open Lumbar Spinal Fusion Surgery. Approximately 194 adult subjects undergoing primary, 1-2 level, open lumbar spinal fusion surgery under general anesthesia are planned for enrollment, in order to have at least 184 evaluable subjects.
This study was prematurely terminated by the sponsor. At the time of termination, the study has enrolled and treated 38 subjects.
The purpose of this SAP is to outline how the collected data will be summarized and presented for the abbreviated study report.
This SAP is developed based on

- Protocol 402-C-409 Amendment 2 issued on 2 August 2017.
- CRF version 1.0 issued on 30 September 2016.

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.

4. STUDY OBJECTIVES

4.1. Primary Objective

The primary objective of this study is to compare postsurgical pain control following local infiltration analgesia (LIA) with EXPAREL admixed with bupivacaine HCl versus LIA with bupivacaine HCl in adult subjects undergoing open lumbar posterior spinal fusion surgery.

4.2. Secondary Objectives

The secondary objectives of this study are to compare additional efficacy, safety, and health economic outcomes following LIA with EXPAREL admixed with bupivacaine HCl versus LIA with bupivacaine HCl in adult subjects undergoing open lumbar posterior spinal fusion surgery.

5. STUDY OVERVIEW

Subjects were screened within 30 days prior to study drug administration and at least one day prior to surgery. During the screening visit, subjects were assessed for past or present neurologic, cardiac, and general medical conditions that in the opinion of the Investigator would preclude them from study participation. After the informed consent form (ICF) was signed, a medical history, surgical history, physical examination, 12-lead electrocardiogram (ECG), vital sign measurements, clinical laboratory evaluations, urine drug screen, alcohol breath test, and urine pregnancy test for women of childbearing potential were collected (see Time and Events Schedule of Study Procedures in Section 12).

Subjects were randomized 1:1 to two treatment groups and stratified by surgery level (1-Level or 2-Level). Subjects in Group 1 received LIA with EXPAREL admixed with bupiviaine HCl and subjects in Group 2 received LIA with bupivacaine HCl.

6. DEFINITIONS

Study Day

Study Day is calculated as the date of event minus the date of study drug administration plus one (1), if the date of event is on or after the date of study drug administration. Study Day equals the date of event minus the date of study drug administration if the date of event is before the date of study drug administration. Study days before the date of study drug administration will have negative values while those on or after the date of study drug administration are positive.

Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are AEs that occur after the administration of the study treatment through 30 days.

Time 0 (zero)

Time 0 is defined as the date and time of the start of study drug administration.

Study Baseline

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

7. ANALYSIS SET

All Subjects: all the listings presented in this SAP will be based on all randomized subjects, unless specified otherwise.

8. STATISTICAL METHODS

8.1. General Principles

Only listings of subject data collected during the study will be provided. All listings will be sorted by treatment group, site ID, subject ID, and, if applicable, collection date and time.

8.1.1. Handling Missing Values

Data will be included in the listing as is. No imputed values will be included in the listings. However, in order to provide the drug safety profile, the missing or partial date/time will be imputed only for the determination of treatment emergency or prior/concomitant status.

8.1.1.1. Study Drug Administration Date or Time

It is expected that all necessary information on study drug administration (start and stop date and time) will be complete. Any such information that is missing and cannot be obtained through

query resolution may be imputed, on a case-by-case basis, in a conservative manner that minimizes bias.

8.1.1.2. Adverse Event or Concomitant Medications Dates or Times

For AEs or concomitant medications with missing or partially missing start/stop date/time, the following imputation rules will be applied when determining AE treatment-emergent status or medication prior/concomitant status:

For partial start date/time:

- If the year is unknown, then the date will be assigned as the date and time of first dose of study treatment.
- If the month is unknown, then:
  - i) If the year matches the year of study drug administration, then the month and day will be imputed to be the date and time of the first dose of study treatment.
  - ii) Otherwise, 'January' will be assigned.
- If the day is unknown, then:
  - i) If the month and year match the month and year of the dose of the study drug administration date, then the day will be imputed to be the day of study drug administration date.
  - ii) Otherwise, '01' will be assigned.
- If the time is unknown, then:
  - i) If the date (day, month, and year) matches the date of administration of study drug, then the time will be imputed to be the time of dose of study drug date.
  - ii) Otherwise, '00:00' will be assigned.

8.2. Subject Disposition

A listing of subject disposition will be provided, which will include information on study completion status among others.

8.3. Demographics and Baseline Characteristics

8.3.1. Demographics

Listing of demographic data will include:

- Age (years)
- Sex
- Ethnicity
- Primary Race

Age is presented as collected.

8.3.2. Baseline Characteristics

Listing of baseline characteristic data will include:

- Height (cm)

- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)

The formula for BMI is $w/(h^2)$, where w is weight in kilograms and h is height in meters. 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. Height in centimeters will be converted to meters using the conversion factor of 100 centimeters to 1 meter.

