Clinical Study Protocol

A Randomized, Single-Blind, Active-Controlled, Dose-Ranging Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Local Administration of DepoTXA for Reduced Postsurgical Bleeding in Subjects Undergoing Total Knee Arthroplasty
Amendment 2

Protocol No.:	404-C-201
EudraCT No.:	Not applicable
IND No.:	128950
Study Phase:	2
Study Drug:	DepoTXA
Date:	27-Sep-2017
Investigator(s) or Study Site(s):	Multicenter study in the US
Sponsor:	Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 Telephone: (973) 254-3560

1. SIGNATURE PAGE

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2. SYNOPSIS

Name of Sponsor/Company: Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 (973) 254-3560	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: DepoTXA		
Name of Active Ingredient: Tranexamic acid		

Title of Study: A Randomized, Single-Blind, Active-Controlled, Dose-Ranging Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Local Administration of DepoTXA for Reduced Postsurgical Bleeding in Subjects Undergoing Total Knee Arthroplasty

Principal Investigator(s): To be determined

Study Center(s): Multicenter study in the United States

Publications (Reference): None

Objectives:

Primary objective: The primary objective of this study is to evaluate the pharmacokinetics of DepoTXA compared to intravenous (IV) tranexamic acid (TXA).

Secondary objectives: The secondary objectives of this study are (1) to evaluate the safety of DepoTXA, (2) to evaluate the efficacy of DepoTXA (over 5 days) compared to IV TXA, and (3) to evaluate DepoTXA for a dose-related response at 800 and 1200 mg (33 mg/mL or 37 mg/mL, whichever formulation is available at the time of the study).

Methodology:

This is a Phase 2, randomized, single-blind, active-controlled dose-ranging study in patients scheduled to undergo total knee arthroplasty (TKA). Approximately 45 patients (15 per treatment group) are planned for enrollment. Patients will be randomized in a 1:1:1 ratio to receive either DepoTXA 800 mg, DepoTXA 1200 mg, or IV TXA (CYKLOKAPRON® 1 gram).

Screening

Patients will be screened within 30 days prior to surgery. During the screening visit, which must take place at least 1 day prior to surgery, patients will be assessed for any past or present medical conditions that, in the opinion of the Investigator, would preclude them from study participation. After the informed consent form (ICF) is signed, patient demographics and baseline characteristics will be recorded, and a medical/surgical history, concomitant medications, physical examination, knee flexion up to 90 degrees, timed-up-and-go (TUG) test, vital sign measurements, clinical laboratory tests (hematology [including hemoglobin and hematocrit], chemistry, and coagulation), neurological assessment, and urine pregnancy test for women of childbearing potential will be conducted..

Day 1 (Day of Surgery)

On Day 1 prior to surgery, the patient's eligibility for participation in the study will be confirmed, any adverse events (AEs) or changes to concomitant medications or medical/surgical history since screening will be recorded, vital signs will be measured, knee and thigh measurements (both legs) will be collected, and clinical laboratory tests (hematology [including hemoglobin and hematocrit], chemistry [with creatinine clearance calculation], and coagulation), a neurological assessment, a 12-lead ECG, numerical rating scale at rest (NRS-R; 0 [no pain] to 10 [worst possible pain]) pain score, and a urine pregnancy test for women of childbearing potential will be conducted. A pre-dose pharmacokinetics (PK) sample will be collected from all patients eligible for randomization.

Name of Sponsor/Company: Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 (973) 254-3560	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
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Qualified Investigators will use their standard technique (open) to perform the TKA. Drains are not permitted. Patients randomized to DepoTXA will receive a single dose of 800 or 1200 mg (33 mg/mL or 37 mg/mL, whichever formulation is available at the time of the study). DepoTXA will be administered by instillation into the joint space by injection through the capsular repair suture line via a catheter just prior to complete watertight capsular closure. Patients randomized to IV TXA will receive 1 gram of IV TXA at the end of surgery prior to tourniquet release or at the end of the surgery if a tourniquet is not used. The tourniquet pressure, if used, should be at least 20 mm Hg above systolic blood pressure. Blood transfusion will be indicated based on each individual institution's protocol. Each institution may follow its own routine venous thromboembolism (VTE) prophylaxis regimen. Additionally, each institution may follow its standard protocol for the control of postsurgical pain; however, patient-controlled analgesia is not permitted. Adverse events will be recorded from the time the ICF is signed through Day 60 (±3 days).

Patients will be required to remain in the research facility for at least 48 hours after study drug administration in order to undergo postsurgical assessments. After discharge, a nurse will visit the patients to conduct the postsurgical assessments through 120 hours. All patients will return for a follow-up visit on Day 7. A telephone call will be made to each patient on Day 14 (±1 day), Day 30 (±3 days) and Day 60 (±3 days) for AE assessments and to record whether the patient has achieved independent ambulation.

Postsurgical Efficacy Assessments

Postsurgical efficacy assessments will include measurement of blood loss (as assessed by hemoglobin [Hb] and hematocrit [Hct] levels), transfusion requirement, knee flexion to 90 degrees, timed up-and-go (TUG) test, numerical rating scale at rest (NRS-R; 0 [no pain]-10 [worst possible pain]) pain score, knee and thigh measurements, days to independent ambulation, and the surgical wound aspect score (SWAS; See Appendix 4).

Postsurgical Safety Assessments

Postsurgical safety assessments will include physical examination, vital signs, neurological assessment, clinical laboratory testing (hematology, chemistry, and coagulation), 12-lead ECGs, and AE monitoring. Patient monitoring will include, but not be limited to, changes in vision, neurologic function, or renal function; and occurrence of hematoma, wound dehiscence/disruption, surgical site infection (per Centers for Disease Control and Prevention definition), nausea, vomiting, and diarrhea.

Adverse events of special interest will include VTE or pulmonary embolism (PE), and oliguria. If an AE of special interest or serious AE (SAE) occurs during the study, an unscheduled PK blood sample must be collected. In addition, vital signs, the neurological assessment, and clinical laboratory tests must be conducted, as appropriate.

Pharmacokinetic Assessment

Blood samples (drawn into pediatric tubes to minimize blood loss) for PK analysis will be obtained at baseline (Day 1 pre-op, prior to study drug administration); at 5, 15, and 30 minutes; and at 1, 2, 4, 6, 8, 12, 16, and 24 hours after the end of study drug administration for all treatment groups. Additional blood samples will be collected at 36, 48, 60, 72, and 96 hours after the end of study drug administration for DepoTXA-treated patients. **It is important that blood draws for PK assessment be timed from the END of infusion of DepoTXA**.

Number of Subjects (Planned): Approximately 45 subjects (15 per treatment group) are planned for enrollment.

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Eligibility Criteria:

Inclusion Criteria:

1. Male or female, ≥18 years of age at screening.
2. Scheduled to undergo elective unilateral open TKA under general, spinal, or regional anesthesia.
3. Currently receiving anticoagulation or antiplatlet therapy for cardiovascular disease or thromboembolic risk.
4. American Society of Anesthesiology (ASA) physical status 1, 2, or 3.
5. Female patient must be surgically sterile; or at least 2 years postmenopausal; or have a monogamous partner who is surgically sterile; or practicing double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or using an insertable, injectable, or transdermal, contraceptive approved by the FDA for greater than 2 months prior to screening. All women of childbearing potential (ie, premenopausal without permanent sterilization) must commit to the use of an acceptable form of birth control for the duration of the study and for 30 days after completion of the study.
6. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

Exclusion Criteria:

1. Currently pregnant, nursing, or planning to become pregnant during the study or within 30 days after study drug administration.
2. Planned concurrent surgical procedure (eg, bilateral TKA).
3. Prior open knee surgery on ipsilateral knee. Prior arthroscopy is permitted.
4. Patients taking a medication with a known procoagulant effect (eg, combination hormonal contraceptives, Factor IX complex concentrates or anti-inhibitor coagulant concentrates, or all-trans retinoic acid).
5. Contraindication or hypersensitivity to TXA.
6. Known active intravascular clotting.
7. Prior subarachnoid hemorrhage.
8. History of epilepsy.
9. History of impaired kidney function, chronic respiratory disease, rheumatoid arthritis, congenital coagulopathy, or loss of sensation in extremities.
10. Renal insufficiency as indicated by serum creatinine >upper limit of normal (by central laboratory assessment).
11. Anemia (Hb level <10 g/dL).
12. Uncontrolled anxiety, psychiatric, or neurological disorder that might interfere with study assessments.
13. Acquired defective color vision.
14. Malignancy in the last 2 years, with the exception of non-metastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
15. Suspected or known history of drug or alcohol abuse within the previous year.
16. Body weight <50 kg (110 pounds) or a body mass index >44 kg/m^2.
17. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the patient's participation in this study.

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Test Product, Dose, Mode of Administration, and Lot Number:

Name: DepoTXA

Active Ingredient: TXA

Dosage: Single dose of 800 mg or 1200 mg (33 mg/mL or 37 mg/mL, whichever formulation is available at the time of the study) according to the randomization schedule.

Lot Number: To be determined.

Mode of Administration: Instillation

Meal Relationship: None

Reference Product, Dose, Mode of Administration, and Lot Number:

Name: CYKLOKAPRON (tranexamic acid injection solution)

Active Ingredient: TXA

Dosage: 1 gram.

Lot Number: To be determined.

Mode of Administration: IV. The IV dose (1 gram) is to be administered at 50 mg/min (ie, over 20 minutes).

Meal Relationship: None

Duration of Patient Participation in Study:

Participation will begin upon signing of the ICF. No more than 30 days should pass between signing the ICF and surgery. A follow-up telephone call will occur on Day 14 (±1 day) Day 30 (±3 days) and Day 60 (±3 days). Therefore, each patient may participate in the study for a maximum of 93 days.

Efficacy Assessments:

The following efficacy measurements will be conducted at the times specified after the beginning of study drug administration:

- Total blood loss as measured by Hb and Hct levels upon arrival at the post-anesthesia care unit (PACU) and at 6, 12, 24, 48, 72, and 120 hours, and Day 7.
- Transfusion requirements consistent with each institution's transfusion policy.
- Physical therapy assessment (TUG test) will be conducted once postsurgically on Day 1; at approximately 8:00 am and 8:00 pm (±2 hours) on Day 2 (ie, the day after surgery); at hospital discharge; and on Day 7 (see Appendix 1).
- Maximum passive and active knee flexion to 90 degrees twice daily at the time of the physical therapy assessment (ie, approximately 8:00 am and 8:00 pm [±2 hours] daily) until hospital discharge.
- Knee and thigh measurements on the morning of Day 2 (ie, the day after surgery), Day 3, and the Day-7 follow-up visit.
- NRS-R pain score (see Appendix 3; 0 [no pain] to 10 [worst possible pain]) upon arrival at the PACU; at each in-hospital vital sign assessment beginning with the 2-hour assessment and ending with the 72-hour assessment; on Day 3; and the Day-7 follow-up visit.
- Days to independent ambulation
- SWAS on the morning of Day 2 (ie, the day after surgery), Day 3, and on Day 7 (at the time of knee measurement; See Appendix 4)

Name of Sponsor/Company: Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 (973) 254-3560	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: DepoTXA		
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Efficacy Endpoints:

- Hb and Hct levels at baseline; upon arrival at the PACU; and at 6, 12, 24, 48, 72, and 120 hours.
- Incidence of transfusion (number of units, number of units/patient, number of patients transfused).
- Time to 90 degrees passive and active knee flexion.
- Time to complete TUG test.
- Change in knee and thigh measurements.
- Pain scores.

Pharmacokinetic Assessment:

Pharmacokinetic parameters will be estimated from plasma TXA measurements using non-compartmental analysis based on the sampling schedule of baseline (Day 1 pre-op, prior to study drug administration); at 5, 15, and 30 minutes; and at 1, 2, 4, 6, 8, 12, 16, and 24 hours after study drug administration for all treatment groups. Additional blood samples will be collected at 36, 48, 60, 72, and 96 hours after study drug administration for DepoTXA-treated patients.

