A RANDOMIZED, DOUBLE-BLIND, PLACEBO- CONTROLLED TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF XG005 TABLETS IN SUBJECTS UNDERGOING BUNIONECTOMY

PROTOCOL PR-XG005-02-BUN-01

Version 5.0

15 Nov 2022

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XGENE PHARMACEUTICAL INC.

SPONSOR SIGNATURE PAGE

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Sponsor: Xgene Pharmaceutical, Inc.

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[redacted] 15 Nov 2022

Sponsor Signature Date

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1.1. Synopsis

Sponsor:	**Xgene Pharmaceutical Inc.**
Protocol #:	PR-XG005-02-BUN-01
Protocol Title:	A Randomized, Double-Blind, Placebo Controlled Trial to Evaluate the Safety and Efficacy of XG005 Tablets in Subjects Undergoing Bunionectomy
Investigational Product:	XG005 (oral tablets)
Planned Study Center:	Three study centers in the United States (US) at minimum
Phase of Development:	Phase 2b
Study Design:	This is a multi-center, randomized, double-blind, parallel-group, placebo-controlled study. Subjects scheduled for bunionectomy surgery must meet all of the inclusion criteria and none of the exclusion criteria below prior to being enrolled and randomized. Eligible subjects will be randomized in a 1:1:1 ratio to receive either 750 mg XG005, 1250 mg XG005, or placebo. Randomized subjects will receive drug per their treatment allocation as follows: • 60 minutes prior to surgery and every 12 hours (± 10 minutes) after the first dose for 72 hours. • Subjects and all study staff performing study assessments will be blinded to treatment allocation. To maintain the blind, a total of 5 tablets will be administered to each treatment group: 5 identical blue tablets (low or high dose XG005 or its placebo) at each time point. Subjects will undergo a Screening (Day -28 to Day -1), Pre-Operative Assessment (within 24 hours prior to surgery) and Surgery/Treatment Visit (beginning Day 1), when the following will occur: • Study medication administered 60 ± 10 minutes prior to surgery, record time. • Surgery performed, record starting time • Record time of end of surgery (as time of last suture closed) • Subjects domiciled in research center for at least 72 hours post-surgery • Efficacy and safety assessments performed over 72-hour period post-surgery "Time 0" will be defined as the actual start time of the first dose from which subsequent 12-hour dosing times will be determined. All study efficacy and safety assessments are anchored to time at end of surgery (last suture). Pharmacokinetic (PK) sampling timepoints correlate with the collection of the 11-pt Numeric Pain Rating Scale (NPRS) efficacy assessments when they overlap. Subjects will be advised at Screening that if they terminate the study prior to 72 hours, it is requested that they remain in the clinic for continued collection of scheduled safety data only. Screening will include subjects' potential placebo response by use of a pre-study personality questionnaire (Appendix B). Subjects will be discharged at a reasonable hour of the day after the end of the 72-hour treatment period, which may include the morning after the end of the 72-hour treatment period. There will be a Follow-up Visit on Day 15. Early Termination visits will include the following assessments: NPRS, Patient Global Assessment (PGA) of pain control, Numeric Nausea Rating Scale (NNRS),

	Sleep Interference Score (SIS) and safety assessments (vital signs, electrocardiogram [ECG], continuous pulse oximetry, laboratory testing, Ramsay Sedation Scale (RSS), and concomitant medications).
Study Assessments	All assessments are anchored to time at end of surgery (last suture). Details of all study assessments are provided in the Schedule of Assessments. **Efficacy and Safety Assessments** Study staff will record subject-reported pain assessments via a standard 11-point NPRS at the following time points post-end of surgery: 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours within a ±10-minute window (Appendix C). NPRS will be collected prior to PK sampling and administration of rescue or study medication. Study staff will record subject-reported PGA of pain control using a 5-point scale (poor, fair, good, very good, excellent) at the following time points post-end of surgery: 24, 48, and 72 hours within a ±10-minute window and just prior to receiving a dose of rescue medication if needed (Appendix D). Study staff will record the time and the dose of rescue medication administered on the rescue medication form. NPRS and PK sampling will be collected immediately prior to administering rescue medication. Nausea will be self-assessed using an 11-point NNRS at the following time points post-end of surgery: 1, 4, 8, 12, 24, 48, 72 hours within a ±10-minute window (Appendix E). Additional NNRS assessments will be collected when an AE of nausea or vomiting is reported or prior to any rescue antiemetic administration. Subject will report Sleep Interference Score (SIS) using an 11-point NRS scale (0-10) at 24, 48 and 72 hours post-end of surgery within a ±15-minute window (Appendix F). Study staff will monitor for adverse events (AEs) and serious AEs (SAEs), ECG data, and vital signs (blood pressure [systolic and diastolic], heart rate, respiratory rate, oral body temperature, and continuous pulse oximetry), and record relevant safety data. Trained staff on hand in the research unit will monitor respiratory safety via respiration rate, continuous pulse oximetry and oxygen saturation (SpO_2) checks every 12 hours post-end of surgery within a ±10minute window. The Ramsay Sedation Scale (RSS, Appendix G) used to assess somnolence to be assessed by study staff within a ±15minute window when NPRS is assessed. The Columbia-suicide severity rating scale **(**C-SSRS, Appendix K**)** will be administered 72 hours after treatment and at the end of study visit to assess suicidal ideation. **Pharmacokinetic** Blood draws will always be performed after each NPRS, nausea, SIS and/or PGA assessment, when applicable, and prior to the first administration of rescue medication. The PK sampling plan uses the post-end-of-surgery schedule to be consistent with the efficacy assessment schedule. Each subject in the PK subgroup (one site only) will have blood samples drawn for PK assessments at the following time points: prior to the first dose (pre-dose), and post end of surgery at 1, 2, 3, 4, 6, 8, 10, 12, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours within a ±15-minute window. The actual clock time when the PK sample is collected will be recorded, and the post-dose time for PK analysis will be calculated based on the recorded clock time.
Number of Subjects:	A total of 450 subjects will be randomized (150 per arm) to achieve 130 evaluable subjects per treatment group. An evaluable subject is defined as one who receives study drug, completes surgery, and has at least 2 post-operative pain assessments.