8.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD Sept. 2016 Enhanced) and will be classified according to the anatomical therapeutic chemical (ATC) classification system term (Level 4) and preferred name.

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).

Listing of prior and concomitant medications will include subject identification, treatment group, ATC class term and preferred name among others.

8.5. Study Drug Exposure

A listing of study drug exposure, which includes volume of injection administered, will be provided.

8.6. Efficacy Analysis

Listing of the following efficacy assessments will be provided:

-Pain intensity scores using the VAS

-Pain Interference Scale (short form 6b)

-Opioid rescue analgesics consumption

-Treatment-emergent opioid-related AEs

-OBAS questionnaire at 24, 48, and 72 hours or upon hospital discharge

-Nurse's satisfaction with overall analgesia

-Modified Postanesthesia Discharge Scoring System (MPADSS) criteria for discharge readiness

8.7. Health Economic Outcomes

Listing of the following health economic outcomes assessments done during the study will be provided: hospital length of stay (LOS), hospital readmissions, use of skilled nursing facility, and use of other health services following hospital discharge.

8.8. Safety Analyses

8.8.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 19.1 or later).

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 through postsurgical Day 30. Cardiac AEs of special interest include chest pain (angina, myocardial infarction), abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles), and shortness of breath requiring intervention. Neurologic AEs of special interest include altered mental status/altered sensorium, rigidity, dysarthria, seizure, tremors, metallic taste, tinnitus, perioral numbness, visual disturbance, and severe or worsening dizziness. In addition, the following events are of special interest if they persist or occur beyond 72-hours postdose: dizziness, hyperesthesia, muscular twitching, and tingling/paresthesia.

If an AE has a partial onset date and time the 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).

A listing of all AEs will be provided, with a flag indicating TEAEs.

8.8.2. Vital Signs

Vital signs are resting heart rate (bpm), respiratory rate (beats per minute), oral body temperature (^{o}C), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg).

Listing of all vital signs collected at screening/Day 1 (pre-op) will be provided.

8.8.3. Electrocardiograms

Data listings for ECG parameters collected at screening will be provided. The investigator's overall interpretation will be included.

8.8.4. Physical examination

Listing of physical examination data collected at screening will be provided.

8.8.5. Clinical Laboratory

Listing of all clinical laboratory (hematology, chemistry, and urinalysis) tests collected at screening will be provided.

8.8.6. Other Analysis (urine drug screen, pregnancy test, alcohol breath test)

A data listing of these will be provided.

8.9. Pharmacokinetic Analysis

Drug concentrations are collected to assist the interpretation of adverse events. A data listing will be provided.

9. SAMPLE SIZE CALCULATIONS

The sample size was calculated based on VAS pain and total opioid results reported in Hughes et al (2016) and length of stay reported in the paper by Zheng et al (2002). Based on the reported efficacy for VAS pain intensity scores and assuming a 2-sided 0.05 alpha and a common SD of 70, a sample size of 50 subjects per treatment group should have at least 80% power to detect a 40-unit treatment difference. For total opioid consumption assuming a 2-sided 0.05 alpha and common standard deviation of the log-dose of 0.6 and 80% power a sample size of 64 subjects per treatment group is needed to detect a 30% difference in total opioid consumption through 48 hours. For length of stay assuming a 2-sided 0.05 alpha and common standard deviation of 2.4 and 80% power a sample size of 92 subjects per treatment group is needed to detect a 1 day difference in length of stay. Allowing for a 5% drop-outs rate a sample size of 97 subjects per treatment group should be enrolled to ensure 92 subjects provide length of stay data. A total study sample size of 184 evaluable subjects will provide 80% power to detect a 1-day difference in length of stay; 92% power to detect a 30% difference in total opioid consumption; and 97% power to detect a 40 point difference in VAS-$AUC_{(0\text{-}72)}$.