Pharmacokinetic Endpoints:

The following PK parameters will be determined:

- Area under the plasma concentration-versus-time curve (AUC) from time 0 to the last collection time after drug administration ($AUC_{0\text{-}tlast}$).
- Area under the plasma concentration-versus-time curve from time 0 extrapolated to infinity after drug administration ($AUC_{0\text{-}\infty}$).
- Maximum plasma concentration (C_{max}).
- Time to maximum plasma concentration (T_{max}).
- The apparent terminal elimination rate constant (λ_z).
- The apparent terminal elimination half-life ($t_{1/2el}$).

Safety Assessments:

The following safety assessments will be conducted after the beginning of study drug administration:

- Presurgical 12-lead ECG and 12-lead ECGs at 1 hour (±15 minutes) and 12 (±2) hours after study drug administration.
- Physical examination at 48 hours.
- Vital signs (resting heart rate and blood pressure) at 5, 15, and 30 minutes, and at 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, and 96 hours after study drug administration.
- Neurological assessment at 12, 24, 36, 48, 60, 72, and 96 hours after study drug administration (see Appendix 2).
- Clinical laboratory testing (chemistry [including lipid profile], hematology, and coagulation [fibrinogen and fibrin split products]) at 48 hours and on Day 7 (see Appendix 5).
- Creatinine clearance calculation at 48 hours and Day 7.
- Reoperation due to hematoma or wound dehiscence.
- Adverse events through Day 60 (±3 days).

Name of Sponsor/Company: Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 (973) 254-3560	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: DepoTXA		
Name of Active Ingredient: Tranexamic acid		

Safety Endpoints:

- Change from baseline in vital signs at each assessed timepoint.
- Summary of neurological assessments (proportion of patients who are oriented, and proportion of patients who have any of the neurologic events) at each assessed timepoint.
- Change from baseline in clinical laboratory data at each assessed timepoint.
- Incidence of reoperation due to hematoma or wound dehiscence.
- Incidence of treatment-emergent AEs (TEAEs) and SAEs through Day 60 (±3 days).

Statistical Methods:

A comprehensive statistical analysis plan will be developed for this study. Demographic and baseline characteristics will be summarized descriptively by treatment group. Blood loss will be estimated using two methods. Efficacy of DepoTXA will be evaluated by each method. Dose response will be evaluated for both efficacy and PK. Safety endpoints will be summarized descriptively by treatment group.

Sample Size

Sample size was not based on statistical considerations.

Table 1. Time and Events Schedule of Study Procedures

	Screen Visit[1]	D1 Preop	OR	PACU Arrival	5 min	15 min	30 min	1h	2h	4h	6h	8h	12h	16h	24h	36h	48h	60h	72h	96h	120h	Day 7	D14 Call	D30 Call	D60 Call
Time Window	**Within 30 days**				**±2 min**	**±3 min**	**±5 min**	**±10 min**	**±15 min**	**±15 min**	**±15 min**	**±30 min**	**±30 min**	**±1h**	**±1h**	**±2h**	**±2h**	**±2h**	**±4h**	**±6h**	**±6h**	**±1d**	**±1d**	**±3d**	**±3d**
Obtain signed ICF	X																								
Assess/confirm eligibility	X	X																							
Record medical and surgical history	X	X																							
Record demographics and baseline characteristics	X																								
Conduct pregnancy test for WOCBP	X	X																							
Perform physical examination[14]	X																X								
Clinical labs (hematology, chemistry)[2]	X	X															X					X			
Coagulation (fibrinogen and fibrin split products)	X	X															X					X			
Creatinine clearance calculation[2]		X															X					X			
Hemoglobin and hematocrit[2]	X	X		X							X		X		X		X		X		X	X			
Perform neurological assessment[3]	X	X											X		X	X	X	X	X	X					
Perform 12-lead ECG recordings[4]		X						X[4]					X[4]												
Measure vital signs[5]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Collect NRS-R pain score		X		X					X	X	X	X	X	X	X	X	X		X			X			
Collect knee and thigh measurements[6]		X[6]															X[6]		X[6]			X[6]			
Assess surgical wound for SWAS parameters[7]																	X		X			X			
Collect PK blood sample from all treatment groups; record date and time[8,15]		X			X	X	X	X	X	X	X	X	X	X	X										
Collect additional PK blood samples for DepoTXA treatment groups; record date and time[15]																X	X	X	X	X					
Randomize patient, prepare study drug		X																							
Administer study drug			X																						
Record start and end time of tourniquet use and max pressure (mm Hg) used			X																						
Record surgery start and stop times			X																						
Perform knee flexion assessment[13]	X											◄----	----	----	----	----	----	----	----	----	►[11]				
Perform TUG test; record date and time[11]	X										◄----	----	----	----	----	----	----	----	----	----	►[11]	X			
Record date and time of discharge																	◄----	----	----	----	►[11]	►[11]			
Record any blood transfusion data (eg, start and stop times, units)				◄----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	►[11]	►[11]			
Record any reoperations due to hematoma or wound dehiscence				◄----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	►[11]	----	►[11]	
Record prior and concomitant medications[12]	◄----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	►[11]	----	►[11]	
Record whether patient has achieved independent ambulation																						◄----	----	►[11]	
Record AEs beginning at time ICF is signed[2,3,5,8,10]	◄----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	►[11]	

Abbreviations: AE = adverse event; d = day; D = day; ECG = electrocardiogram; h = hours; ICF = informed consent form; max = maximum; min = minutes; OR = operating room; PACU = post-anesthesia care unit; PK = pharmacokinetic; Preop = preoperative; TUG = timed up-and-go; WOCBP = women of childbearing potential.

* Postsurgical assessments will be conducted at the timepoints specified after the beginning of study drug administration.

[1] The screening visit must take place at least 1 day prior to surgery.

[2] Also conduct clinical laboratory tests if a patient experiences an AE of special interest or a serious AE (SAE), if appropriate; see footnote 10.

[3] Also conduct a neurological assessment if a patient experiences an AE of special interest or an SAE, if appropriate; see footnote 10.

[4] Postsurgical 12-lead ECGs will be performed at 1 hour (±15 minutes) and 12 (±2) hours after study drug administration

[5] Vital signs will be measured after the patient has rested in a supine position for at least 5 minutes. Also measure vital signs if a patient experiences an AE of special interest or an SAE, if appropriate; see footnote 10.

[6] Collect knee and thigh measurements of both legs on Day 1 pre-op and of the surgical leg only on the morning of Day 2 (ie, the day after surgery), Day 3, and Day 7.

[7] The surgical wound will be assessed for the SWAS parameters (wound oozing, erythema, ecchymosis, and blisters) at the time of knee measurements on the morning of Day 2 (ie, the day after surgery), Day 3, and on Day 7.

[8] Also collect a PK sample if a patient experiences an AE of special interest or an SAE; see footnote 10.

[9] Record date and time of all medications starting at least 30 days prior to study drug administration through 120 hours after study drug administration. Record medications administered for treatment of an AE through Day 60 (±3 days).

[10] Adverse events of special interest include VTE or PE, and oliguria. If an AE of special interest or serious AE (SAE) occurs during the study, an unscheduled PK blood sample must be collected. In addition, vital signs, the neurological assessment, and clinical laboratory tests should be conducted, as appropriate.

[11] Postsurgical "Timed Up-and-Go" will be assessed once on the day of the surgery following surgery; at approximately 8:00 am and 8:00 pm (±2 hours) on Day 2 (ie, the day after surgery); at hospital discharge; and on Day 7.

[12] Each institution may follow its standard protocol for the control of postsurgical pain; however, patient-controlled analgesia is not permitted.

[13] Maximum passive and active knee flexion to 90 degrees will be assessed twice daily at the time of the physical therapy assessment (ie, approximately 8:00 am and 8:00 pm [±2 hours] daily) until hospital discharge.

[14] Collect weight during the physical examination at screening

[15] **It is important that blood draws for PK assessment be timed from the END of infusion of DepoTXA.**

3. TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ACRONYMS/ABBREVIATIONS AND DEFINITIONS OF TERMS

4.1. List of Acronyms/Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ASA	American Society of Anesthesiologists
$AUC_{0\text{-}tlast}$	Area under the plasma concentration-versus-time curve from the time of administration to the time of the last quantifiable concentration
$AUC_{0\text{-}\infty}$	Area under the plasma concentration-versus-time curve from the time of administration extrapolated to infinity
BV	Blood volume
CFR	Code of Federal Regulations
cm	Centimeter
C_{max}	The maximum observed plasma concentration obtained directly from the experimental data without interpolation
CRF	Case report form
C_{tlast}	Time of the last quantifiable concentration
DVT	Deep vein thrombosis
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hb	Hemoglobin
Hct	Hematocrit
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
NRS-R	Numerical rating scale at rest
PCA	Patient-controlled analgesia
PACU	Post-anesthesia care unit
PE	Pulmonary embolism

4.1. List of Acronyms/Abbreviations

PI	Package insert
PK	Pharmacokinetic
PT	Preferred term
PTAE	Pretreatment adverse event
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SWAS	Surgical wound aspect score
TUG	Timed up-and-go
$t_{1/2el}$	The apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
TKA	Total knee arthroplasty
T_{max}	The time to maximum plasma concentration
TXA	Tranexamic acid
ULN	Upper limit of normal
US	United States of America
VTE	Venous thromboembolism
WHO	World Health Organization
λ_z	The apparent terminal elimination rate constant

4.2. Definition of Terms

Pharmacokinetic (PK) terms are defined in Section 12.4.

5. ETHICS

5.1. Institutional Review Board/Independent Ethics Committee

Prior to screening patients into this study, each study site will obtain the approval of an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that complies with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and/or the United States (US) Food and Drug Administration (FDA) Title 21 Code of Federal Regulations (CFR) Part 56. Attention is directed to the basic elements that are required to be incorporated into the informed consent form (ICF) under 21 CFR Part 50.25 and ICH GCP.

5.2. Ethical Conduct of the Study

This study will be conducted in accordance with the clinical research guidelines established by the FDA Title 21 CFR, Parts 50, 54, 56, and 312, and the ICH GCP. Study documents will be maintained in accordance with applicable regulations.

5.3. Patient Information and Consent

Before a patient undergoes any study-specific screening procedures, the Investigator or designee will thoroughly explain to the patient the purpose of the study, the associated procedures, and any expected effects and potential adverse reactions. A copy of the IRB- or IEC-approved ICF will be provided to the patient, who will be given sufficient time and opportunity to inquire about the details of the study and decide whether or not to participate. The patient, and the study staff with whom he or she discusses the ICF, will sign and date the ICF. A photocopy of the signed ICF will be given to the patient.

The Investigator will explain to the patient that he or she is completely free to decline entry into the study and may withdraw from the study at any time, for any reason, without risking his or her medical care. Similarly, the Investigator and/or Pacira Pharmaceuticals, Inc. (Pacira) is free to withdraw the patient at any time for safety or administrative reasons. Any other requirements necessary for the protection of the human rights of the patient will also be explained, according to the current ICH GCP (E6) and the Declaration of Helsinki (1964, and as amended through 2013).

6. INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

Information regarding the Investigators, sites, laboratories, and other service providers is available upon request to the IRB/IECs and regulatory agencies.

7. INTRODUCTION

Tranexamic acid (TXA) is a well-recognized antifibrinolytic that is marketed world-wide and used for a variety of clinical conditions where hemorrhage or significant blood loss and associated complications are a concern. In the US, LYSTEDA® (tranexamic acid) tablets are approved for the treatment of cyclic heavy menstrual bleeding, and CYKLOKAPRON® (tranexamic acid injection) is approved for short-term use in patients with hemophilia to reduce

or prevent hemorrhage and to reduce the need for replacement therapy during and following tooth extraction (LYSTEDA package insert [PI]; CYKLOKAPRON PI).