	A PK subgroup of 90 subjects (30 subjects per study arm) will be assessed at 1 site only.
Surgical and Anesthetic Protocol:	Subjects will undergo primary, unilateral, first metatarsal Austin bunionectomy. The surgical procedure should be limited to a maximum duration of 90 minutes. End of surgery will be defined as completion of the last suture. The surgery will be performed under regional anesthesia via a local Mayo block using lidocaine (20 mL, 2.0%) without epinephrine, with intravenous (IV) propofol for sedation. Propofol induction (dose per discretion of anesthesiologist) will be given as an initial bolus followed by a continuous infusion of up to 250 µg/kg/min for intraoperative sedation. A small dose of lidocaine (up to 5 mL of 1% lidocaine without epinephrine) may be administered to reduce vein irritation at the infusion site. Intraoperatively, all subjects will be given 50 µg of fentanyl IV around the time of induction with propofol. Once sedated, a Mayo block of the first metatarsal will be induced using lidocaine (20 mL, 2.0%) without epinephrine. Midazolam 1 mg IV may be administered preoperatively for anxiolysis. A pneumatic ankle tourniquet inflated between 150 and 250 mmHg will be applied to achieve homeostasis.
Study Arms:	1. Placebo [matching tablets Q12 hours] 2. XG005 [750 mg Q12 hours] 3. XG005 [1250 mg Q12 hours]
Rescue Medication:	First-line rescue pain medication, IV acetaminophen 1 g, will be administered Q 6 hours, PRN, up to 4 g in 24 hours. If a patient is unable to tolerate acetaminophen or if there is insufficient pain relief, 50 mg tramadol will be administered Q 4 hours, PRN, up to 300 mg in 24 hours.
Permitted Medications	If a subject receives inadequate analgesia from study treatment and allowed rescue medication, they may terminate from the efficacy portion of the study and receive open-label standard of care analgesia excluding NSAIDs or gabapentinoids as per the discretion of the investigator. At the time of receiving standard of care analgesia, the following assessments will be performed prior to receiving standard of care analgesia: • NPRS • PGA • PK sample Because subjects will remain in the unit and continue to have all other assessments performed there is no need to do anything else at this time. If a subject is not willing to remain in the unit, then they should have all assessments as detailed in the current protocol language for early termination. Subjects who terminate early due to lack of efficacy will continue to receive their allotted study treatment and will continue to undergo all safety and pharmacokinetic assessments as scheduled. These subjects will also continue with all scheduled follow up visits (unless the subject withdraws consent). Subjects who withdraw because of an AE, would not continue to receive study medication. *Antiemetics* No pretreatment for potential nausea and vomiting is permitted. Administration of antiemetic medications are limited to subjects with active vomiting, subjects with a score ≥5 on the NNRS, or by subject request only.
Study Objectives:	*Primary Efficacy*

	• To evaluate the efficacy of high dose XG005 [1250 mgQ12] compared to placebo for pain control in subjects undergoing bunionectomy *Secondary Efficacy* • To evaluate the efficacy of low dose XG005 [750 mg Q12] compared to placebo for pain control in subjects undergoing bunionectomy • To evaluate high and low dose XG005 compared to placebo for total rescue consumption and time to first use from end of surgery • To evaluate high and low dose XG005 compared to placebo for PGA • To evaluate high and low dose XG005 compared to placebo for postoperative nausea • To evaluate the efficacy of high dose XG005 compared to low dose XG005 for pain control in subjects undergoing bunionectomy *Tertiary Efficacy (All Treatment Arms)* • To evaluate rescue medication consumption at 24, 48, and 72 hours, time to first use of rescue medication from end of surgery, and proportion of subjects requiring rescue medication. • To evaluate nausea assessment scores at various timepoints • To evaluate high and low dose XG005 compared to placebo for SIS *Exploratory* • To estimate subject's potential placebo response by use of a pre-study personality questionnaire at Screening *Safety and Tolerability* • To evaluate the safety and tolerability of XG005 in a perioperative population *Pharmacokinetics* • To investigate the PK of XG005 in a perioperative population
Primary Efficacy Endpoint:	Summed pain intensity from end of surgery to 48 hours post-surgery (SPI48) for high dose XG005 vs placebo
Secondary Endpoints:	*Key Secondary Endpoints:* 1. SPI48: low dose XG005 vs placebo 2. Total tramadol rescue medication consumption in morphine equivalents (MEQs) over 48 hours: high dose XG005 vs placebo 3. Total tramadol rescue medication consumption in morphine equivalents (MEQs) over 48 hours: low dose XG005 vs placebo *Additional Endpoints:* 4. Time to first use of rescue medication from end of surgery: high dose XG005 vs placebo 5. Time to first use of rescue medication from end of surgery: low dose XG005 vs placebo 6. PGA at 48 hours: high dose XG005 vs placebo 7. PGA at 48 hours: low dose XG005 vs placebo 8. Cumulative Nausea (NNRS) assessment scores through 24 hours: high dose XG005 vs placebo 9. Cumulative Nausea (NNRS) assessment scores through 24 hours: low dose XG005 vs placebo 10. SPI48: high dose XG005 vs low dose XG005
Tertiary Endpoints:	*Tertiary Endpoints for All Treatment Arms:* • Total rescue medication consumption at 24, 48, and 72 hours