10. TIME AND EVENTS SCHEDULE OF STUDY PROCEDURES

Table 1. Time and Events Schedule of Study Procedures

	Screen Visit	D1 Preop	0 min	OR	PACU Arrival	4h	6h	8h	10h	12h	24h	28h	32h	36h	48h	52h	56h	60h	72h	D14 Visit	D30 Call
Time Window	Within 30 days					±15 min	±30 min	±30 min	±1h	±1h	±1h	±2h	±2h	±2h	±2h	±2h	±2h	±2h	±4h	±3d	±3d
Obtain signed ICF	X																				
Assess/confirm eligibility	X	X[a]																			
Record medical and surgical history	X	X[a]																			
Record demographics and baseline characteristics	X																				
Conduct pregnancy test for WOCBP	X	X[a]																			
Conduct urine drug screen	X	X[a]																			
Alcohol breath test	X																				
Perform physical examination	X																			X	
Measure vital signs (temperature, heart rate, respiratory rate and blood pressure)	X	X[a]																			
Clinical labs (direct bilirubin and either GGT and LDH or ALT and AST)	X																				
Perform 12-lead ECG	X																				
Record VAS pain intensity score[1,2,3,4]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Randomize subject, prepare study drug		X																			
Administer scheduled presurgical medications[5]		X																			
Administer study drug according to randomization schedule; record start and stop times			X																		
Record intraoperative opioids administered and doses				X																	
Record surgery start and stop times				X																	
Record times and doses of all opioid rescue medication administered					←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→
Administer scheduled postsurgical analgesics[1,6]					←	-	-	-	-	-	-	-	-	-	-	-	-	-	→		
Complete OBAS questionnaire[4]											X				X				X		
Nurse's satisfaction with postsurgical pain control[4]											X				X				X		
Pain Interference Scale		X																		X	
Record date and time of actual discharge															←	-	-	-	-	→	
Document any hospital readmissions																				X	X
Document use of skilled nursing facility																				X	X
Document any unscheduled phone calls or office visits related to pain after discharge																				X	X
Document any unscheduled visits to the ER after discharge																				X	X
Record prior and concomitant medications[7]	←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→
Record AEs (beginning at the time ICF is signed)[8]	←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→

Abbreviations: AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; d = day; D = day; ECG = electrocardiogram; ER = emergency room; GGT=Gamma-glutamyl transpeptidase; h = hours; ICF = informed consent form; LDH = lactate dehydrogenase; min = minutes; OBAS = overall benefit of analgesia score; OR = operating room; PACU = post-anesthesia care unit; Preop = preoperative; q12h = every 12 hours; VAS = visual analog scale; WOCBP = women of childbearing potential.

a: If the Screening Visit is conducted within 10 days of the date of surgery, the following Day-1 pre-op assessments are not required: assess/confirm eligibility; record medical and surgical history; conduct pregnancy test for WOCBP; conduct urine drug screen; and measure vital signs (temperature, heart rate, respiratory rate and blood pressure)

* Postsurgical assessments will be conducted at the timepoints specified after the end of surgery. All assessments conducted after baseline (ie, study drug administration) will be timed from the end of surgery, defined as the time of last suture/staple. **At timepoints when multiple assessments coincide, the VAS pain intensity assessment will be conducted first**.

1 Timepoints shown through 72 hours. Note: if discharge occurs before 72 hours, the study coordinator must stress to the patient the importance of completing the scheduled pain intensity assessments up to 72 hours. These assessments should be recorded by the patient in the patient log provided upon discharge.

2 The preoperative pain intensity assessment should be conducted prior to administration of any premedication.

3 Also record VAS pain intensity scores immediately prior to each administration of rescue pain medication, and just prior to hospital discharge.

4 And just prior to hospital discharge. Note: if discharge occurs before 72 hours, the study coordinator must stress to the patient the importance of completing the scheduled OBAS questionnaire up to 72 hours. Completion of the questionnaire should be recorded by the patient in the patient log provided upon discharge.

5 Administer presurgical analgesics (ie, acetaminophen 975-1000 mg orally (PO), celecoxib 200 mg PO [or naproxen 500 mg PO twice a day or meloxicam 7.5 mg PO once a day in case of allergy], and gabapentin up to 900 mg PO).

6 Administer scheduled post-surgical analgesics (ie, acetaminophen 975-1000 mg PO every 8 hours (q8h) [maximum of 3000 mg per day; acetaminophen IV can be used if the patient is unable to tolerate oral acetaminophen], celecoxib 200 mg PO every 12 hours up to 48 hours (q12h; or naproxen 500 mg PO twice a day or meloxicam 7.5 mg PO once a day in case of allergy), cyclobenzaprine 10 mgq8h, and gabapentin up to 900 mg PO q8h).

7 Instruct subject to discontinue prohibited medications. Record date and time of all medications starting at least 30 days prior to study drug administration until hospital discharge. Record medications administered for treatment of an AE through Day 30.

8 If a cardiac AE (eg, chest pain [angina, myocardial infarction], abnormal/irregular heart rate [bradycardia, tachycardia, extrasystoles], or shortness of breath), neurological AE (eg, altered mental status/altered sensorium, dizziness, dysarthria, hyperesthesia, metallic taste, peroral numbness, seizure, tinnitus, tremors, visual disturbance, muscular twitching or rigidity beyond 72 hours postdose, or tingling/paresthesia beyond 72 hours postdose), or serious AE (SAE) occurs during the study, a 12-lead ECG, vital signs, PK draw, and any appropriate clinical laboratory tests should be conducted as close as possible to when the event occurs.