During the 18th Expert Committee on the Selection and Use of Essential Medicines by the World Health Organization (WHO), the Committee agreed in March 2011 to the addition of TXA injection to the Model List of Essential Medicines for the treatment of adult patients with trauma and significant risk of ongoing hemorrhage. The Committee concluded that there is sufficient evidence to support the proposal that listing TXA may contribute to a reduction in trauma-related deaths.

Based upon the WHO recommendation and published literature, off-label use of TXA to reduce blood loss in a variety of postsurgical settings is widespread. This trend has been seen in the US as evidenced by the clinical practice guidelines finalized in December 2015 for the American Academy of Orthopedic Surgeons, which concluded that there is strong evidence to support that, in patients with no known contraindications, treatment with TXA decreases postsurgical blood loss and reduces the necessity of postsurgical transfusions following total knee arthroplasty (TKA).

Patients undergoing TKA are at an increased risk of postsurgical bleeding. In a survey from Maniar (2012), estimated blood losses reported for TKA ranged from 800 to 1800 mL. Such blood loss may have a negative impact on patient recovery. In regard to the need for transfusion, Seo (2013) reported that 10 to 38% of patients undergoing TKA or hip replacement surgery required 1 to 2 units of blood. However, a study of patients undergoing TKA and receiving TXA or placebo with a well-established blood conservation program, showed that relatively few patients require allogeneic transfusion (approximately 2.2% of TXA-treated patients and 12% of placebo-treated patients; Álvarez, 2008) when such a program is incorporated (note that in this study the percentage of patients in each treatment group receiving reinfusion of blood recovered from drains was 4% and 73%, respectively). Allogeneic transfusion carries risks of immunological reaction and the transmission of disease and, thus, is avoided when possible. The application of a pneumatic tourniquet during surgery may also decrease intra-operative blood loss, but trauma induces fibrinolysis, and release of the tourniquet may contribute to postsurgical bleeding (Fahmy, 1981; Burkart, 1994).

The DepoFoam® drug delivery system is a proprietary, injectable technology that provides a sustained release of therapeutic compounds. The DepoFoam system consists of microscopic, spherical, lipid-based particles composed of numerous non-concentric, aqueous chambers containing the drug in solution. Each chamber in this multivesicular liposome is separated from adjacent chambers by lipid membranes. The DepoFoam particle components are naturally occurring or synthetic analogues of common lipids.

DepoTXA is a DepoFoam-based product containing encapsulated TXA, and is intended to prolong the delivery of TXA locally (at the surgical site), thereby enhancing its efficacy in the reduction of postoperative hemorrhage.

7.1. Summary of Nonclinical Studies of DepoTXA

7.1.1. Summary of Nonclinical DepoTXA Studies

The toxicology studies completed to support the local and systemic safety of the DepoTXA product include the following:

1. A subcutaneous single-dose local tolerability study in rats
2. A surgical wound instillation single-dose local tolerance study in dogs
3. A subcutaneous 14-day (4-dose) study evaluating both local and systemic safety in dogs.

In all toxicology studies, TXA was present in the DepoTXA formulation at a concentration of approximately 40 mg/mL, with an equal amount of TXA on the inside and outside of the DepoTXA particles. The concentration of TXA in the DepoTXA formulation evaluated is similar to the initial clinical formulation (33 mg/mL, with an approximately equal amount of TXA on the inside and outside of the particles [encapsulated in DepoFoam and unencapsulated, respectively]). The dog was selected as the most appropriate nonclinical species for the bridging toxicity studies because of dose volume limitations in the rat. Toxicokinetics were studied in the surgical single-dose and subcutaneous multiple-dose dog studies to compare systemic exposure following the administration of TXA alone vs. DepoTXA.

In the dog studies, both reference TXA and DepoTXA were well tolerated both locally and systemically at doses up to 120 mg/kg. The only compound-related findings were local inflammation associated with TXA and granulomatous infiltration at the administration site observed with DepoTXA. Both of the observed local inflammatory findings were minimal to moderate in severity, displayed reversibility, and were not considered adverse. The granulomatous infiltration is thought to be associated with the clearance of excess lipid and has been commonly observed in toxicology studies with the other approved products utilizing the DepoFoam formulation. The high dose of 120 mg/kg TXA evaluated in the dog represented the maximum feasible dose based on the formulation and dose volume. In both dog studies, the mean values for terminal elimination half-life ($t_{1/2}$) were roughly equivalent for DepoTXA vs. the reference TXA, but there was a notable difference with respect to mean residence time (MRT; defined as the average time drug resides in a compartment before being eliminated). The average MRT for the DepoTXA groups at 120 mg/kg was approximately 2 to 2.6-fold greater than the average MRT for the reference TXA group. As MRT describes the average amount of time that a molecule of drug is in the systemic circulation and takes into account the totality of the plasma concentration vs. time data, this increase in MRT indicates that the DepoTXA formulation functions as it was designed.

In conjunction with (a) historical nonclinical studies demonstrating no biologically significant microscopic changes considered to be related to DepoFoam (alone) in the joint area of rabbits or dogs, and (b) clinical studies demonstrating that instillation of TXA in solution into the joint space of humans undergoing TKA is safe and effective (Shemshaki 2015, Wang 2015b, Yue 2015, Zhang 2014), the results of the nonclinical studies summarized here are sufficient

justification for testing of DepoTXA via instillation into the joint space in humans undergoing TKA.

7.1.2. Safety Margins

The recommended dose regimen for LYSTEDA is 1.3 grams orally, 3 times per day for up to 5 days per month (which represents a total daily dose of 3.9 grams/day). The recommended dose regimen for CYKLOKAPRON is 10 mg/kg (700 mg for a 70 kg person), IV, up to 4 times per day (the total recommended daily dose is 2.8 grams/day) for 2 to 8 days.

Refer to Section 11.4.1 for the rationale behind the IV dose of 1 gram selected for the comparator treatment group in this study.

The TXA 120 mg/kg high dose evaluated in the dog is 6-fold higher than the maximum TXA dose of 1200 mg in this first-time-in human DepoTXA Phase 2 study. In addition, the 120 mg/kg high dose evaluated in the dog studies is 12-fold higher than the approved 10 mg/kg IV dose of CYKLOKAPRON and 6-fold higher than the approved 20 mg/kg oral dose of LYSTEDA.

7.2. Relevant Clinical Studies of TXA in Humans

Relevant published clinical studies of TXA in humans are discussed in Section 11.4.

8. OBJECTIVES

8.1. Primary Objectives

The primary objective of this study is to evaluate the pharmacokinetics of DepoTXA compared to intravenous (IV) TXA.

8.2. Secondary Objectives

The secondary objectives of this study are (1) to evaluate the safety of DepoTXA, (2) to evaluate the efficacy of DepoTXA (over 5 days) compared to IV TXA, and (3) to evaluate DepoTXA for a dose-related response at 800 and 1200 mg (33 mg/mL or 37 mg/mL, whichever formulation is available at the time of the study).

9. STUDY DESIGN AND PLAN

9.1. Study Design

This is a Phase 2, randomized, single-blind, active-controlled dose-ranging study in patients scheduled to undergo TKA. Approximately 45 patients (15 per treatment group) are planned for enrollment. Patients will be randomized in a 1:1:1 ratio to receive either DepoTXA 800 mg, DepoTXA 1200 mg, or IV TXA (CYKLOKAPRON 1 gram).

9.1.1. Screening

Patients will be screened within 30 days prior to surgery. During the screening visit, which must take place at least 1 day prior to surgery, patients will be assessed for any past or present medical conditions that, in the opinion of the Investigator, would preclude them from study participation.

After the ICF is signed, patient demographics and baseline characteristics will be recorded, and a medical/surgical history, physical examination, vital sign measurements, clinical laboratory tests (hematology, chemistry, and coagulation), neurological assessment, and urine pregnancy test for women of childbearing potential will be conducted.

9.1.2. Day 1 (Day of Surgery)

Prior to surgery on Day 1, the patient's eligibility for participation in the study will be confirmed, any adverse events (AEs) or changes to concomitant medications or medical/surgical history since screening will be recorded, vital signs will be measured, knee and thigh measurements (both legs) will be collected using the measuring tape provided, and clinical laboratory tests (hematology, chemistry [with creatinine clearance calculation], and coagulation), a neurological assessment, a urine pregnancy test for women of childbearing potential, and a12-lead electrocardiogram (ECG) will be conducted. A pre-dose PK sample will be collected from all patients eligible for randomization.

Qualified Investigators will use their standard technique (open) to perform the TKA. Drains are not permitted.

Patients randomized to DepoTXA will receive a single dose of 800 or 1200 mg (33 mg/mL or 37 mg/mL, whichever formulation is available at the time of the study). DepoTXA will be administered by instillation into the joint space by injection through the capsular repair suture line via a catheter just prior to complete watertight capsular closure. Patients randomized to IV TXA will receive 1 gram of IV TXA at the end of surgery prior to tourniquet release or at the end of the surgery if a tourniquet is not used. The tourniquet pressure, if used, should be at least 20 mm Hg above systolic blood pressure.

Blood transfusion will be indicated based on each individual institution's protocol. Each institution may follow its own routine venous thromboembolism (VTE) prophylaxis regimen. Additionally, each institution may follow its standard protocol for the control of postsurgical pain; however, patient-controlled analgesia is not permitted. Adverse events will be recorded from the time the ICF is signed through Day 60 (±3 days).

Patients will be required to remain in the research facility for at least 48 hours after study drug administration in order to undergo postsurgical assessments. After discharge, a nurse will visit the patients to conduct the postsurgical assessments through 120 hours. All patients will return for a follow-up visit on Day 7. A telephone call will be made to each patient on Day 14 (±1 day), Day 30 (±3 days) and Day 60 (±3 days) for an AE assessment and to record whether the patient has achieved independent ambulation.

9.1.3. Postsurgical Efficacy Assessments

Postsurgical efficacy assessments will include measurement of blood loss (as assessed by hemoglobin [Hb] and hematocrit [Hct] levels), transfusion requirement, knee flexion to 90 degrees, timed up-and-go (TUG) test, knee and thigh measurements (surgical leg only), pain scores and days to independent ambulation. In addition, a modification of the surgical wound aspect score (SWAS) developed by Torres-Claramunt, et al (Torres-Claramunt, 2015) will be

calculated from the knee measurements collected on the morning of Day 2 (ie, the day after surgery) and on Day 7 and an assessment of the surgical wound at these times for signs of oozing, erythema, ecchymosis, and blisters (see Appendix 4).

9.1.4. Postsurgical Safety Assessments

Postsurgical safety assessments will include physical examination, vital signs, neurological assessment, clinical laboratory testing (hematology, chemistry, and coagulation), 12-lead ECG, and AE monitoring. Patient monitoring will include, but not be limited to, changes in vision, neurologic function, or renal function; and occurrence of hematoma, wound dehiscence/disruption, surgical site infection (per Centers for Disease Control and Prevention definition), nausea, vomiting, and diarrhea.

Adverse events of special interest (AESI) include VTE or pulmonary embolism (PE), and oliguria. If an AESI or serious AE (SAE) occurs during the study, an unscheduled PK blood sample must be collected. In addition, vital signs, the neurological assessment, and clinical laboratory tests must be conducted, as appropriate.

Pharmacokinetic Assessment

Blood samples (drawn into pediatric tubes to minimize blood loss) for PK analysis will be obtained at baseline (Day 1 pre-op, prior to study drug administration); at 5, 15, and 30 minutes; and at 1, 2, 4, 6, 8, 12, 16, and 24 hours after the end of study drug administration for all treatment groups. Additional blood samples will be collected at 36, 48, 60, 72, and 96 hours after the end of study drug administration for DepoTXA-treated patients. **It is important that blood draws for PK assessment be timed from the END of infusion of DepoTXA**.

9.1.5. Duration of the Study and Patient Participation

Participation will begin at the signing of the ICF. No more than 30 days should pass between signing of the ICF and the administration of study drug. The time from study drug administration through the end of participation is 60 ± 3 days. Therefore, patients may participate in the study for up to 93 days.