	• Nausea (NNRS) assessment scores at 1, 4, 8, 12, 24, 48, and 72 hours • SPI at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours • Pain intensity at various timepoints • SIS at 24, 48 and 72 hours • Percentage of subjects requiring rescue at various timepoints • PGA of pain control at various timepoints • Ramsay Sedation Scale at various timepoints *Exploratory:* • Estimate of subject susceptibility to placebo response at Screening using a pre-study personality questionnaire
Safety and PK Endpoints	*Safety* Safety and tolerability of XG005 compared with placebo measured by AE reporting (incidence of AEs and SAEs), vital signs, SPO_2, ECGs, and laboratory values. Sedation will be assessed by study staff by use of the Ramsay Sedation Scale (RSS) when NPRS can be assessed. Nausea will be self-assessed using an 11-point NNRS. *Pharmacokinetics* Plasma PK parameter endpoints to include the following: • Area under the plasma concentration-time curve from time zero to time t of the last measured concentration above the limit of quantification (AUC_{last}) • Area under the plasma concentration-time curve from zero to infinity (AUC_{inf}) • Maximum plasma concentration (C_{max}) • Trough plasma concentration prior to each dose (C_{trough}) • Time to reach maximum plasma concentration (T_{max}) • Terminal elimination rate constant (λz) with the respective half-life ($t_{1/2}$).
Inclusion Criteria:	1. Willing and able to sign the informed consent form (ICF) approved by the Institutional Review Board (IRB) 2. Male or female aged 18–80 years 3. Scheduled to undergo unilateral first metatarsal bunionectomy 4. Capable of undergoing a bunionectomy under anesthesia as described in the study surgical and anesthetic protocol 5. Weight > 50 kg and a body mass index (BMI) < 39 kg/m^2 6. No additional planned surgeries other than bunionectomy during the course of the study 7. Have negative urine drug screen for drugs indicative of illicit drug use (unless results can be explained by a current prescription or acceptable over-the-counter [OTC] medication at Screening as determined by the Investigator) and no detectable results on the alcohol test (breath or saliva) indicative of alcohol abuse at Screening, and/or prior to surgery (may be repeated if the Investigator suspects a false-positive result) Note: For those subjects who test positive for tetrahydrocannabinol (THC), if they are willing to abstain from use or consumption of THC-containing products from Screening through end of the subject's participation in the study, they may be allowed to participate in the study. 8. Biological female subjects must be non-lactating. They must also be either sterile (bilateral tubal ligation, bilateral salpingectomy, or hysterectomy), post-menopausal for at least 1 year, have a partner who is sterile, be abstinent, have a same-sex partner, use a highly effective double-contraception method (hormonal protection is insufficient), or use an FDA-approved contraceptive for greater

	than 2 months prior to Screening visit and commit to an acceptable form of birth control for the duration of the study and for 30 days from completion of the study. 9. Willing and able to complete the study procedures and pain scales and to communicate meaningfully in English with study personnel. 10. Negative result of COVID-19 test within 3 days before Day 1 visit.
Exclusion Criteria:	1. **Medical condition or history** that in the investigator's opinion could adversely impact the subject's participation or safety or the conduct of the study, or interfere with the pain assessments, including the following: a. Serious breathing difficulties or respiratory risk factors (including clinically significant use of opioid pain medicines and other drugs that depress the central nervous system [CNS]) and conditions such as chronic obstructive pulmonary disease (COPD) that reduce lung function) b. Clinically unstable hypertension, cardiovascular disease, or history of cerebrovascular events. Hypertension must be stable without known end organ damage c. Concurrent painful conditions that may require analgesic treatment during the study period d. History of significantly reduced hepatic function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], or lactase hydrogenase [LDH] ≥ 1.5 x upper limit of normal [ULN] or renal function (creatinine ≥1.5 x ULN), angle closure glaucoma, or convulsive disorder e. Recent history of urinary retention f. History of gastrointestinal ulcer, bleeding, perforation, or recent surgery of gastrointestinal tract g. Subject is currently taking or has taken a chronic opioid at a dose greater than or equal to 20 mg hydrocodone per day ([≥ 20 MEQs] more than 30 consecutive days of daily use) for pain in the 2 months prior to surgery. h. Active cutaneous disease, or other disease, at the surgical site i. Peripheral vascular disease, sickle cell disease, vascular grafts, or vasospastic disorders j. Known bleeding disorder or is taking agents affecting coagulation preoperatively. Deep venous thrombosis (DVT) prophylaxis of the surgeon's choice is permitted postoperatively k. Diabetes mellitus (uncontrolled). Diabetes must be controlled without known end organ damage (hemoglobin A1C [HgbA1c] <7%) l. History of malignancy in the past 5 years with the exception of cured skin squamous cell or basal cell carcinoma m. Prior bunionectomy on the index foot or other foot surgery on the index foot that could impact the surgery or data collection endpoints n. Presence of, history of or family history of keloid and/or hypertrophic scar 2. **Use of disallowed medications** at the window specified below and planned to use throughout the study period, including the following: a. Pain medication (opioids, NSAIDs, COX-2 inhibitors, tramadol, ketamine, clonidine, gabapentin, pregabalin, and/or cannabinoids, etc.) within 2 days prior to Day -1. b. CNS active drugs such as benzodiazepines, tricyclic antidepressants, Serotonin, and norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), or any other serotonergic medications within 7 days prior to Day -1. The use of lorazepam and other sleep medications, except those containing analgesic properties, is permitted. c. Use of parenteral or oral corticosteroid(s) within 14 days prior to Day -1. d. Antihypertensive agent or diabetic regimen at a dose that has not been stable for at least 30 days, or which is not expected to remain stable throughout the study.

	e. Digoxin, warfarin lithium, theophylline preparations, aminoglycosides, and all antiarrhythmics except beta-blockers within 7 days prior to Day -1 and throughout the study. f. Current use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days. 3. Positive results for hepatitis B surface antigen (HbsAg) and/or hepatitis B anti-core antibody (anti-HBc) but negative results for anti-surface antibody (anti-HBs) at the Screening Visit. 4. Positive results for hepatitis C antibody unless patient received curative therapy and a negative viral load is documented. 5. Human immunodeficiency virus (HIV) infection or positive HIV serology at the Screening Visit. 6. Known positive COVID-19 viral test during screening or suspected COVID-19 infection at the Day 1 Visit 7. History of illicit drug use, or prescription medicine or alcohol abuse within the past 2 years. 8. History of opioid dependence. 9. History of NSAID-induced bronchospasm or presence of nasal polyps, history of asthma or chronic rhinitis. 10. Significant history of allergic reactions or known intolerance to naproxen, pregabalin or any gabapentinoid, or to any rescue medication used in the study, or any medication used in the surgical and anesthetic protocol. 11. Biological female subjects who are pregnant or lactating, who plan to get pregnant, or who have a positive pregnancy test at Screening or at Day 1 (prior to surgery). 12. Participated in another clinical trial within 30 days, or previously participated in a clinical study with a similar investigational product. 13. Presence of severe depression as indicated by Patient Health Questionnaire (PHQ-9) total score of ≥20 or item 9 score >0 at the Screening Visit. 14. Presence of severe anxiety as indicated by General Anxiety Disorder (GAD-7) score of ≥15 at the Screening Visit. 15. Presence of history of suicidal behavior or ideation as indicated by the Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening Version at Screening Visit.