11. TABLE OF CONTENTS FOR LISTING MOCK-UPS

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.1-7: Randomization – All Subjects

		Randomization					
Subject	Site Number	Date/ Day[1]	Time	Number	Treatment	Surgery type	Screw type
XXX-YYYY	XXX	yyyy-mm-dd/ xxx	hh:mm	XXXXX	XXXXXX	2-Level	pedicle

[1]Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_1-7.sas *DateTime*

Note to programmer: *Analysis set will by 'Y' if subject in set, blank otherwise.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.2-1: Subject Disposition – All Subjects

Treatment:

Subject	Informed Consent Date/ Day[1]	Randomization Date/ Day[1]	First Dose Date/ Day[1]	Last Visit Date/ Day[1]	End of Study Status	Primary Reason for Early Termination
XXX-YYYY	yyyy-mm-dd/ xxx	yyyy-mm-dd/ xxx	yyyy-mm-dd/ xxx	yyyy-mm-dd/ xxx	Completed	Study Terminated By Sponsor

[1]Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-1.sas *DateTime*

Note to programmer: *End of study status for subject who early terminated from the study is the primary reason for termination. If subject discontinued due to an AE then the reason should read 'ADVERSE EVENT, AE # X'. If subject discontinued due to death the reason should read 'DEATH ON DDMONYYYY'. For those reasons that also collected a specify text, concatenate into "Primary Reason" as "Other, Specify: ….".*

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Listing 16.2-2: Demographics – All Subjects

Treatment:

Subject	Subject Initials	Birth Date	Age (yrs)	Sex	Child Bearing Potential?	Primary Race	Ethnicity	ASA Class	Country
XXX-YYYY	AMZ	yyyy-mm-dd	XX	XXXXXX		XXXXXXXXXXXXXXXXXX	XXXXXXXXX		XXXXXXX

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-2.sas *DateTime*

Note to programmer: *If Primary Race is 'other' then Primary Race should be 'Other: other-specify-text'.*

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Listing 16.2-3: Baseline Characteristics – All Subjects

Treatment:

Subject	Date	Height (cm)	Weight (kg)	Body Mass Index (kg/m^2)
XXX-YYYY	yyyy-mm-ddThh:mm	XXX.X	XXX.X	XX.X

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-3.sas *DateTime*

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Listing 16.2-4: Protocol Deviation – All Subjects

Treatment:

Subject	Date of Deviation / Day[1]	Time of Deviation	Deviation Type	Deviation Description	Action Taken	If Other, specify
XXX-YYYY	yyyy-mm-dd/ xxx	Thh:mm	Study Drug Error	xxxxxxxxxxxxxxx	Staff Retraining	

[1]Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-4.sas *DateTime*

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Listing 16.2-5: Inclusion/Exclusion Criteria – All Subjects

Treatment:

Subject	Met all eligibility criteria?	Category	Criterion ID Failed	Protocol Version Enrolled under
XXX-YYYY	No	Exclusion		Original

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-5.sas *DateTime*

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Listing 16.2-6: Medical History - All Subjects

Treatment:

Subject ID	V: Verbatim Term S: System Organ Class[1] P: Preferred Term[1]	Start Date	Stop Date
xxx-xxxx xxx-xxxx	V: vvvvvvvvvvvvvvvvvvvvvvvvv S: sssssssssssssssssssssss P: pppppppppppppppppp	YYYY-MM-DD	YYYY-MM-DD
xxx-xxxx xxx-xxxx	V: vvvvvvvvvvvvvvvvvvvvvvvvv S: sssssssssssssssssssssss P: pppppppppppppppppp	YYYY	Ongoing
xxx-xxxx xxx-xxxx	V: vvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvv S: sssssssssssssssssssssssssssssssss P: ppppppppppppppppppppppppppp	YYYY-MM-DD	Ongoing
	V: vvvvvvvvvvvvvvvvvvvvvvvvv S: sssssssssssssssssssssssssssssssssssssss P: pppppppppppppppppp	YYYY-MM	Ongoing
xxx-xxxx	V: vvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvvv S: ssssssssss P: pppppppppppp	YYYY-MM-DD	YYYY-MM-DD

Programming note: For subjects with multiple records, present in the order of onset date.

[1] MedDRA vxx.x.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-6.sas
DateTime

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.2-7: Study Drug Exposure – All Subjects

Treatment:

Subject	Date/ Day[1]	Start Time	Stop Time	Total Volume (mL)
XXX-YYYY	yyyy-mm-dd/ xxx	HH:MM	HH:MM	XXX

[1]Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-7.sas *DateTime*

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Listing 16.2-8: Visits – All Subjects

Treatment:

Subject	Visit	Visit Date/ Day[1]
XXX-YYYY	Screening	yyyy-mm-dd/ xxx
	D1 (Preop)	yyyy-mm-dd/ xxx
	D14	yyyy-mm-dd/ xxx
	D30 Call	yyyy-mm-dd/ xxx
. . .	. . .	