9.1.6. Study Stopping Rules

Patient data will be reviewed by the Pacira Medical Monitoring Team on a continuous basis. If 4 or more patients experience serious AESIs prior to or when the first 12 patients have been dosed, a review process will be triggered for prompting the Safety Stopping Rules. Subject dosing and/or study enrollment will be halted until the toxicity data can be further reviewed. After this review is completed the study may be amended or terminated.

If after the first 12 patients have been treated and the Safety Stopping Rules have not been triggered, the Pacira Medical Monitoring Team will continue to evaluate subject data on an ongoing basis which also includes documented periodic reviews of patient safety data, the frequency of which will be determined by the pace of enrollment into the trial.

Any unexplained death will be thoroughly reviewed and appropriate action taken.

9.2. Discussion of Study Design

This Phase 2, multicenter, randomized, single-blind, active-controlled, dose-ranging study is designed to evaluate the pharmacokinetics, safety, and efficacy of local administration of DepoTXA for reduced postsurgical bleeding in patients undergoing TKA. The single-blind study design is intended to eliminate bias resulting from the patient's knowledge of the assigned treatment.

Patients will receive a single dose of either DepoTXA (800 mg or 1200 mg) or IV TXA 1 gram. The DepoTXA dosage will be selected from this first-in-human study for further evaluation based on the PK, safety, and efficacy data for DepoTXA compared to standard of care IV TXA.

TXA is used in TKA in many countries globally but no specific recommendations are provided in the US PI. Therefore, Pacira is utilizing an administration technique from the Australian PI that supports a recommended rate of infusion for a bolus or loading dose of 50 mg/min. To administer 50 mg/min to the patient, the solution is diluted to 1% TXA with normal saline for injection (ie, 1 g in 100 mL or 10 mg/mL). TXA may be administered at 5 mL/min (20 minutes).

The AEs of special interest (VTE or PE, and oliguria) were selected based on the known adverse effects of TXA. If an AE of special interest or SAE occurs during the study, an unscheduled PK blood sample must be collected. In addition, vital signs, the neurological assessment, and clinical laboratory tests must be conducted, as appropriate.

Refer to Section 12.7 for the rationale behind the selection of key efficacy endpoints and the use of Hb as a surrogate marker for blood loss.

10. STUDY POPULATION

10.1. Inclusion Criteria

Patients eligible for study entry must meet all of the following criteria:

1. Male or female, ≥18 years of age at screening.
2. Scheduled to undergo elective unilateral open TKA under general, spinal, or regional anesthesia.
3. Currently receiving anticoagulation or antiplatlet therapy for cardiovascular disease or thromboembolic risk.
4. American Society of Anesthesiology (ASA) physical status 1, 2, or 3.
5. Female patient must be surgically sterile; or at least 2 years postmenopausal; or have a monogamous partner who is surgically sterile; or practicing double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or using an insertable, injectable, or transdermal, contraceptive approved by the FDA for greater than 2 months prior to screening. All women of childbearing potential (ie, premenopausal without permanent sterilization) must commit to the use of

an acceptable form of birth control for the duration of the study and for 30 days after completion of the study.

6. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

10.2. Exclusion Criteria

A patient will not be eligible for the study if he or she meets any of the following criteria:

1. Currently pregnant, nursing, or planning to become pregnant during the study or within 30 days after study drug administration.
2. Planned concurrent surgical procedure (eg, bilateral TKA).
3. Prior open knee surgery on ipsilateral knee. Prior arthroscopy is permitted.
4. Patients taking a medication with a known procoagulant effect (eg, combination hormonal contraceptives, Factor IX complex concentrates or anti-inhibitor coagulant concentrates, or all-trans retinoic acid).
5. Contraindication or hypersensitivity to TXA.
6. Known active intravascular clotting.
7. Prior subarachnoid hemorrhage.
8. History of epilepsy.
9. History of impaired kidney function, chronic respiratory disease, rheumatoid arthritis, congenital coagulopathy, or loss of sensation in extremities.
10. Renal insufficiency as indicated by serum creatinine >upper limit of normal (by central laboratory assessment).
11. Anemia (Hb level <10 g/dL).
12. Uncontrolled anxiety, psychiatric, or neurological disorder that might interfere with study assessments.
13. Acquired defective color vision.
14. Malignancy in the last 2 years, with the exception of non-metastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
15. Suspected or known history of drug or alcohol abuse within the previous year.
16. Body weight <50 kg (110 pounds) or a body mass index >44 kg/m^2.
17. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the patient's participation in this study

10.3. Removal of Patients From Therapy or Assessment

Every reasonable effort should be made to maintain patient compliance and participation in the study. Reasons for discontinuation of any patient from the study will be recorded.

If a patient who withdraws from the study has an ongoing AE, every effort must be made to follow such events until satisfactory resolution is obtained, or further follow-up is otherwise no longer warranted.

10.3.1. Withdrawal Secondary to Adverse Events

If a patient experiences an AE that renders him or her incapable of continuing with the remaining study assessments, then he or she will be discontinued from further participation in the study. A final evaluation should be performed so that the patient's study participation can be terminated in a safe and orderly manner.

10.3.2. Voluntary or Study Investigator Withdrawal

Patients are free to discontinue from the study at any time, without prejudice to future treatment. Nevertheless, patients will be encouraged to complete at least the study safety assessments. In addition, a patient may be discontinued from the study if he or she refuses to comply with study procedures. Reasons for discontinuation from the study will be recorded.

If a patient is discontinued by the Investigator or voluntarily withdraws from the study after receiving study drug, the patient will be asked to complete a final evaluation so that he or she can be withdrawn in a safe and orderly manner. In the final evaluation, vital signs (heart rate and blood pressure), the neurological assessment, and clinical laboratory tests will be conducted, and any changes in the patient's health status will be recorded.

After termination from the study, the patient may be followed for safety including monitoring of AEs through Day 60 (±3 days).

11. TREATMENTS

11.1. Treatment to be Administered

Patients will receive a single dose of either DepoTXA DepoTXA 800 mg, DepoTXA 1200 mg, or IV TXA (CYLOKAPRON 1 gram) according to the randomization schedule.

11.1.1. Administration Technique

Patients randomized to DepoTXA will receive a single dose, which will be administered by instillation into the joint space at the time of watertight closure of the capsule by injection through the capsular repair suture line. DepoTXA will be applied to the joint space via a catheter beneath the closed capsule using a steady pressure and rate.

Patients randomized to IV TXA will receive a single IV dose at the end of surgery after closure of the capsule. This will occur at a parallel timepoint to when DepoTXA patients receive their instillation into the joint space. The IV dose (1 gram) is to be administered at 50 mg/min (ie, over 20 minutes).

11.1.2. Study Drug Administration Considerations

The potential risks of TXA are well characterized (CYKLOKAPRON PI, LYSTEDA PI, DepoTXA Investigator's Brochure) and include dizziness, hypotension, visual or ocular adverse effects, allergic reaction (rash), nausea, and thromboembolism (particularly in persons with a history of intravascular clotting or persons taking other medications with a procoagulant effect). The CYKLOKAPRON PI cautions that because TXA is eliminated unchanged in urine, plasma levels increase with decreasing renal function, and a reduction in dosage is recommended in patients with renal impairment. These risks are widely believed to be outweighed by the potential benefits of reduced postsurgical bleeding (eg, reduced blood loss, reduced red blood cell [RBC] transfusion requirement, and reduced Hb decrease) (Yue 2015).

Because DepoTXA has not yet been studied in humans, its non-TXA-related potential risks are surmised from nonclinical studies of DepoFoam (approved) and of DepoTXA. The known safety of the DepoFoam component of already approved products using the DepoFoam delivery technology (EXPAREL®, DepoDur®, and DepoCyt®) in humans also contributes to the safety profile of DepoFoam. No clinical or nonclinical findings have been considered to be adverse (ie, there have been no identified risks) for DepoFoam. The DepoFoam membrane constituents (ie, triglycerides, phospholipids, cholesterol) are believed to be cleared through the lymphatics and metabolized as nutrients. Refer to the Investigator's Brochure for additional details.

11.2. Identity of Investigational Product(s)

11.2.1. Description of DepoTXA

DepoTXA is a sterile, non-pyrogenic, white to off-white, preservative-free, aqueous suspension of multivesicular lipid-based particles (DepoFoam drug delivery system) containing TXA, intended for local prolonged release following administration for the reduction of postsurgical bleeding. Tranexamic acid, the drug substance, is present in DepoTXA at a concentration of approximately 33 mg/mL or 37 mg/mL, whichever formulation is available at the time of the study. The free drug is thought to provide an immediate effect for initial clot stabilization followed by the slow release of additional TXA to further aid in clot stabilization and minimization of blood loss.

The DepoFoam technology developed by Pacira provides a platform by which drugs are encapsulated within aqueous chambers of the multivesicular liposomal particles. After administration of the drug product, drug is slowly released from the particles providing high local concentration of the drug at the site of administration. The release profile and duration of drug release are largely dependent on the lipid composition of the particles but other factors such as physicochemical properties of the drug and the presence of other excipients that may interact or retain the drug within the particles may also have an impact.

11.2.2. Description of Reference Product

CYKLOKAPRON (TXA) is a white crystalline powder. The aqueous solution for injection has a pH of 6.5 to 8.0. Each mL of the sterile solution for IV injection contains 100 mg TXA and Water for Injection to 1 mL.

11.2.3. Description of Diluents

Not applicable.

11.3. Method of Assigning Patients to Treatment

11.3.1. Randomization Scheme

Approximately 45 patients (15 per treatment group) are planned for enrollment. Patients will be randomized in a 1:1:1 ratio to receive a single dose of DepoTXA 800 mg, DepoTXA 1200 mg, or IV TXA (CYKLOKAPRON 1 gram).

The randomization code will be generated by a centralized randomization system, which will also be used to communicate patient randomizations to study sites. All randomized patients will have both a unique patient identifier and a unique random code identifier. No patient or random code identifiers are to be reused once assigned.

11.3.2. Randomization Procedures

Once a patient is identified as being qualified for the study per the eligibility criteria (see Section 10.1 and Section 10.2), and is at the study site for surgery, the research pharmacist or designee will obtain a randomization assignment. The patient will be considered randomized into the study once the study treatment assignment is received.

11.3.3. Replacement of Patients

Patients who are randomized but are withdrawn from the study before receiving study drug or do not undergo the surgical procedure may be replaced. Once assigned, patient numbers will not be reused; patients enrolled to replace those who withdraw will be assigned a unique patient number and randomized to treatment according to the procedures outlined above.

11.4. Selection of Doses in the Study

11.4.1. Justification of the Dose, Route, and Timing of Administration of the Comparator

Precedent includes five published randomized, placebo-controlled studies of TXA in TKA, each of which included one group of patients that received a single IV dose of TXA at the end of surgery (Maniar 2012; Drosos 2016; Hiippala 1995; Orpen 2006; and Tanaka 2001). Doses ranged from less than 1000 mg to an estimated approximately 1200 mg, a similar IV dosing regimen to that of the comparator group in the current study (IV TXA 1 gram at the end of surgery).

- In a prospective, randomized, partially blinded (patients, floor nurses, and laboratory technicians), controlled trial, Maniar (2012) gave patients IV TXA **10 mg/kg** 15 minutes before deflation of the tourniquet (weight was not reported, but mean body mass index in the group was 29.4; for a 65-kg patient, this would represent a dose of 650 mg). Drain loss, blood loss on postsurgical Days 1 and 2, total blood loss, and number of patients indicated for transfusion, respectively, were lower in the TXA group (n=40) by 12.8%, 26.8%, 24.9%, and 20% than in the control group (n=40; not significant). Two TXA-treated patients had

clinical suspicion of deep vein thrombosis (DVT); however, neither was confirmed by duplex Doppler.