Statistical Considerations:	*Statistical Hypotheses* This primary efficacy endpoint is to test the mean difference of summed pain intensity from end of surgery to 48 hours post-surgery (SPI48) between high dose XG005 and Placebo groups. The study null hypothesis is XG005 high dose and placebo have the same effect. And the alternative hypothesis is XG005 high dose and placebo have different effect. These will be tested at a two-tailed alpha of 0.05, and the Null hypothesis will be rejected if p-value < 0.05. *Sample Size Determination* One hundred thirty (130) evaluable subjects per study arm will yield 90% power to detect a standardized effect size of 40% (Wang 2010; Wu J, Jiang J, Wei W. Confidence intervals of effect size in randomized comparative parallel-group studies. *Stat Med*. 2006;25(4):639-51.; Vevea J, Woods CM. Publication bias in research synthesis: sensitivity analysis using A priori weight functions. *Psychological Methods*. 2005;10(4):428–43.; Singla NK, Chelly JE, Lionberger DR, et al. Pregabalin for the treatment of postoperative pain: results from three controlled trials using different surgical models. *J Pain Res*. 2015;8:9-20.) at a two-tailed α= 0.05 for the familywise type one error. Recruitment goals will be 150 subjects per arm or N=450 total. *Randomization Strata* • Study Site *Multiplicity Adjustment* A serial gatekeeping procedure will be used to control the overall type-1 error rate at 0.05 for primary and secondary endpoints. If the primary endpoint is not significant at a two-tailed alpha of 0.05, there is no testing on secondary endpoints. If the primary endpoint is significant at a two-tailed alpha of 0.05, the secondary endpoints will be tested following the hierarchy testing procedure with a pre-specified order as above. If any secondary endpoint is not significant, the successive secondary endpoints will not be tested. *Analysis Populations* • The Intent-to-Treat (ITT) population is defined as all randomized subjects. Subjects will be analyzed according to the treatment group to which they were randomized. • The Safety Population is defined as all subjects who receive study medication. Subjects will be analyzed according to the actual treatment they receive. • The modified Intent-to-Treat (mITT) Population is defined as all ITT subjects who received at least one dose of study medication and have at least 2 NPRS assessments post-end of surgery. • The Per-Protocol Population is defined as all mITT subjects who have no major protocol violations which may potentially bias efficacy analysis of the study. *Efficacy* The primary endpoint of the comparison of summed pain intensity (SPI) from end of surgery to 48 hours post-surgery (SPI48) for high dose XG005 vs placebo will be analyzed, using analysis of covariance (ANCOVA) model. The model will use treatment as main effect, and study site as a covariate. More details for efficacy analyses will be specified in SAP.

	Safety The Medical Dictionary for Regulatory Activities (MedDRA® version 23 or higher) will be used to classify all AEs with respect to system organ class and preferred term. AEs will be summarized by treatment. Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Physical examination findings will be presented in a data listing. *Pharmacokinetics* Individual plasma concentrations of naproxen, pregabalin and XG005 (as appropriate) will be listed by subject and summarized by gender, dose, and nominal time point using descriptive statistics (i.e., N, arithmetic mean, SD, percent coefficient of variation [CV%], median, minimum, maximum, and geometric mean). PK analyses will be addressed in a separate PK Analysis Plan. *Handling of Missing data* For the PK analysis, concentrations that are below the limit of quantification (BLQ) will be treated as zero for descriptive statistics with the exception that a BLQ value between two quantifiable concentrations will be set as missing. Missing concentrations will be treated as missing from the PK parameter calculations. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing. For efficacy analyses, when rescue medication is used, the last pain intensity measure prior to the use of rescue medication will be used (imputed) for the subsequent protocol-specified time points for measurement of pain intensity after the time of the rescue medication. Missing data as a result of discontinuation due to adverse event or lack of efficacy will be imputed with worst observation carry forward (WOCF) method. For safety analyses, missing data will not be imputed in general, otherwise specified. More details will be described in the SAP. *Protocol deviations and violations* Protocol deviations will be identified on an ongoing basis by the clinical study team. *Subgroup analyses* Analyses by subgroup may be further described in the SAP. *Interim Analysis* No formal interim analysis will be performed in this study.

1.2. Schedule of Assessments

	Screen	Day 1: Surgery		Treatment Period (Hours Post End of Surgery)											End of Study/Early Termination[v]
Assessment	**Days -28 to -1**	**Pre-Surgery[a]**	**Surgery**	**0**	**1**	**2**	**4**	**8**	**12**	**24**	**36**	**48**	**60**	**72**	**Clinic Visit, Day 15 (±2)**
Written Informed Consent[b]	X														
Inclusion/Exclusion Criteria[c]	X	X													
Medical History	X	X													
Physical Examination[d]	X														
Vital Signs[e]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram[f]	X														X
Clinical Laboratory Testing[g]	X													X	X
Pregnancy Test[h]	X	X													X
Urine Drug Screen[g]	X														
COVID-19 test[w]	X	X[w]													
Adverse Events Monitoring[i]	◄														►
Prior/Concomitant Medications	◄														►
Pre-study personality questionnaire[j]	X														
C-SSRS Baseline/Screening Version Appendix J	X														

	Screen	Day 1: Surgery		Treatment Period (Hours Post End of Surgery)											End of Study/Early Termination[v]
Assessment	**Days -28 to -1**	**Pre-Surgery[a]**	**Surgery**	**0**	**1**	**2**	**4**	**8**	**12**	**24**	**36**	**48**	**60**	**72**	**Clinic Visit, Day 15 (±2)**
C-SSRS Since Last Visit Version Appendix K														X	X
Patient Health Questionnaire-9 (PHQ-9)	X														
General Anxiety Disorder (GAD-7)	X														
Domiciled in Clinic		◄												►	
Enrollment/ Randomization		X													
Study Drug Dosing (XG005 or Placebo)[k]		X 60 min prior to surgery		Every 12 hours after the first dose defined as "Time 0" for dosing purposes only											
Blood Sample for Pharmacokinetic Assessment[l]		X Pre-dose			Drawn at 1, 2, 3, 4, 6, 8, 10, 12, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours (±15 min window) after the end of surgery (last suture) ◄ ►										
Anesthesia and Bunionectomy Surgery[m]			X												
Continuous Pulse Oximetry[n]									X	X	X	X	X	X	
Rescue Medication				PRN											
Numeric Pain Rating Scale (NPRS)[p,q]					Measure at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours after the end of surgery (±10 min window)										X (ET only)
Patient Global Assessment (PGA) of Pain Control[r]										X		X		X	X (ET only)