[1]Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-8.sas *DateTime*

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Listing 16.2-9.1: Admission and Discharge - All Subjects

Treatment:

Subject	Date of admission to surgical facility/ Day[1]	Time of admission to surgical facility	Date of admission to PACU/ Day[1]	Time of admission to PACU	Date of discharge from surgical facility/ Day[1]	Time of discharge from surgical facility
XXX-YYYY	yyyy-mm-dd/ xxx	hh:mm	yyyy-mm-dd/ xxx	hh:mm	yyyy-mm-dd/ xxx	hh:mm
XXX-YYYY	yyyy-mm-dd/ xxx	hh:mm	yyyy-mm-dd/ xxx	hh:mm	yyyy-mm-dd/ xxx	hh:mm
XXX-YYYY	yyyy-mm-dd/ xxx	hh:mm	yyyy-mm-dd/ xxx	hh:mm	yyyy-mm-dd/ xxx	hh:mm
XXX-YYYY	yyyy-mm-dd/ xxx	hh:mm	yyyy-mm-dd/ xxx	hh:mm	yyyy-mm-dd/ xxx	hh:mm
. . .	. . .					

[1]Day = Visit date - first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date - first dose date.

Source: *list SAS datasets used to create table*

M:\402C409\production\programs\tlf\L16_2-9_1.sas *DateTime*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.2-9.2: Surgery – All Subjects

Treatment:

Subject	Date/ Day[1]	Start Time	End Time	Procedure Name	Level of Surgery	Surgery performed by	Total Incision Length	Type of Anesthesia	Intraoperative opioids administered?
XXX-YYYY	yyyy-mm-dd/ xxx	hh:mm	hh:mm					Other:xxx_specify_	No
XXX-YYYY	yyyy-mm-dd/ xxx	hh:mm	hh:mm						
XXX-YYYY	yyyy-mm-dd/ xxx	hh:mm	hh:mm						
XXX-YYYY	yyyy-mm-dd/ xxx	hh:mm	hh:mm						
. . .	. . .								

[1]Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-9_2.sas *DateTime*

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Listing 16.2-10: Pain Intensity - Visual Analog Scale – All Subjects
Treatment:

Subject	Date/ Day[1]	Timepoint	Time	Pain assessment [2]
XXX-YYYY	yyyy-mm-dd/ xxx	PACU Arrival	hh:mm	xxx
	yyyy-mm-dd/ xxx	4 Hours	hh:mm	xxx
	yyyy-mm-dd/ xxx	6 Hours	hh:mm	xxx
	yyyy-mm-dd/ xxx	8 Hours	hh:mm	xxx
	. . .	. . .		

. . .

[1]Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.
[2] How much pain are you experiencing right now (in VAS, cm)?

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-10.sas *DateTime*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.2-11: Pain Interference – All Subjects

Treatment:

Subject	Date/ Day[1]	Timepoint	Question	Response[2]
			In the past seven days,	
XXX-YYYY	yyyy-mm-dd/ xxx	24 Hours	1. How much did pain interfere with your enjoyment of life?	2
			2. How much did pain interfere with your ability to concentrate?	1
			3. How much did pain interfere with your day to day activities?	1
			4. How much did pain interfere with your enjoyment of recreational activities	4
			5. How much did pain interfere with doing your tasks away from home?	5
			6. How often did pain keep you from socializing with others?	3
. . .				

[1]Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.
[2] For questions 1 to 5, 1 = Not at all, 2 = A little bit, 3 = Somewhat, 4 = Quite a bit, 5 = Very much.
For question 6, 1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Often, 5 = Always.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-11.sas *DateTime*

Note to programmer: *Sort by date and time within subject.*

Continue for Timepoint = 48 Hours, 72 Hours

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.2-12: Discharge Readiness – All Subjects

Treatment:

Subject	Timepoint	Date/ Day[1]	Time	Vital Sign[2]	Ambu Lation[3]	Nausea and Vomiting[4]	Pain[4]	Surgical Bleeding[4]
XXX-YYYY	Day of Surgery	yyyy-mm-dd/ xxx	hh:mm	2	1	0	1	2

[1] Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.
[2] 2 = <=20% of preoperative value, 1 = 20%-40% of preoperative value, 0 = >40% of preoperative value
[3] 2 = Steady gait/no dizziness, 1 = With assistance, 0 = None/dizziness
[4] 2 = Minimal, 1 = Moderate, 0 = Severe

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-12.sas *DateTime*

Note to programmer:

Sort by date and time within subject.