- In a prospective, randomized, controlled trial, Drosos (2016) gave patients IV TXA (**1 g**) at the start of wound suturing. The treated group showed significantly lower blood loss (16.3%) and a significantly lower likelihood of transfusion (90%) than the saline control group. There were no thromboembolic complications in either group.
- In a prospective, randomized, controlled trial, Hiippala (1995) gave patients IV TXA **15 mg/kg** 2 to 5 minutes before deflating the tourniquet (mean weight of patients in the group was 72 kg, so the average dose was 1080 mg). Total blood loss among TXA-treated patients (n=15) was 45.3% lower than that reported for the placebo-treated patients (n=13; $p<0.001$). Units of blood transfused per patient were 54.5% lower in the TXA group than in the placebo group ($p<0.005$). Two placebo-treated patients experienced confirmed DVT vs. none in the TXA-treated group.
- In a prospective, randomized, double-blind, controlled trial, Orpen (2006) gave patients **15 mg/kg** at the time of cementing of the prosthesis, before deflation of the tourniquet (mean weight of patients in the group was 83 kg, so the average dose was 1245 mg). Compared to saline controls (n=14), a statistically significant ($p=0.006$) decrease in blood loss in the early postoperative period was noted in the group receiving TXA (n=15). Total blood loss and Hb drop were also lower in the TXA-treated patients than in controls (not significant). There was no evidence of DVT in either group on duplex ultrasound screening of the lower limbs.
- In a prospective, randomized, double-blind (patients and surgeons), controlled trial Tanaka (2001) gave patients IV TXA **20 mg/kg** 10 minutes before deflation of the tourniquet (mean weight of patients in the group was 60 kg, so the average dose was 1200 mg). Total blood loss in the TXA-treated patients (n=22) was 39.1% lower than that in placebo-treated patients (n=26), and the number of patients transfused was 23% lower. (Statistics were reported for this TXA dosing regimen combined with two others, ie, pooled TXA groups, and were significant in favor of TXA over placebo.) One TXA-treated patient had mild nausea, and no patients had clinical signs of DVT or pulmonary embolism.

The dose and timing of IV TXA for the comparator group in this study were also selected based on their suitability for later side-by-side comparison of PK parameters of a single dose given at the end of surgery for both IV TXA- and DepoTXA-treated patients.

11.4.2. Justification of the Route and Timing of Administration of DepoTXA

Note that the justification for the dose of (and the safety margins for) DepoTXA are included in the discussion of nonclinical studies in Section 7.1.

A review of six high-level-of-evidence meta-analyses published between 2013 and 2015 comparing TXA routes of administration revealed the following safety and efficacy findings relevant to "topical" administration of TXA, so named to include various methods gleaned from the literature of surgical instillation into the joint space (Panteli 2013, Zhang 2014, Wang 2015b,

and Yue 2015 [topical TXA and placebo control]; Shemshaki 2015 and Wu 2015 [topical TXA, systemic TXA, and placebo control]):

- There was no significant difference in the incidence of DVT reported between TXA and control. Shemshaki (2015) reported the risk ratio for "thromboembolic events" as 0.68 (not significant). Panteli (2015) did not report on DVT or PE. In the 4 meta-analyses that reported DVT, the risk ratio ranged from 0.78 to 1.02. A risk ratio <1.0 indicates a reduction in risk. In the 3 meta-analyses that reported PE, risk ratio ranged from 0.49 to 0.66. Wu (2015) reported PE in 2/705 TXA patients (all TXA, meaning IV + topical) and 7/706 controls.
- Mean total blood loss was significantly lower with topical TXA than without it. In the 5 meta-analyses reporting mean difference between control and topical TXA (ie, control minus TXA), the mean differences ranged from 220 mL to 396 mL. Wu reported standard mean difference as significant (significance in the same direction).The Hb drop reduction between topical TXA and control was significant in the 5 meta-analyses that reported it, and ranged from 0.65 g/dL to 0.94 g/dL. Shemshaki did not report Hb drop.
- The transfusion requirement risk ratio was significantly reduced with topical TXA compared to control in 5/6 meta-analyses and ranged from 0.22 to 0.47. Wang (2015b) reported the risk ratio as 0.33 and p-value as 0.14.

Much clinical evidence supports that topical administration of TXA in solution is both safe and effective at reducing blood loss, but no consensus has been reached in the published literature on the most effective dose, regimen, or technique of application. Successful reduction of blood loss has been demonstrated using intra-articular TXA application after closure (Craik 2014; Yang 2015; Wang 2015a) and in the absence of a drain (Craik 2014; Yang 2015; Wang 2015a; Wong 2010).

The nonclinical studies of DepoTXA indicate that TXA stays at a surgical wound site in dogs and is released from DepoTXA over a period of up to 72 hours. The first 6 hours of plasma TXA was due primarily to the free TXA in the DepoTXA formulation used in the toxicology studies.

Given the short half-life of approximately 2 hours following IV administration of TXA and the extended period of fibrinolysis associated with surgery (approximately 2 to 3 days), a combination DepoFoam and TXA product (DepoTXA) may provide an opportunity to significantly improve the PK profile of a vital medication by creating a long-acting product to reduce ongoing bleeding over an extended duration.

11.5. Blinding

11.5.1. Blinding Procedures

This is a single-blind study (ie, the study staff, but not the patients, know which patients are receiving which treatment).

11.5.2. Unblinding Procedures

Not applicable.

11.6. Prior and Concomitant Therapy and Medications

Medications with a known procoagulant effect (eg, combination hormonal contraceptives, Factor IX complex concentrates or anti-inhibitor coagulant concentrates, or all-trans retinoic acid) are not permitted.

At all times during the study, administration of TXA by any mode is prohibited except for the single dose of study treatment to which the patient is randomized.

The physicochemical incompatibilities of DepoTXA with other drugs/compounds has not been assessed. Direct contact of DepoTXA with certain drugs/compounds may alter the intended release profile of TXA from the particles. Therefore, do not admix DepoTXA with other drugs/compounds (including antiseptics [eg, povidone iodine [Betadine®]) prior to administration.

All medications taken within 30 days prior to study drug administration through 120 hours after study drug administration or until the patient is withdrawn from the study, whichever is sooner, will be recorded on the case report form (CRF).

Each institution may follow its standard protocol for the control of postsurgical pain; however, patient-controlled analgesia is not permitted.

Additionally, any medications administered in association with an AE will be recorded through Day 60 (±3 days).

11.7. Treatment Compliance

Not applicable, since study drug will be administered by the study staff during surgery.

11.8. Accountability of Study Drug

Any shipment of study drug will contain an investigational drug transmittal and receipt form to assist the Investigator or designee (eg, pharmacist) in maintaining current and accurate inventory records. At a minimum, the pharmacist or designee will maintain accurate records demonstrating dates and units of drug received, lot numbers, patients to whom drug was administered, and accounts of any drug destroyed accidentally or deliberately. The Investigator must retain vials containing used, unused, or expired study drug for return or destruction, as instructed by Pacira, following confirmation of drug accountability data by a study monitor. A record of drug return or destruction will be maintained and provided to Pacira. Inventory records must be readily available for inspection by the study monitor and appropriate regulatory authorities at any time. A copy of the inventory records, drug accountability information, and notice of return or destruction will be returned to Pacira at the end of the study. Only authorized personnel identified by the Investigator will have the ability to access and administer the drug.

12. STUDY ENDPOINTS AND MEASUREMENTS

12.1. Efficacy Assessments

The following efficacy measurements will be conducted at the times specified after the beginning of study drug administration:

- Total blood loss as measured by Hb and Hct levels upon arrival at the post-anesthesia care unit (PACU) and at 6, 12, 24, 48, 72, and 120 hours, and Day 7.
- Transfusion requirement.
- Postsurgical "Timed Up-and-Go" will be assessed once on the day of the surgery following surgery; at approximately 8:00 am and 8:00 pm (±2 hours) on Day 2 (ie, the day after surgery); at hospital discharge; and on Day 7 (see Appendix 1).

  Maximum passive and active knee flexion twice daily at the time of the physical therapy assessment (ie, approximately 8:00 am and 8:00 pm [±2 hours] daily) until hospital discharge.
- Knee and thigh measurements (surgical leg only) on the morning of Day 2 (ie, the day after surgery), Day 3, and at the Day-7 follow-up visit.
- Numerical rating scale at rest (NRS-R) pain score (see Appendix 3; 0 [no pain] to 10 [worst possible pain]) upon arrival at the PACU; at each in-hospital vital sign assessment beginning with the 2-hour assessment and ending with the 72-hour assessment; on Day 3; and at the Day-7 follow-up visit.
- Days to independent ambulation, assessed beginning at the Day-7 follow-up visit
- SWAS on the morning of Day 2 (ie, the day after surgery), and on Day 7

12.2. Efficacy Endpoints

The efficacy endpoints listed below will be assessed based on the efficacy measurements conducted at the times specified after the beginning of study drug administration:

- Total blood loss as measured by Hb and Hct levels upon arrival at the PACU and at 6, 12, 24, 48, 72, and 120 hours, and Day 7.
- Incidence of transfusion (number of units, number of units/patient, number of patients transfused).
- Time to 90 degrees passive and active knee flexion.
- Time to complete TUG test.
- Change in knee and thigh measurements.
- Pain scores.

12.3. Pharmacokinetic Analysis

Blood samples (drawn into pediatric tubes to minimize blood loss) for PK analysis will be obtained at baseline (Day 1 pre-op, prior to study drug administration); at 5, 15, and 30 minutes;

and at 1, 2, 4, 6, 8, 12, 16, and 24 hours after the end of study drug administration for all treatment groups. Additional blood samples will be collected at 36, 48, 60, 72, and 96 hours after the end of study drug administration for DepoTXA-treated patients. **It is important that blood draws for PK assessment be timed from the END of infusion of DepoTXA.**

Blood samples for PK analysis may be drawn using a properly maintained indwelling cannula (PICC line) at the discretion of the Investigator.

12.4. Pharmacokinetic Endpoints

Pharmacokinetic parameters will be estimated from the plasma TXA measurements using non-compartmental analysis. The following parameters will be determined:

$AUC_{0\text{-}tlast}$ The area under the plasma concentration-versus-time curve from the time of administration to the time of the last quantifiable concentration calculated using the log-linear trapezoidal rule.

$AUC_{0\text{-}\infty}$ The area under the plasma concentration-versus-time curve from the time of administration extrapolated to infinity. The residual area from the time of the last quantifiable concentration (C_{tlast}) to infinity is to be calculated using the approximation: $AUC_{t\text{-}\infty} = Ct_{last}/\lambda_z$.

C_{max} The maximum observed plasma concentration obtained directly from the experimental data without interpolation.

T_{max} The time to maximum plasma concentration (C_{max}).

λ_z The apparent terminal elimination rate constant determined by log-linear regression of the terminal log-linear segment of the plasma concentration-versus-time curve.

$t_{1/2el}$ The apparent terminal elimination half-life calculated as $0.693/\lambda_z$.

12.5. Safety Assessments

The following safety assessments will be conducted after the beginning of study drug administration:

- Physical examination at 48 hours.
- Vital signs, (resting heart rate and blood pressure) at 5, 15, and 30 minutes, and at 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, and 96 hours after study drug administration.
- Neurological assessment at 12, 24, 36, 48, 60, 72, and 96 hours after study drug administration (see Appendix 2).
- 12-lead ECG at 1 hour (±15 minutes) and 12 (±2) hours.
- Clinical laboratory testing (chemistry [including lipid profile], hematology, and coagulation [fibrinogen and fibrin split products]) at 48 hours and on Day 7.
- Creatinine clearance calculations at 48 hours and on Day 7.
- Reoperation due to hematoma or wound dehiscence.
- Adverse events through Day 60 (±3 days).

12.6. Safety Endpoints

The following safety endpoints will be assessed based on the safety measurements conducted at the specified timepoints:

- Change from baseline in vital signs at each assessed timepoint.
- Summary of neurological assessments (proportion of patients who are oriented, and proportion of patients who have any of the neurologic events) at each assessed timepoint.
- Change from baseline in clinical laboratory data at each assessed timepoint.
- Change from baseline in ECG data at each assessed timepoint.
- Incidence of reoperation due to hematoma or wound dehiscence.
- Incidence of treatment-emergent AEs (TEAEs) and SAEs through Day 60 (±3 days).