	Screen	Day 1: Surgery		Treatment Period (Hours Post End of Surgery)											End of Study/Early Termination[v]
Assessment	**Days -28 to -1**	**Pre-Surgery[a]**	**Surgery**	**0**	**1**	**2**	**4**	**8**	**12**	**24**	**36**	**48**	**60**	**72**	**Clinic Visit, Day 15 (±2)**
Numeric Nausea Rating Scale (NNRS)[s]					X		X	X	X	X		X		X	X (ET only)
Sleep Interference Score (SIS)[t]										X		X		X	X (ET only)
Ramsay Sedation Scale (Somnolence)[u]					Measure at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours after the end of surgery (±10 min window) ←→										X (ET only)
Discharge[v]														X	

Abbreviations: PRN = as needed

a) Signed informed consent must be obtained prior to a subject undergoing any study procedures or assessments.
b) Subject's must meet all of the study inclusion criteria as shown in Section 5.1 and none of the exclusion criteria as shown in Section 5.2. All inclusion and exclusion criteria must be verified by the Investigator or designee at Screening (Day -28 to Day -1) and Pre-Surgery (Day 1).
c) All Pre-surgery assessments to be performed within 24 hours prior to surgery. For inclusion/exclusion criteria and medical history only, assess updates since Screening and evaluate for continued eligibility. The Investigator or designee may repeat lab tests and vitals/ECGs prior to randomization.
d) A PE will be obtained at Screening. A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, neck (including thyroid), lungs, cardiovascular, abdomen, lymph nodes and extremities. The subject's height and weight will be measured to determine body mass index at Screening to determine eligibility. It is not necessary to collect information regarding well-healed surgical scars or tattoos. If abnormalities are noted during the Screening, they should be also recorded on the Adverse Event eCRFs or Medical History, as appropriate. Subjects will be advised at Screening that if they terminate the study prior to 72 hours, it is requested that they remain in the clinic for continued collection of scheduled safety data only.
e) Vital signs (blood pressure [systolic/diastolic], heart rate, respiratory rate, oral body temperature) will be collected from all subjects at Screening, before the first dose Pre-Surgery (±10 minutes) and Hours 0, 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72, and Day 15/Early Termination (±10 minutes). Monitoring of continuous pulse oximetry begins at Hour 0 (start of the domiciling period). Vital signs may be obtained at any other times as deemed necessary by the Investigator. Vital signs throughout the study should be obtained supine after resting for approximately 5 minutes. Automated blood pressure machines may be used to standardize measurements. Body temperature will be determined by obtaining oral temperature (°C).
f) 12-lead ECG data will be collected from all subjects at Screening and at the Day 14 clinic visit, and from any subject who is determined to be exhibiting any relevant abnormality per the discretion of the investigator. 12-lead ECGs will be obtained at each time point using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. QTcF will also be calculated. 12-lead ECGs will be measured in the supine position, after the subject has been supine for at least 10 minutes.
g) Clinical laboratory parameters include standard **chemistry** (albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase [ALT], aspartate aminotransferase [AST], blood urea nitrogen [BUN], creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase

[LDH], and uric acid; **hematology** (HbA1c [Screening only], hemoglobin, hematocrit, red blood cell [RBC] count, RBC indices, mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], platelet count, and white blood cell [WBC] count including differential; coagulation panel (prothrombin time [PT], partial thromboplastin time [PTT], and fibrinogen); **serology** (human immunodeficiency virus [HIV] antibody, hepatis B virus surface antigen, hepatitis B anti-core antibody (anti-HBc) and anti-surface antibody, and hepatitis C virus antibody); **urinalysis** (pH, specific gravity, blood and leukocyte esterase, glucose, protein, and ketones), and **urine drug screen** (amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine [PCP], tetrahydrocannabinol [THC], methamphetamine, methadone, and ecstasy).

h) For premenopausal women, a serum pregnancy test will be conducted at Screening visit, a urine pregnancy test will be conducted pre-surgery on Day 1 and at Exit Visit. Premenopausal women must have a negative serum pregnancy test to be included in study. Results must be available before surgery.

i) Reporting of treatment-emergent AEs begins at the time of first dose of study drug and ends 30 days after the last dose of study drug. Non-treatment emergent AE reporting begins at Screening after signing of ICF until the first dose of study drug is administered.

j) Subjects will be assessed at Screening on their potential placebo response by use of a pre-study personality questionnaire (Appendix B). This is a exploratory analysis for information purposes only.

k) Study drug will be administered 60 minutes prior to start of surgery and every 12 hours for 72 hours after the time of first dose. The clock time of first dose is noted as “Time 0”, and it will be recorded to facilitate the PK analyses.

l) Blood draws will always be performed after NPRS assessment and prior to the first administration of rescue medication. Considering the surgery time may largely vary among subjects, the PK sampling plan used the post-end-of-surgery schedule to be consistent with the efficacy assessment schedule. Each subject in the PK group (one site only) will have blood samples collected for PK assessments at predose and at the following intervals post-surgery (last suture) 1, 2, 3, 4, 6, 8, 10, 12, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours (±15 min window). XG005, naproxen, and pregabalin concentrations in plasma will be measured. The actual clock time when the PK sample is collected will be recorded, and the post-dose time for PK analysis will be calculated based on the recorded clock time. All subjects will have blood samples collected for PK assessments at any time in which a subject is determined to be exhibiting any relevant abnormality per the discretion of the investigator.

m) Subjects will undergo primary, unilateral, first metatarsal Austin bunionectomy. The surgical procedure should be limited to a maximum duration of 90 minutes. End of surgery will be defined as completion of the last suture.

n) Subjects will be on continuous pulse oximetry monitoring throughout the confinement period but, absent a respiratory AE, oxygen saturation ($Sp0_2$) will be recorded every 12 hours post-end of surgery.