Continue for Timepoint = Day 2 Morning, Day 2 Evening, Discharge

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.2-13: Nurse Satisfaction – All Subjects
Treatment:

Subject	Date/ Day[1]	Time	Timepoint	Nurse's Overall Satisfaction [2]
XXX-YYYY	yyyy-mm-dd/ xxx	hh:mm	24 Hours	2
. . .				

[1] Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.
[2] Nurse's overall satisfaction with the pain medication received after surgery:
1 = Extremely dissatisfied, 2 = Dissatisfied, 3 = Neither satisfied nor dissatisfied,
4 = Satisfied, 5 = Extremely satisfied

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-13.sas *DateTime*

Note to programmer:

Sort by date and time within subject.

Continue for Timepoint = 48 Hours, 72 Hours

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.2-14: OBAS Questionnaire – All Subjects

Treatment:

Subject	Date/ Day[1]	Time	Timepoint	Question	Response
XXX-YYYY	yyyy-mm-dd/ xxx	hh:mm	24 Hours	1. Was the OBAS Questionnaire Completed?	
				2. Please rate your current pain at rest	
				3. Please grade any distress and bother from vomiting in the past 24 h	
				4. Please grade any distress and bother from itching in the past 24 h	
				5. Please grade any distress and bother from sweating in the past 24 h	
				6. Please grade any distress and bother from freezing in the past 24 h	
				7. Please grade any distress and bother from dizziness in the past 24 h	
				8. How satisfied are you with your pain treatment during the past 24 h	
				9. Number of days in the Nursing Facility	
. . .					

[1]Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-14.sas *DateTime*

Note to programmer: *Sort by date and time within subject.*

Continue for Timepoint = 48 Hours, 72 Hours

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.2-15: Last Phone Call – All Subjects

Treatment:

Subject	Date/ Day[1]	Question	Response
XXX-YYYY	yyyy-mm-dd/ xxx	1. Was Day 29 Phone Call made to the subject?	Yes
		2. Were there any unscheduled pain-related calls since subject discharge?	Yes
		3. Number of pain-related phone calls	2
		4. Were there any unscheduled pain-related visits since subject discharge?	No
		5. Number of pain-related office visits	0
		6. Were there any Emergency Department Visits since subject discharge?	Yes
		7. Number of Emergency Department Visits	1
		8. Was there any Skilled Nursing Facility admission since subject discharge?	No
		9. Number of days in the Nursing Facility	0
		10. Was there any hospital readmission since subject discharge?	No
		11. Number of hospital readmission	0
. . .			

[1]Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-15.sas *DateTime*

Note to programmer: *Sort by date within subject.*

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Listing 16.2-16.1: All Adverse Events – All Subjects

Treatmernt:

Subject ID	Start Date/ Day[1]	Stop Date/ Day[1]	Duration (Day)[2]	TEAE	V: Verbatim S: System Organ Class[3] P: Preferred Term[3]	S: Severity R: Relationship SAE: Serious	F: Frequency A: Action Taken O: Outcome	I: AESI
xxxxx	YYYY-MM-DD/ XXX	YYYY-MM-DD/ XXX	XXX	Yes	V: vvvvvvvvvvvvvvvvvvvvvvvvv S: sssssssssssssssssssss P: ppppppppppppppppp	S: Moderate R: Not Related SAE: Death	F: xxx A: Hospitalization O: Fatal	
	YYYY-MM-DD/ XXX	YYYY-MM-DD/ XXX	XXX	Yes	V: vvvvvvvvvvvvvvvvvvvvvvvv S: sssssssssssssssssssssss P: pppppppppppppppppppppp	S: Mild R: Possible SAE: Life Threatening	F: xxx A: Study Drug Disc O: Recovered	
xxxxx	YYYY-MM-DD/ XXX	YYYY-MM-DD/ XXX	XXX	No	V: vvvvvvvvvvvvvvvvvv S: sssssssssssssssssssss P: pppppppppppppppppppppppp	S: Severe R: Probable SAE: Incapacity	F: xxx A: Nonpharm Therapy O: Recovered with Sequelae	
	YYYY-MM-DD/ XXX			Yes	V: vvvvvvvvvvvvvvvv S: sssssssssssssss P: pppppppppppppppppp	S: Severe R: Definite SAE: Hospital	F: xxx A: Other: xxx O: Not Recovered	

Programming instructions: Sort by Subject ID, then Start Date.