12.7. Appropriateness of Measures

Endpoints selected for this study were based on validated methodologies and other well established clinical measurements used in peer-reviewed studies in both the peer reviewed literature and at regulatory authorities.

12.7.1. Rationale for Key Efficacy Endpoints

Pacira recently (March 2016) performed a systematic literature review of 12 large (≥50 patients), randomized, placebo-controlled trials published in the past 10 years that used TXA (IV and/or topical) in TKA (Alshryda 2013; Wong 2010; Yang 2015; Maniar 2012; Carvalho 2015; Roy 2012; Georgiadis 2013; Wang 2015a; Wang 2015c; Aguilera 2015; Seo 2013; Craik, 2014).

12.7.2. Hb and Hct as Surrogate Markers for Total Blood Loss

Statistical significance was achieved in favor of a better Hb outcome (for patients) with TXA than with placebo control for all the studies that reported Hb values (n=11 studies; Maniar did not report Hb). The Hb findings (all findings significant) were consistent with the blood loss results (better outcome [for patients] with TXA than with placebo control, all findings significant). Thus, and logically, decrease in Hb is an excellent surrogate marker for blood loss. By extension, analogous reasoning can be applied to Hct.

12.7.2.1. Calculated Total Blood Loss

As a widely accepted reporting convention, in all 12 studies, blood volume (BV) was estimated (calculated) adjusted for the weight, height, and sex of the patient. Blood loss was estimated (calculated) by one of several published methods, which were based on the maximum postsurgical decrease in Hb level. Some formulae also took transfusion volumes into account. Calculated blood loss should theoretically give a better estimation of the combined external loss (ie, intraoperative loss plus drain loss) and the internal (hidden) blood loss. In some studies, intraoperative blood loss was not included in the total blood loss figures; however, it will be included in the calculated blood loss metric for this study.

13. STUDY PROCEDURES

A time and events schedule for all study procedures is provided in Table 1.

13.1. Instructions for Conducting Procedures and Measures

All assessments conducted after baseline will be timed from the beginning of study drug administration.

At timepoints when multiple assessments coincide, the vital signs will be conducted first, the blood draw for PK analysis will be collected second, and the physical therapy assessment will be conducted last, as applicable.

Day 1 is defined as the day on which study drug is administered. The beginning of surgery is defined as the time of the first incision. The end of surgery is defined as the time of the last suture. Postsurgical is defined as after the end of surgery.

13.1.1. Knee Flexion Assessment

The knee flexion to 90 degrees assessment will be conducted during the screening visit and twice daily at the time of the physical therapy assessments (ie, approximately 8:00 am and 8:00 pm [±2 hours] daily) until hospital discharge).

Knee flexion (passive and active) will be measured by a standard physical medicine/rehabilitation technique with the patient stable in either a sitting or supine position using a goniometer, aligning the fulcrum of the goniometer with the fulcrum of the joint.

13.1.2. Timed Up-and-Go Test

The TUG test will be conducted during the screening visit. Postsurgical TUG will be assessed once on the day of the surgery following surgery; at approximately 8:00 am and 8:00 pm (±2 hours) on Day 2 (ie, the day after surgery); at hospital discharge; and on Day 7. Details are provided in Appendix 1.

13.1.3. Neurological Assessment

A neurological assessment will be conducted at screening; baseline (Day 1 pre-op, prior to surgery); and at 12, 24, 36, 48, 60, 72, and 96 hours. The examination will include the patient's orientation. Additionally, the patient will be asked whether he or she is experiencing any numbness of the lips, the tongue, or around the mouth; a metallic taste in the mouth; vision problems; hearing problems; or muscle twitching (see Appendix 2).

If the patient answers “yes” to any of these questions, the event must be recorded as an AE.

13.1.4. Clinical Laboratory Tests

Hemoglobin and hematocrit will be measured at screening; baseline (Day 1 pre-op, prior to surgery); upon arrival at the PACU; and at 6, 12, 24, 48, 72, and 120 hours, and Day 7. Clinical laboratory tests (chemistry [including lipid profile], hematology, and coagulation [fibrinogen and fibrin split products]) will be conducted at screening; baseline (Day 1 pre-op, prior to surgery); at

48 hours; and on Day 7 (see Appendix 5). Creatinine clearance will be calculated for Day 1 prior to surgery, for 48 hours, and for Day 7.

Clinical laboratory tests, as appropriate, must also be conducted if a patient experiences an AE of special interest or an SAE (see Section 13.1.10).

13.1.5. Vital Signs

The scheduled vital signs (heart rate and blood pressure) will be measured after the patient has rested in a supine position for at least 5 minutes at screening; baseline (Day 1 pre-op, prior to surgery); at 5, 15, and 30 minutes; and at 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, and 96 hours after study drug administration. Vital signs must also be measured if a patient experiences an AE of special interest or an SAE (see Section 13.1.10). The patient will remain in a supine position during the assessment.

13.1.6. Physical Examination

A physical examination will be conducted at screening and at 48 hours.

13.1.7. Knee and Thigh Measurements

Knee and thigh measurements of both legs will be collected on the day of surgery prior to surgery. Knee and thigh measurements of the surgical leg only will be collected on the morning of Day 2 (ie, the day after surgery), on Day 3, and at the Day-7 follow-up visit.

With the patient in the supine position and using the measuring tape provided, measure the circumference of the knee at 1 centimeter (cm) proximal to the base of the patella and the thigh at 10 cm above the border. Measurements are to be recorded to the nearest tenth of a cm.

The provided tape measure should be used for all patients. Additionally, to reduce inter-rater variability in the placement of the measuring tape, the first examiner (prior to surgery) should make multiple marks (no fewer than four marks per measurement) on the patient's surgical leg along the top of the measuring tape for each of the four measurements. These marks will be used to position the tape measure for subsequent measurements.

13.1.8. Electrocardiogram

The scheduled 12-lead ECGs will be conducted after the patient has rested in a supine position for at least 5 minutes at baseline (Day 1 pre-op, prior to surgery) and at 1 hour (±15 minutes) and 12 (±2) hours after study drug administration.

13.1.9. Numerical Rating Scale at Rest Pain Score

The NRS-R (0 [no pain]-10 [worst possible pain]) provided in Appendix 3 will be used to record pain scores on the day of surgery prior to surgery; upon arrival at the PACU; at each in-hospital vital sign assessment beginning with the 2-hour assessment and ending with the 72-hour assessment; and at the Day-7 follow-up visit.

13.1.10. Adverse Events of Special Interest

Adverse events of special interest include VTE or PE, and oliguria. If an AE of special interest or SAE occurs during the study, an unscheduled PK blood sample must be collected. In

addition, vital signs, the neurological assessment, and clinical laboratory tests must be conducted, as appropriate.

13.1.11. Surgical Wound Aspect Score

A modification of the surgical wound aspect score developed by Torres-Claramunt, et al (Torres-Claramunt, 2015) will be calculated from the knee measurements collected on the morning of Day 2 (ie, the day after surgery) and on Day 7 and an assessment of the surgical wound at these times for signs of oozing, erythema, ecchymosis, and blisters (see Appendix 4).

13.2. Screening Procedures

- Explain study purpose and procedures.
- Obtain signed ICF.
- Assess eligibility.
- Record relevant medical/surgical history, demographics, and baseline characteristics.
- Conduct urine pregnancy test for women of childbearing potential.
- Perform physical examination (including height and weight).
- Conduct TUG test (see Appendix 1).
- Perform passive and active knee flexion assessment.
- Perform neurological assessment (see Appendix 2).
- Conduct clinical laboratory tests (hematology [including Hb and Hct], chemistry, and coagulation; see Appendix 5).
- Measure vital signs (heart rate and blood pressure) after patient has rested in a supine position.
- Record prior and concomitant medications.
- Record AEs starting at signing of the ICF.

13.3. Baseline Procedures (Day 1 Pre-op - Prior to Study Drug Administration)

- Confirm eligibility.
- Update relevant medical and surgical history.
- Conduct urine pregnancy test for women of childbearing potential.
- Perform neurological assessment (see Appendix 2).
- Measure vital signs (heart rate and blood pressure) after patient has rested in a supine position.
- Record NRS-R pain score (see Appendix 3; 0 [no pain] to 10 [worst possible pain])
- Collect knee and thigh measurements of both legs (mark position of tape measure on the subject's surgical leg to aid in collection of future measurements).

- Collect blood samples for clinical laboratory testing (hematology [including Hb and Hct], chemistry [including calculation of creatinine clearance] and coagulation; see Appendix 5).
- Collect baseline blood sample for PK analysis.
- Perform presurgical 12-lead ECG after patient has rested a supine position
- Randomize patient and prepare study drug.
- Record changes to concomitant medications since screening.
- Record AEs and any treatment(s) for the events.

13.4. Intraoperative Procedures

- Administer study drug per Section 11.1.1; record start and stop times.
- Record start and stop times of tourniquet use and the maximum pressure (mmHg) used.
- Record start and stop times of surgery.
- Record concomitant medications.
- Record AEs and any treatment(s) for the events.
- Refer to Section 13.1.10 for additional procedures in the event an AESI or SAE occurs.

13.5. Upon Arrival at the Post-Anesthesia Care Unit

- Collect blood sample for hemoglobin and hematocrit.
- Record any blood transfusion data (eg, start and stop times, number of units).
- Record concomitant medications.
- Record AEs and any treatment(s) for the events.
- Record NRS-R pain score (see Appendix 3; 0 [no pain] to 10 [worst possible pain])
- Refer to Section 13.1.10 for additional procedures in the event an AESI or SAE occurs.

13.6. Postsurgical Assessments Through Hour 120

- Measure vital signs (heart rate and blood pressure) after patient has rested in a supine position at 5, 15, and 30 minutes, and at 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, and 96 hours.
- Record NRS-R pain score (see Appendix 3; 0 [no pain] to 10 [worst possible pain]) at each in-hospital vital sign assessment beginning with the 2-hour assessment and ending with the 72-hour assessment.
- For all patients: Collect scheduled blood samples for PK analysis at 5, 15, and 30 minutes; and at 1, 2, 4, 6, 8, 12, 16, and 24 hours after the end of study drug administration for all treatment groups. Record the date and time each sample is collected. **It is important that blood draws for PK assessment be timed from the END of infusion of DepoTXA.**
- For DepoTXA-treated patients only: Additional blood samples will be collected at 36, 48, 60, 72, and 96 hours after the end of study drug administration. Record the date and time

each sample is collected. **It is important that blood draws for PK assessment be timed from the END of infusion of DepoTXA.**

- Collect blood sample for hemoglobin and hematocrit at 6, 12, 24, 48, 72, and 120 hours.
- Collect blood samples for clinical laboratory testing (hematology [includes hemoglobin and hematocrit], chemistry [including calculation of creatinine clearance], and coagulation) at 48 hours.
- Perform 12-lead ECG at 1 hour (±15 minutes) and 12 (±2) hours after study drug administration
- Perform physical examination at 48 hours.
- Collect knee and thigh measurements of the surgical leg on the morning of Day 2 (ie, the day after surgery) and Day 3.
- Assess the surgical wound for the SWAS parameters (see Appendix 4) when collecting the knee measurement on the morning of Day 2 (ie, the day after surgery).
- Conduct the TUG test once on the day of the surgery following surgery; at approximately 8:00 am and 8:00 pm (±2 hours) on Day 2 (ie, the day after surgery); at hospital discharge; and on Day 7 (see Appendix 1).
- Perform passive and active knee flexion assessment twice daily at the time of the physical therapy assessments (ie, approximately 8:00 am and 8:00 pm [±2 hours] daily) until hospital discharge.
- Perform neurological assessment at 12, 24, 36, 48, 60, 72, and 96 hours (see Appendix 2).
- Record any blood transfusion data (eg, start and stop times, number of units).
- Record any reoperations due to hematoma or wound dehiscence.
- Record concomitant medications (patient-controlled analgesia for control of postsurgical pain is not permitted)
- Record date and time of discharge from hospital.
- Record AEs and any treatment(s) for the events.
- Refer to Section 13.1.10 for additional procedures in the event an AESI or SAE occurs.