o) Subjects will be permitted rescue medication throughout the 72-hour inpatient domiciling period as follows to manage breakthrough pain only if it occurs while domiciled: IV acetaminophen 1 g, will be administered Q 6 hours, PRN, up to 4 g in 24 hours. If a patient is unable to tolerate acetaminophen or if there is insufficient pain relief, 50 mg tramadol will be administered Q 4 hours, PRN, up to 300 mg in 24 hours. Study staff will record the time and the dose of rescue medication administered on the rescue medication form. NPRS and PK sampling will be collected immediately prior to administering rescue medication. Only the protocol-defined rescue medication is permitted in the study.

p) Study staff will record subject-reported pain assessments via a standard 11-point NPRS at the following time points post-end of surgery: 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours within a ±10-minute window (Appendix C). NPRS will be collected prior to PK sampling and administration of rescue medication.

q) Pain intensity assessments scheduled between 24:00 and 06:00 may be skipped if the subject is sleeping. However, consecutive pain assessments may not be skipped, and the Hour 12, Hour 24, and Hour 48 pain assessments must be completed even when they fall asleep between 24:00 and 06:00.

r) Study staff will record subject-reported PGA of pain control using a 5-point scale (poor, fair, good, very good, excellent) at the following time points post-end of surgery: 24, 48, and 72 hours within a ±10-minute window and just prior to receiving a dose of rescue medication (Appendix D). PGA will also be performed and recorded at early termination.

s) Nausea will be measured after the end of surgery by using the 11-point NNRS at the indicated time points with a ± 10-minute window (Appendix E). PK sampling blood draws will always be performed after NNRS assessment. Additional NNRS time points will be collected when an AE of nausea or vomiting is reported or prior to any rescue antiemetic medication. Administration of antiemetic medications are limited to subjects with active vomiting, subjects with a score ≥5 on the NNRS, or by subject request only. No pretreatment for potential nausea and vomiting is permitted.
t) Sleep Interference Score using the 11-point NRS scale (0=no interference to sleep, 10=worst interference imaginable) to be assessed at 24, 48 and 72 hours post-surgery within a ±15-minute window.
u) Ramsay Sedation Scale to be determined by observation of subject by study staff when NPRS is assessed (Footnote p, above).
v) Subjects will be discharged at a reasonable hour of the day after the end of the 72-hour treatment period, which may include the morning after the end of the 72-hour treatment period. Early termination visits will include the following assessments: NPRS, PGA, NNRS, SIS, and safety assessments (vital signs, ECG, laboratory testing, and concomitant medications).
w) All subjects will be tested for COVID-19 during Screening and within 3 days prior to surgery. COVID-19 testing samples will be taken prior to surgery on Day 1 from subjects that are in the PK sampling groups. The result of that test is not necessary before surgery.

2. INTRODUCTION

2.1. Background

Xgene Pharmaceutical has developed XG005, a prodrug conjugating pregabalin, an anti-hyperalgesic, antiallodynic, and analgesic, with naproxen, an analgesic and anti-inflammatory agent. It is the first in a new class of "dual-acting" conjugate analgesics that has been engineered to reduce the gastrointestinal (GI) safety risks associated with naproxen and improve clinical efficacy in the treatment of acute and chronic pain. XG005 has been evaluated in preclinical and Phase 1 clinical studies. In the first Phase 1 study in healthy volunteers, oral XG005-01 (capsule formulation) demonstrated an acceptable safety profile with no additional adverse events compared with pregabalin or naproxen (parent drugs). Xgene Pharmaceutical has since developed an improved tablet formulation (XG005) which showed improved bioavailability for pregabalin and naproxen. In two Phase 1 single and multiple ascending dose studies with XG005 tablet formulation, a clinically relevant dose range was evaluated in healthy volunteers. These studies showed a safety profile consistent with pregabalin and naproxen.

In general, pain symptoms are classified into two broad mechanism-based pain categories: tissue-injury pain (nociceptive) or nervous-system-injury pain (neuropathic). Some of the chronic pain, such as the low back pain or moderate to severe arthritis pain, have been shown to be the result of neuropathic as well as nociceptive pain mechanisms. It has been demonstrated that the analgesic effects can be enhanced by co-administration of gamma-aminobutyric acid (GABA) analogs, such as pregabalin or its predecessor gabapentin together with non-steroidal anti-inflammatory drugs (NSAIDs) (Yu et al. 2011; Corleto et al. 2014; Banoob et al. 2002; Petroski 1993; Van Gossumet et al. 1993; D'Haens et al. 1993; Ivey et al. 1980). They can interact in a synergistic or additive manner to control pain in the preclinical animal models as well as in the clinical practices. The synergy of these two classes of drugs can potentially allow a reduction in the dose required of each compound, leading to a reduction in the side effects, and the enhancement of the clinical utility of these compounds. Furthermore, combining the prodrug strategy and the potential complimentary synergy between the two drugs may lead to an optimal clinical outcome in terms of improved clinical efficacy and reduced GI events in patients with chronic pain.

2.2. Unmet Medical Need

Both acute and chronic pain remain as high unmet medical needs with high global burden of disease (Enright et al. 2016; Blyth et al. 2019). Acute pain is the most common reason for visiting an emergency department, and surgical procedures are associated with acute postoperative pain (Sinatra 2010). Chronic pain causes significant suffering as indicated by the Global Health Burden of Disease survey demonstrating that headache and low back pain were the leading causes of years lived with disability (GBD 2017).

Multimodal approaches are used for the treatment of pain for both inflammatory and neuropathic pain conditions to limit the use of opioid analgesics (Finnerup 2019). There remains a significant unmet medical need for treatment of chronic pain with non-opioid drugs that are safe and tolerable. In an effort to develop a better analgesic to address these needs, Xgene Pharmaceutical

has designed an orally bioavailable "dual-acting" prodrug conjugating two well-established analgesics with different mechanisms of action: naproxen and pregabalin conjugated with a linker that has been previously approved in a product Horizant® (Horizant [pregabalin] 2013).

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the management of pain. Naproxen, a cyclo-oxygenase inhibitor, is a potent inhibitor of prostaglandin synthesis. It is one of the most prescribed NSAIDs in the world, available over the counter, for the treatment of pain and inflammation and has the most favorable cardiovascular side effect profile in this class (Naprosyn 2017; Trelle et al. 2011; Coxib and traditional NSAID Trialists' (CNT) Collaboration et al. 2013; Inza 2019).