TEAE: Treatment-emergent AE (Yes=TEAE/No=Not TEAE)
[1] Day=event date – first dose date +1 if event occurred on/after first dose; Otherwise Day=event date – first dose date.
[2] Duration=Stop Date – Start Date +1.
[5] MedDRA version 19.0.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-16_1.sas *DateTime*

Note to programmer: *If AE is ongoing, put ONGOING in stop row. Do not split an AE across pages.*
Insert a page break between subjects.
Use this mock-up for the following listings:

Listing 16.2-16.2: All Serious Adverse Events – All Subjects

Listing 16.2-16.3: Treatment-emergent Serious Adverse Events – All Subjects
Listing 16.2-16.4: Treatment-emergent Serious Adverse Events leading to study discontinuation – All Subjects
Listing 16.2-16.5: Treatment-emergent Opioid-Related Adverse Events – All Subjects
Listing 16.2-16.6.1: Cardiac Treatment-emergent Adverse Events of Special Interest – All Subjects
Listing 16.2-16.6.2: Neurologic Treatment-emergent Adverse Events of Special Interest – All Subjects

Note:
Cardiac AEs of special interest include chest pain (angina, myocardial infarction), abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles), and shortness of breath requiring intervention. Neurologic AEs of special interest include altered mental status/altered sensorium, rigidity, dysarthria, seizure, tremors, metallic taste, tinnitus, perioral numbness, visual disturbance, and severe or worsening dizziness. In addition, the following events are of special interest if they persist or occur beyond 72-hours postdose: dizziness, hyperesthesia, muscular twitching, and tingling/paresthesia.

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Listing 16.2-17: Pharmacokinetics – All Subjects

Treatment:

Subject	Collection Date/ Day[1]	Collection Time	Vaule	Reason for PK Collection	If Other, Specify
XXX-YYYY	yyyy-mm-dd/ xxx	hh:mm	xxx	AE Special Interest	
		hh:mm	xxx	Other	xxxxxxxxxxxx
		hh:mm	xxx	SAE	
		hh:mm	xxx		
	. . .				
. . .					

[1]Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-17.sas *DateTime*

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Listing 16.2-18: Vital Signs Assessment – All Subjects
Treatment:

Subject	Date/ Day[1]	Time	Timepoint	Heart Rate (bpm)	Oral Temperature (°C)	Blood Pressure (mmHg)	
						Systolic	Diastolic
XXX-YYYY	yyyy-mm-dd/ xxx	hh:mm	Screening	XX	XX.X	XXX	XX
		hh:mm	Day 1 (Pre-op)	XX	XX.X	XXX	XX

[1]Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-18.sas *DateTime*

Note to programmer: *Sort by date and time within subject.*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409

Listing 16.2-19.1: Concomitant Medications – All Subjects

Treatment:

Subject ID	Start Date (day)[1] Stop Date (day)[1]	V: Verbatim D: Generic Name[2] C: Medication Class[2]	D: Dose & Unit R: Route & Form F: Frequency	Indication AE: AE number MH: Medical History
xxxxx	YYYY-MM-DD (XX) Continuing	V: mmmmmmmmmmmmmmmm D: nnnnnnnnnnnnnnn C: pppppppppppp	D: ddddddddd uuuuuuu R: rrrrrrrr F: ffffffff	AE: xx
xxxxx	YYYY-MM-DD (XX) YYYY-MM-DD (XX)	V: mmmmmmmmmmmmmmmm D: nnnnnnnnnnnnnnn C: pppppppppppp	D: ddddddddd uuuuuuu R: rrrrrrrr F: ffffffff	MH: Hypertension
	YYYY-MM-DD (XX) YYYY-MM-DD (XX)	V: mmmmmmmmmmmmmmmm D: nnnnnnnnnnnnnnn C: pppppppppppp	D: ddddddddd uuuuuuu R: rrrrrrrr F: ffffffff	Prophylactic
xxxxx	YYYY Continuing	V: mmmmmmmmmmmmmmmm D: nnnnnnnnnnnnnnn C: pppppppppppp	D: ddddddddd uuuuuuu R: rrrrrrrr F: ffffffff	aaaaa bbbbbb ccccc
	YYYY-MM Continuing	V: mmmmmmmmmmmmmmmm D: nnnnnnnnnnnnnnn C: pppppppppppp	D: ddddddddd uuuuuuu R: rrrrrrrr F: ffffffff	aaaaa bbbbbb ccccc

Programming note: Display 'Ongoing' for Stop Date if stop date is missing and the Ongoing tick box is checked. Within a subject, medications should be presented in order of earliest start date. Do not display day for incomplete dates. If Reason for Use is 'Prophylactic', display 'Prophylactic' in the respective Indication cell. If unit, route, and frequency is other, include other specify text

[1] Day = Medication date – First dose date + 1.
[2] Preferred Term and ATC4, WHODD version xxx.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-19_1.sas *DateTime*

Listing 16.2-19.2: Prior Medications – All Subjects

Replace foonote [1] with "Day = Medication date – First dose date"

Listing 16.2-19.3: Intraoperative Opioids – All Subjects

Listing 16.2-19.4: Rescue Medication – All Subjects

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.2-20: Electrocardiogram Findings – Investigator Assessment – All Subjects