13.7. Day 7 Visit

- Record NRS-R pain score (see Appendix 3; 0 [no pain] to 10 [worst possible pain])
- Collect blood sample for hemoglobin and hematocrit
- Collect blood samples for clinical laboratory testing (hematology [including Hb and hematocrit], chemistry [with creatinine clearance calculation], and coagulation).
- Collect knee and thigh measurements of the surgical leg.
- Assess the surgical wound for the SWAS parameters (see Appendix 4) when collecting the knee measurement.
- Conduct TUG test (see Appendix 1).

- Record date and time of discharge, if applicable.
- Record any blood transfusion data (eg, start and stop times, number of units).
- Record any reoperations due to hematoma or wound dehiscence.
- Record AEs and any treatment(s) for the events.
- Refer to Section 13.1.10 for additional procedures in the event an AESI or SAE occurs.
- Record whether patient has achieved independent ambulation

13.8. Day 14 (±1 day) Telephone Call

- Record any blood transfusion data (eg, start and stop times, number of units).
- Record any reoperations due to hematoma or wound dehiscence.
- Record AEs and any treatment(s) for the events.
- Record whether patient has achieved independent ambulation

13.9. Day 30 (±3 days) Telephone Call

- Record any blood transfusion data (eg, start and stop times, number of units).
- Record any reoperations due to hematoma or wound dehiscence.
- Record AEs and any treatment(s) for the events.
- Record whether patient has achieved independent ambulation

13.10. Day 60 (±3 days) Telephone Call

- Record SAEs, AESI, other AEs, and any treatment(s) for the events.
- Record whether patient has achieved independent ambulation

14. ADVERSE EVENT REPORTING

Consistent with the current regulatory guidance provided by the US FDA CFR Part 312 and the ICH GCP, AEs and SAEs are defined in Section 14.1.1 and Section 14.2.1, respectively.

The concepts of AEs and SAEs represent regulatory instruments used to evaluate and monitor the safety of clinical study patients. Therefore, these terms only apply in light of their regulatory definition. The term serious, in a regulatory sense, does not necessarily mean severe. The SAE concept is used primarily to identify, during the conduct of the study, those SAEs that may require expedited reporting to regulatory authorities.

14.1. Adverse Events

14.1.1. Definitions

Definition of Adverse Event (AE)*:* Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about

causality. An AE can arise from any use of the drug (eg, off-label use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

An AE can be any unfavorable and unintended change in a body structure or body function. Adverse events include any clinically significant deterioration of a patient's medical status. The AE may involve any organ or system and can be represented by the new onset or deterioration of a disease, a syndrome, a symptom, a physical sign, as well as by findings and results of instrumental examinations and laboratory tests. Any medically relevant and untoward change after the patient signs the ICF, including frequency or pattern changes for a fluctuating condition (eg, migraine) is considered an AE.

An AE that occurs after the ICF is signed and before the start of the study drug administration is identified as a pretreatment AE (PTAE). A TEAE will be any adverse event or pre-existing medical condition that worsens in intensity after the start of study drug and within 30 days of the last dose.

Definition of Adverse Reaction: Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Definition of Suspected Adverse Reaction*:* Any AE for which there is a reasonable possibility that the drug caused the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug. Suspected adverse reactions are a subset of all AEs for which there is a reasonable possibility that the drug caused the event.

14.1.2. Recording Adverse Events

It is the responsibility of the Investigator to document all AEs (ie, PTAEs and TEAEs) with an onset after the patient signs the ICF. For the purpose of this study, all AEs that occur through Day 60 (±3 days) must be recorded regardless of whether or not they are considered related to study drug. Whenever feasible, AE terms should be documented as medical diagnoses (highest possible level of integration); otherwise, the AEs should be reported separately as individual signs or symptoms. Only one AE per line should be recorded in the AE CRF; for example, an AE of nausea and vomiting should be listed as two separate events: the event of nausea and the event of vomiting. If a diagnosis is established after symptoms are recorded on the AE CRF, the diagnosis should be recorded and the symptoms collapsed (removed; ie, lined through and initialed). Whenever possible, abnormal laboratory results should be reported as their clinical corollary (eg, low potassium should be recorded as hypokalemia).

A continuous AE with varying grades of severity should be recorded as one AE. The highest grade of severity experienced by that patient during the course of the continuous AE should be recorded.

Any condition noted before the patient signs the ICF will be listed as medical history and is considered a pre-existing condition. If a pre-existing condition changes (ie, becomes more severe or more frequent) at any time after the ICF is signed, or after study drug administration,

it is considered an AE. Note: A change in treatment for a pre-existing condition (eg, new high blood pressure medication), does not necessarily indicate an AE.

Information recorded on the AE CRF will include the AE term, the date and time of onset, severity, seriousness, relationship to study drug, action taken with patient because of an AE, and the outcome of the AE, including the date and time of resolution, if applicable.

14.1.3. Severity of Adverse Events

In general, the severity of an AE should be categorized using the following guidelines:

Mild:	An AE that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
Moderate:	An AE that is discomforting and interferes with normal everyday activities.
Severe:	An AE that prevents normal everyday activities.

The term severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as serious, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

14.1.4. Relationship of Adverse Events to Study Drug

The Investigator will assess the relationship of the AE to study drug after careful medical consideration on a case-by-case basis. General guidelines for determining the AE's causality to the study drug are provided below.

Unrelated:	A causal relationship between the study drug and the AE can be easily ruled out (eg, based on the temporal sequence, absence of a reasonable pathophysiological mechanism, or direct evidence of actual cause).
Unlikely:	A clinical event with a temporal relationship to study drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide a plausible explanation;
Possible:	A clinical event with a reasonable time sequence to administration of the study drug but which could also be explained by a concurrent disease or other drugs or chemicals;
Probable:	A clinical event with a reasonable time sequence to administration of the study drug unlikely to be attributed to a concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (dechallenge); or

Definite:	The pharmacological properties of the study drug(s) or of the substance class, and the course of the AE after dechallenge and, if applicable, after rechallenge, and/or specific test indicate involvement of the study drug(s) in the occurrence/worsening of the AE, and no indication of other causes exists.

14.1.5. Outcome of Adverse Events

The Investigator will assess the outcome of the AE after careful medical consideration, on a case-by-case basis. General guidelines are provided below:

Recovered/Resolved:	The event resolved and the patient recovered from the AE.
Recovered/Resolved with Sequelae:	The initial event resolved, but has a continuing abnormal condition as a result of the AE.
Not Recovered/ Not Resolved:	At the time of last assessment, the event was ongoing, with an undetermined outcome. Note: ongoing AEs are not to be considered resolved as a result of death.
Recovering/Resolving:	At the time of last assessment, the event was decreasing in frequency, severity, etc., and a resolution was expected.
Fatal:	The AE directly caused death.
Unknown:	There was an inability to access the patient or the patient's records to determine the outcome (eg, patient withdrew consent or was lost to follow-up).

14.1.6. Action Taken with Patient Because of an Adverse Event

The Investigator will provide any actions taken regarding the patient (eg, treatment, diagnostic tests, laboratory tests, or therapy) for each reported AE.

- None.
- Medication.
- Non-pharmaceutical therapy. (The specific therapy used must be recorded in the CRF.)
- Discontinued from study.
- Other. (The specific action taken must be recorded.)

14.2. Serious Adverse Events

14.2.1. Definition of a Serious Adverse Event

Definition of a Serious Adverse Event (SAE): An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death[1]

- A life-threatening adverse event[2]
- Inpatient hospitalization or prolongation of existing hospitalization[3]
- A persistent or significant incapacity[4]
- Congenital anomaly/birth defect
- Medically significant[5]

[1]**Death:** Any event resulting in a patient's death must be reported as an SAE. However, death, in and of itself, is not an AE; it is an outcome. The cause of death is the AE. Therefore, the Investigator should make every effort to obtain and document the cause of death for all patients who die during the study. If, despite all efforts, the cause of death remains unknown, the AE should be documented as an "unspecified fatal event."

[2]**Life-threatening**: An AE is considered life-threatening if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE that had it occurred in a more severe form might have caused death.

[3]**Hospitalization**: It should be noted that hospitalization, in and of itself, does not represent an SAE. It is the AE leading to the patient's hospitalization that becomes "serious" when it requires inpatient care. Consequently, an SAE should not be reported in case of preplanned hospitalizations for a pre-existing condition that did not worsen during the study. However, any medical condition that delays a patient's discharge from the hospital (ie, prolonged hospitalization) or requires the patient to be readmitted should be reported as an SAE.

[4]**Persistent or significant incapacity**: A substantial disruption of a person's ability to conduct normal life functions.

[5]**Medically Significant**: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medically significant events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.2.2. Reporting Serious Adverse Events

Any SAE or death that occurs at any time after the patient signs the ICF through Day 60 (±3 days), whether or not related to study drug, must be reported by the Investigator or designee to Pacira Drug Safety within 24 hours of discovery by either email (drugsafety@pacira.com) or fax (973-201-0649). In addition, the Investigator or designee is encouraged to contact the Medical Monitor to discuss the case, as needed.

Investigators should not wait to receive additional information to fully document the event before notifying Pacira Drug Safety or designee of the SAE. The fax or email report should be followed by a full written summary using the SAE Form detailing relevant aspects of the SAE in question. Where applicable, information from relevant hospital records and autopsy reports

should be obtained and all patient-identifying information redacted prior to forwarding to Pacira. In the event of a fatal or life-threatening SAE, any required follow-up must be provided to Pacira Drug Safety or designee immediately. The Investigator will follow all SAEs until resolved or the condition stabilizes and further follow-up is not warranted.

If the Investigator is made aware of any SAEs after Day 60 (±3 days), these should also be reported to Pacira Drug Safety or designee provided the SAE is considered related to study drug. The site would then provide a completed SAE form within 1 business day and the event would be followed until resolution, or until adequate stabilization is met.

15. STATISTICAL METHODS

A comprehensive statistical analysis plan (SAP) will be developed for this study.

15.1. Study Hypothesis

No formal hypothesis testing will be conducted in this study.

15.2. Study Endpoints

The endpoints to be assessed in this study are listed in Section 12.2 (Efficacy Endpoints), Section 12.4 (PK Endpoints), and Section 12.6 (Safety Endpoints).

15.3. Determination of Sample Size

Sample size was not based on statistical considerations.

15.4. Analysis Populations

The following analysis sets are planned:

Safety: The safety analysis set will include all patients who receive study drug and will be based on actual treatment received.

Efficacy: The efficacy analysis set will include all patients in the safety analysis set who undergo the planned surgery and will be based on randomized treatment, regardless of actual treatment received.

Pharmacokinetic: The PK analysis set will include all patients in the safety analysis set who receive study drug, provide sufficient samples to allow for calculation of PK parameters required for analysis, and do not have significant protocol deviations that may invalidate or bias the results.

15.5. Handling Patient Dropouts and Discontinuations

Data imputation rules will be described in the SAP.

15.6. Statistical Analyses

15.6.1. Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group.

15.6.2. Study Compliance

The percentage of patients in each analysis set and the percentage who fail to complete the study (as well as the reasons for discontinuation) will be displayed by treatment group.

15.6.3. Efficacy Analyses

All efficacy analyses will be based on randomized treatment, regardless of actual treatment received.