Pregabalin is structurally related to the naturally occurring amino acids L-leucine and gamma-aminobutyric acid (GABA). Pregabalin was approved in 2004 to manage peripheral neuropathic pain, fibromyalgia in adults (Lyrica 2013) and is now available as a generic drug. The dose range in humans is 150 to 600 mg per day. Pregabalin binds to the alpha2-delta protein, an auxiliary subunit protein of voltage-gated calcium channels with high affinity (IC50 = 37 nM), which is required for its pharmacology. The (R)-enantiomer of pregabalin was 10-fold less potent than its (S)-enantiomer (Lyrica 2013).

XG005 is intended for use in both acute and chronic pain conditions. Due to the unique mechanism of action of this prodrug on both neuropathic and inflammatory mechanisms of pain, it is expected to have a better benefit in pain management than currently available medications and reduce the use of potentially more harmful drugs such as opioids.

2.3. XG005 Clinical Experience in Healthy Subjects

Xgene Pharmaceutical has completed a Phase 1 single-ascending dose (SAD) study (XG005-01; capsule formulation) and a Phase 1 SAD/multiple ascending dose (MAD) study (XG005; tablet formulation) in healthy subjects at clinical sites in Australia.

Study XG005-01

The completed Phase 1 SAD study in 40 healthy subjects demonstrated that area under the plasma concentration-time curve from time 0 to the last quantifiable point (AUC_{0-t}) of naproxen and pregabalin increased with dose level of XG005-01 across the dose range 50 mg to 1000 mg, with the increase being linear with dose for naproxen but less than dose proportional for pregabalin. There was no dose or treatment-related trend in the incidence of treatment-emergent adverse events (TEAEs; defined as adverse events reported after treatment was received) for subjects who received XG005 compared with subjects who received placebo. Most TEAEs reported during this study were mild in intensity, none was severe. The most commonly reported adverse event was dizziness in 8 of 30 subjects (27%). No deaths, serious adverse events (SAEs) or TEAEs leading to study withdrawal were reported.

Study XG005-02

The second Phase 1 study (XG005-02; NCT04067947) evaluated safety, tolerability, and PK profile of XG005 (tablet formulation) in 32 healthy volunteers in each SAD and MAD cohorts. XG005 was evaluated at the doses of 250, 500, 1000, 1250 mg in the single dose and twice-a-day

(BID) dose up to 7 days. Following single and multiple dose administration of XG005, AUCs and maximum concentration in plasma (C_{max}) of XG005, naproxen, and pregabalin increased in a dose proportional manner. There was no dose or treatment-related trend in the incidence of TEAEs for subjects who received XG005 compared with subjects who received placebo. Most TEAEs reported during this study were mild in intensity, none was severe. The most commonly reported adverse event (AE) was dizziness (9 [37.5%] of 24 XG005 subjects) in the SAD cohort, and somnolence (7 [29.17%] of 24 XG005 subjects) in the MAD cohort. In comparison, in the LYRICA controlled trials in adult patients, dizziness was experienced by 30% of LYRICA-treated patients and somnolence was experienced by 23% of LYRICA-treated patients (Lyrica 2013). No deaths or SAEs were reported during this study. None of the subjects in XG005 groups discontinued study drug due to TEAEs.

Study XG005-02-PK-02

This Phase 1 bridging MAD study in Chinese healthy volunteers enrolled 16 subjects. 8 subjects were administered 750 mg or 1250 mg XG005 BID for 6.5 days, respectively, following titration to target dose levels. All subjects had good tolerance to study drug. No new drug-related TEAEs other than those known for naproxen or pregabalin. Notable TEAEs were dizziness, somnolence, constipation, and oral ulcer. But all were mild in severity and no subject discontinued from the study.

The Investigator's Brochure summarizes the nonclinical and clinical experience with XG005, naproxen, and pregabalin (XG005 IB 2022). Additional efficacy and safety information for the marketed products can be found in the package insert for naproxen (Naprosyn 2017) and pregabalin (Lyrica 2013).

2.4. Study Rationale

XG005 is being developed for the management of pain. Pre-clinical animal models have demonstrated improved efficacy for pain and inflammation compared with naproxen alone (Hurley et al. 2002), and pilot human studies have shown that both pregabalin and naproxen could reduce pain in a bunionectomy model with a possible synergistic effect (Wang et al 2010). By targeting both neuropathic and inflammatory aspects of pain in a single prodrug, therapeutic advantages are expected. With the use of this conjugate approach, there is a potential for a better benefit risk profile compared with available drugs, with lowered use of opiates.

This study will evaluate the safety, efficacy, and PK of low dose (750 mg) and high-dose (1250 mg) XG005 oral tablets compared with placebo in subjects undergoing bunionectomy.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Efficacy:	
• To evaluate the efficacy of high dose XG005 [1250 mg Q12] compared to placebo for pain control in subjects undergoing bunionectomy.	• Summed pain intensity from end of surgery to 48 hours post-surgery (SPI48) for high dose XG005 vs placebo
Secondary Efficacy:	
• To evaluate the efficacy of low dose XG005 [750 mg Q12] compared to placebo for pain control in subjects undergoing bunionectomy. • To evaluate high and low dose XG005 compared to placebo for total rescue consumption and time to first use from end of surgery. • To evaluate high and low dose XG005 compared to placebo for PGA • To evaluate high and low dose XG005 compared to placebo for postoperative nausea. • To evaluate the efficacy of high dose XG005 compared to low dose XG005 for pain control in subjects undergoing bunionectomy	*Key Secondary Endpoints:* 1. SPI48: low dose XG005 vs placebo 2. Total tramadol rescue medication consumption in MEQs over 48 hours: high dose XG005 vs placebo 3. Total tramadol rescue medication consumption in MEQs over 48 hours: low dose XG005 vs placebo *Additional Analgesic Endpoints:* 4. Time to first use of rescue medication from end of surgery: high dose XG005 vs placebo 5. Time to first use of rescue medication from end of surgery: low dose XG005 vs placebo 6. PGA at 48 hours: high dose XG005 vs placebo 7. PGA at 48 hours: low dose XG005 vs placebo 8. Cumulative nausea (NNRS) assessment scores through 24 hours: high dose XG005 vs placebo 9. Cumulative Nausea (NNRS) assessment scores through 24 hours: low dose XG005 vs placebo 10. SPI48: high dose XG005 vs low dose XG005
Tertiary Efficacy (All Treatment Arms):	
• To evaluate rescue medication consumption at 24, 48, and 72 hours, time to first use of rescue medication from end of surgery, and proportion of subjects requiring rescue medication. • To evaluate nausea assessment scores at various timepoints. • To evaluate high and low dose XG005 compared to placebo for SIS	• Total oral opioid rescue medication consumption at 24, 48, and 72 hours • Nausea (NNRS) assessment scores at 1, 4, 8, 12, 24, 48, 72 hours • SPI at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours • Pain intensity at various timepoints • SIS at 24, 48 and 72 hours • Percentage of subjects requiring rescue at various timepoints • PGA of pain control at various timepoints • Ramsay Sedation Scale at various timepoints