Treatment:

Subject	Assessment Date/ Day[1]	Assessment Time	Visit	Finding	Specify
XXX-YYYY	yyyy-mm-dd/ xxx	hh:mm	Screening	Normal	
XXX-YYYY	yyyy-mm-dd/ xxx	hh:mm	Screening	Abormal-CS	xxxxxxxxxx

[1]Day=Visit date – first dose date +1 if Visit is on/after first dose date;
Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-20.sas *DateTime*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.2-21: Physical Examination – All Subjects

Treatment:

Subject	Visit	Assessment Date /Day[1]	Assessment time	Body System	Condition	Abnormality
XXX-YYYY	Screening	yyyy-mm-dd/ xxx	hh:mm	General Appearance	Normal	
				HEENT	Abnormal	L thyroid mass-2x3cm; immobile, nontender; NCS
				Cardiovascular	Normal	
				Bronchopulmonary	No Change	
				Abdomen/Gastrointestinal	Normal	
				Lymphatic	Normal	
				Musculoskeletal	Normal	
				Integumentary (skin, hair, nails, etc.)	Normal	
				Neurologic	Normal	
				Extremities	Normal	

[1]Day=Visit date – first dose date +1 if Visit is on/after first dose date;
Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-21.sas *DateTime*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.2-22: Urine Drug Screen – All Subjects
Treatment:

Subject	Timepoint	Date/	Day[1]	Time	Specimen Type	Result
XXX-YYYY	Screening	yyyy-mm-dd/	xxx	hh:mm	Urine	Negative

[1]Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-22.sas *DateTime*

Note to programmer:

Sort by date and time within subject.

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.2-23: pregnancy test for Women of Child Bearing Potential – All Subjects
Treatment:

Subject	Timepoint	Date/ Day[1]	Time	Specimen Type	Result
XXX-YYYY	Screening	yyyy-mm-dd/ xxx	hh:mm	Urine	Negative

[1]Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-23.sas *DateTime*

Note to programmer:

Sort by date and time within subject.

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-40

Listing 16.2-24: Clinical Laboratory Tests-Hematology – All Subjects

Treatment:

Subject ID	Parameter (Units)	Reference Range	Visit	Date / Day[1]	Result	Normal Range Indicator
XXX-YYYY	Hemoglobin (g/dL)	xxx – xxx	Screening	YYYY-MM-DD/-XX	XXXXXXXXX	Normal
	Hematocrit (%)	xxx – xxx	Screening	YYYY-MM-DD/-XX	XXXXXXXXX	High
	...					

Programming note: Order the lab parameters the same as shown in CRF. Any unscheduled lab results should be presented with scheduled data in date order. Number of decimal places for results should be as reported by the lab.

[1] Day = Visit date – first dose date +1 if Visit is on/after first dose; Otherwise Day=Visit date – first dose date.

Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-24.sas *DateTi*

Same shell for:

Listing 16.2-25: Clinical Laboratory Tests-Chemistry – All Subjects

Listing 16.2-26: Clinical Laboratory Tests-Urinalysis – All Subjects

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.2-27: Unique Adverse Events Terms and Associated Coded Terms

MedDRA Terms SOC Preferred Term	Verbatim(s)
SOC1	XXXXXXXXXXXXXXXXXXXXXXXXXX
PT1.1	XXXXXXXXXXXXXXXXXXXXXXXXXX
	XXXXXXXXXXXXXXXXXXXXXXXXXX
	XXXXXXXXXXXXXXXXXXXXXXXXXX
PT1.2	XXXXXXXXXXXXXXXXXXXXXXXXXX
	XXXXXXXXXXXXXXXXXXXXXXXXXX
SOC2	
PT2.1	XXXXXXXXXXXXXXXXXXXXXXXXXX
	XXXXXXXXXXXXXXXXXXXXXXXXXX

Coded using MedDRA
Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-27.sas *DateTime*

Note to programmer: *Sort by SOC and preferred term in alphabetical order*

Pacira Pharmaceuticals (Page X of Y) Protocol: 402-C-409
Listing 16.2-28: Unique Medication Terms and Associated Coded Terms

Who Drug Dictionary Terms ACT1 ACT2 ACT3 ACT4 Preferred name	Verbatim(s)
ATC1	
ATC1.2	
PN1.2.1	XXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXX
PN1.2.2	XXXXXXXXXXXXXXXXXXXXXXXXXX
ATC2	
ATC2.2	
ATC2.3	
ATC2.4	
PN2.2.3.4.1	XXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXX

Coded using Who Drug Dictionary
Source: *list SAS datasets used to create table*
M:\402C409\production\programs\tlf\L16_2-28.sas *DateTime*

Note to programmer: *Sort by ATC1, ATC2, ATC3, ATC4 and preferred name in alphabetical order*