15.6.3.1. Total Blood Loss

Total loss will be calculated separately using two separate methods. The first method is based on Hct and the second method is based upon Hb for 6, 12, 24, 48, 72, and 120 hours postsurgically and Day 7 for each patient. Descriptive statistics summarizing the total blood loss will be summarized by postsurgical timepoint and treatment group for the efficacy analysis population for each method. Baseline is considered the last value measured before the surgery.
Total BV in mL will be calculated using the Nadler formula (Nadler 1962) at baseline by

$$BV_{baseline} = (a * h^3 + b * w + c)$$

where h = height (m), w = baseline weight (kg), {a=0.3669, b=0.03219, c=0.6041} for males and {a=0.3561, b=0.03308, c=0.1833} for females. The BV at baseline is used in methods 1 and 2 to determine blood loss.

Method 1 (Gibon 2013):
Total blood loss is in mL calculated by the following formula:

$$= BV_{baseline} * \left(Hct_{baseline} - Hct_{post-op\ hour}\right) + \mathrm{BV}_{transfused}$$

where $Hct_{baseline}$ is measured as a proportion, $Hct_{post-op\ hour}$ is measured as a proportion at the specified postsurgical timepoint in hours, total BV is measured in mL, and $\mathrm{BV}_{transfused}$ is the mL volume of blood transfused to the patient.

Method 2 (Goa 2015):
Total blood loss in mL is calculated by the following formula:

$$= \frac{1000 * BV_{baseline} * \left(Hb_{baseline} - Hb_{post-op\ hour}\right) * 0.001 + \mathrm{BV}_{transfused}}{Hb_{baseline}}$$

where $Hb_{baseline}$ is measured in g/L, $Hb_{post-op\ hour}$ is measured in g/L at the specified postsurgical timepoint in hours, $BV_{transfused}$ is the mL volume of blood transfused to the patient, and total BV is measured in mL.

15.6.3.2. Other Efficacy Analyses

Descriptive statistics will be provided for the incidence of transfusion, the time to 90 degrees passive and active knee flexion, results of the TUG test, knee and thigh measurements, pain scores, days to independent ambulation, and SWAS by postsurgical timepoint and treatment group for the efficacy analysis population. Further details will be described in the SAP.

15.6.4. Pharmacokinetic Analyses

Pharmacokinetic parameters will be estimated from the PK analysis set, using plasma drug concentration-time profiles, where appropriate, by non-compartmental analysis.

Actual sampling time will be used for all calculations of the PK parameters. If there is any doubt in the actual time a sample was taken, then the scheduled time will be used.

Descriptive statistics will be used to summarize the PK parameters.

Dose Modeling based on Pharmacokinetic Parameters

Dose models will be estimated from the PK analysis set, using pharmacokinetic parameters, to aid in the dose selection (DepoTXA 800 mg, DepoTXA 1200 mg) for future studies.

15.6.5. Safety Analyses

All safety analyses will be based on actual treatment received.

15.6.5.1. Adverse Events

Adverse event verbatim terms will be mapped to preferred terms and related system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). Events that start prior to the start of study drug administration will be identified in listings only. Incidence rates of TEAEs and the proportion of patient prematurely withdrawn from the study because of a TEAE will be shown for each treatment group. Incidence rates will also be displayed for each treatment group for study drug-related TEAEs and by severity. Incidence rates of SAEs will also be shown for each treatment group. All incidence rates will be categorized and displayed by system organ class and preferred term.

15.6.5.2. Vital Signs

Descriptive statistics for each vital sign for baseline, each timepoint, and change from baseline at each timepoint will be summarized for each treatment group.

15.6.5.3. Clinical Laboratory Data

Descriptive statistics for each laboratory test for baseline, each timepoint, and change from baseline at each timepoint will be summarized for each treatment group.

15.6.5.4. Electrocardiograms

Descriptive statistics for each ECG parameter for baseline, each timepoint, and change from baseline at each timepoint will be summarized for each treatment group.

15.6.5.5. Neurological Assessment

The proportion of patients who are oriented at each timepoint will be summarized for each treatment group. The proportion of patients who have at least one of the neurological events will be summarized for each treatment group.

15.7. Significance Testing

No formal significance testing will be conducted in this study.

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17. INVESTIGATOR AGREEMENT

Printed Name of Investigator: _____

Printed Title/Position: _____

Printed Institution Address: _____

_____

_____

_____

_____

I have reviewed this protocol (including Appendices) and agree:

- To assume responsibility for the proper conduct of the study at this site;
- To conduct the study in compliance with this protocol, with any future amendments, and with any other study conduct procedures provided by Pacira Pharmaceuticals, Inc. (Pacira) or designee. I also agree to comply with Good Clinical Practice and all regulatory requirements;
- Not to implement any changes to the protocol without agreement from Pacira or designee and prior review and written approval from the Independent Ethics Committee, except where it is necessary to eliminate an immediate hazard to the patients or for administrative aspects of the study (where permitted by applicable regulatory requirements);
- That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and with other relevant information (eg, the Investigator's Brochure);
- To ensure that all persons assisting me with the conduct of this study are adequately informed about the investigational product(s) and about their study-related duties and functions as described in this protocol;
- That I am aware that regulatory authorities may require Investigators to disclose all information about significant ownership interests and/or financial ties related to the Sponsor and/or the investigational product(s). Consequently, I agree to disclose all such significant financial information to Pacira and to update this information promptly if any relevant changes occur during the course of the study through 1 year following completion of the study. I also agree that any information regarding my significant financial interest related to Pacira and/or the investigational product(s) will be disclosed to the regulatory authorities by Pacira.

_____ _____

Signature of Investigator Date

18. APPENDICES

Appendix 1: Timed Up-and-Go Test

The TUG test will be conducted during the screening visit. Postsurgically, conduct the TUG test once on the day of the surgery following surgery; at approximately 8:00 am and 8:00 pm (±2 hours) on Day 2 (ie, the day after surgery); at hospital discharge; and on Day 7.

EQUIPMENT REQUIRED

- Timer/stop watch
- Standard chair (seat height: approximately 17 inches) with two arm rests (arm rest height: approximately 26 inches)
- Ruler to measure seat height and arm rest height
- Measuring tape to measure 3 meters away from the chair (approximately 9 feet 10 inches)
- Tape or other marker to mark the distance so that it is easily seen by the patient

Therapist Instructions

1. Patient begins seated on a standard chair with arm rests. Ensure the chair cannot slide backwards by placing it against a wall or otherwise bracing it (eg, physical therapist braces with foot).
2. Patient is instructed to sit facing forward, with both feet on the floor, and their buttocks touching the back of the seat
3. A line is placed on the floor 3 meters in front of the chair. Use a measuring tape to measure this distance. Alternatively, place the chair 3 meters away from an existing marker (eg, floor tile).
4. Patient is instructed that "On the word GO you will stand up, walk to the line on the floor, turn around, and walk back to the chair and sit down. Walk at your regular pace."
5. The physical therapist then says "GO" and starts the stopwatch and records the time of assessment.
6. The physical therapist walks alongside the patient, for safety purposes, and notes the amount of physical assistance required.
    a. Total assistance (patient contributes <25% of the effort or is unable to do the task)
    b. Maximal assistance (patient provides less than half of the effort (25–49%))
    c. Moderate assistance (patient still performs 50–75% of the task)
    d. Minimal assistance (requiring incidental hands-on help only (patient performs >75% of the task)
    e. Supervision (requiring only standby assistance or verbal prompting or help with set-up)
    f. Modified independence (requiring the use of a device but no physical help)
    g. Complete independence (fully independent)

7. The goal of the test is to measure the patient's ability to complete the activity without assistance. The therapist should endeavor to not provide assistance unless required for safety reasons.
8. After the patient has completed the activity, the physical therapist stops the stopwatch and records the time lapsed in seconds
    a. If the test is not performed, the physical therapist will record the specific reason.
    b. Patient should be encouraged to complete the test. Time will continue to run until therapist determines it cannot be completed and the test is stopped.
9. The same chair should be used for all assessments, while on study.

Patient Instructions

1. Start by sitting in the chair with your back resting on the backrest and your hands on the armrest.
2. On "GO," stand up, walk to the mark, turn around, return, and sit back into the chair with your back resting on the back of the chair.
3. Walk at your normal pace as safely as you can.
4. Get ready and GO.

Scoring

1. The test starts on the signal to start ("GO") and terminates once the participant sits back down fully with their back resting on the back of the chair.
2. The duration of the test is recorded to nearest 10th of a second.
3. A walking aid is allowed and should be recorded, if used.
4. Record the physical assistance required.

Appendix 2: Neurological Assessment

The neurological assessment will be conducted at screening, baseline (Day 1 pre-op, prior to surgery); and at 12, 24, 36, 48, 60, 72, and 96 hours.

The examination will include the patient's orientation.

- Is the patient oriented?
  Yes ☐ No ☐ Not Assessable

If the patient is not oriented, the event must be recorded as an AE.

Additionally, the patient will be asked the following questions:

- Do you have numbness of the lips, the tongue, or around the mouth?
  Yes ☐ No
- Do you have a metallic taste in your mouth?
  Yes ☐ No
- Are you having problems with your hearing not related to the use of a hearing aid?
  Yes ☐ No
- Are you having problems with your vision not related to the use of eye glasses?
  Yes ☐ No
- Are your muscles twitching?
  Yes ☐ No

If the patient answers “yes” to any of these questions, the event must be recorded as an AE (see Section 13.1.10).

Appendix 3: Numerical Rating Scale at Rest Pain Scores

Patients will be evaluated for pain using the numerical rating scale at rest (NRS-R) on the day of surgery prior to surgery, upon arrival at the PACU, at each in-hospital vital sign assessment beginning with the 2-hour assessment and ending with the 72-hour assessment, and at the Day-7 follow-up visit.

Pain Intensity Scale

On a scale of 0 to 10, where 0 = no pain and 10 = worst possible pain, circle the number that best describes how much pain you are having right now. (Circle only one number.)

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

Appendix 4: Surgical Wound Aspect Score

The surgical wound aspect score, adapted from Torres-Claramunt, et al (Torres-Claramunt, 2015), will be calculated based on the knee measurements collected on the morning of Day 2 (ie, the day after surgery) and on Day 7 and the following wound parameters scored at the time of the knee measurements on the morning of Day 2 (ie, the day after surgery), and on Day 7.

WOUND OOZING

Upon removal of the dressing, assess the surgical wound for oozing and score oozing as:

No signs of blood on the gauze	0
1-2 spots of blood on the gauze	1
>2 spots of blood on the gauze	2

ERYTHEMA

Assess the surgical wound for the presence/extent of erythema and score the presence/extent of erythema as:

Erythema absent	0
Erythema at wound edges	1
Erythema beyond wound edges	2

ECCHYMOSIS

Assess the surgical wound for the presence/extent of ecchymosis and score the presence/extent of ecchymosis as:

Ecchymosis absent	0
Ecchymosis at wound edges	1
Ecchymosis beyond wound edges	2

BLISTERS

Assess the surgical wound for the presence/size of blisters and score the presence/size of blisters as:

Blisters absent	0
1-2 blisters of < 2 cm each	1
>2 blisters of any size **or** ≥1 blister >2 cm	2

Appendix 5: Clinical Laboratory Tests

The scheduled clinical laboratory tests (hematology, coagulation, and chemistry) will be conducted at screening; baseline (Day 1 pre-op, prior to surgery); 48 hours; and Day 7. Clinical laboratory tests, as appropriate, must also be conducted if a patient experiences an AE of special interest or an SAE (see Section 13.1.10).

Basic Metabolic Profile

Glucose
Calcium
Sodium
Potassium
Carbon dioxide (bicarbonate)
Chloride
Blood urea nitrogen
Creatinine
Total cholesterol
High-density lipoprotein (HDL) cholesterol
Low-density lipoprotein (LDL) cholesterol
Triglycerides

Coagulation

Fibrinogen
Fibrin split products

Hematology

White blood cells
Red blood cells
Hemoglobin
Hematocrit
Mean corpuscular volume
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Red cell distribution width
Platelets
Mean platelet volume
Absolute/percent neutrophil count
Absolute/percent lymphocyte count
Absolute/percent monocyte count
Absolute/percent eosinophil count
Absolute/percent basophil count