Objectives	**Endpoints**
• Exploratory purposes only: To estimate subject's potential placebo response by use of a pre-study personality questionnaire at Screening.	• Estimated of subject susceptibility to placebo response at Screening using a pre-study personality questionnaire
Safety:	
• To evaluate the safety and tolerability of XG005 in a perioperative population	Safety and tolerability of XG005 compared with placebo measured: • The incidence, intensity, relationship, and seriousness of TEAEs by treatment group. • The number and percentage of premature withdrawals due to AEs in each treatment group. • Treatment-emergent changes in vital signs (blood pressure, heart rate, body temperature, respiratory rate, continuous pulse oximetry) and $Sp0_2$ after each Treatment Period dose and the Follow-up Visit compared to Baseline values. • Treatment-emergent changes in clinical laboratory tests and ECGs compared to Baseline.
Pharmacokinetics	
• To investigate the PK of XG005, naproxen, and pregabalin in a perioperative population	• Area under the plasma concentration-time curve from time zero to time t of the last measured concentration above the limit of quantification ($AUC_{0\text{-}last}$) • Area under the plasma concentration-time curve from zero to infinity ($AUC_{0\text{-}inf}$) • Maximum plasma concentration (C_{max}) • Trough plasma concentration prior to each dose (C_{trough}) • Time to reach maximum plasma concentration (T_{max}) • Terminal elimination rate constant (λz) with the respective half-life ($t_{1/2}$).

4. STUDY DESIGN

4.1. Overall Design

This is a multi-center, randomized, double-blind, parallel-group, placebo-controlled study in subjects undergoing bunionectomy.

Subjects scheduled for bunionectomy surgery who meet all of the inclusion criteria and none of the exclusion criteria below will be enrolled and randomized.

Eligible subjects will be randomized in a 1:1:1 ratio to receive either 750 mg XG005 (low dose), 1250 mg XG005 (high dose), or placebo. Randomized subjects will receive drug per their treatment allocation as follows:

- 60 minutes prior to surgery, then
- Every 12 hours (± 10 minutes) after the first dose for 72 hours.

Subjects and all study staff performing study assessments will be blinded to treatment allocation. To maintain the blind, a total of 5 tablets will be administered to each treatment group: 5 identical blue tablets (low or high dose XG005 or its placebo) at each time point.

Subjects will undergo a Screening Visit (Day -28 to Day -1), Pre-Operative Assessment (within 24 hours prior to surgery), and a Surgery/Treatment Visit (beginning on Day 1), when the following will occur:

- Study medication administered
- Surgery performed within 60 minutes of first study drug administration
- Time of end of surgery recorded (as time of last suture closed)
- Subjects domiciled in research center for at least 72 hours post-surgery
- Efficacy, safety, and PK assessments performed over 72-hour period post-surgery

“Time 0” will be defined as the start time of first dose from which subsequent 12-hour dosing times will be determined. All study efficacy, safety, and PK assessments are anchored to time of end of surgery (last suture). PK sampling timepoints correlate with the collection of the 11-pt NPRS efficacy assessments when they overlap.

Screening will include subjects’ potential placebo response by use of a pre-study personality questionnaire (Appendix B).

Subjects will be advised at Screening that if they terminate the study prior to 72 hours, it is requested that they remain in the clinic for continued collection of scheduled safety data only.

Subjects will be confined in the clinic from check-in through 72 hours post last dose to monitor subject safety. Subjects will be discharged at a reasonable hour of the day after the end of the 72-hour treatment period, which may include the morning after the end of the 72-hour treatment period.

There will be a Follow-up Visit on Day 15.

The Schedule of Assessments is shown in Section 1.2.

4.2. Scientific Rationale for Study Design

Preemptive administration of analgesic medication is more effective than medication given after the onset of the painful stimulus (**Error! Reference source not found.**; **Error! Reference source not found.**; Ménigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. *Anesth Analg*. 2005;100:1394–9.). It has been suggested that the treatment before or during surgery prevents or alleviates the formation of peripheral and/or central sensitization which may reduce the development of pain for some time after surgery. In the current study, we included both preoperative and postoperative dosing to achieve maximal "preventive" analgesia that covers a wider window of opportunity to inhibit the formation of peripheral/central sensitization and treat postsurgical pain. In addition, by dosing preoperatively, it makes T_{max} match the time of anticipated onset of pain. Furthermore, the efficacy of pre- and post-operative pain relief using the combination of naproxen and pregabalin after bunionectomy surgery has been reported (Wang et al 2010). The present study is a double-blind, placebo-controlled randomized trial of preemptive analgesia with XG005, a prodrug of naproxen and pregabalin in adult patients.

The three Phase-I studies showed favorable PK characteristics of naproxen and pregabalin following administration of XG005, in particular, the C_{max} of both naproxen and pregabalin occur simultaneously following oral administration of XG005, with T_{max} at approximately 4 hours. This PK characteristic may result in simultaneous onset of drug effects (additive or synergetic) of naproxen and pregabalin that offers a great pharmacological benefit to clinical needs for acute pain treatment. Since the pain-relieving efficacy of XG005 is solely associated with the systemic exposure of naproxen and pregabalin resulted from the XG005 absorption and subsequent hydrolysis, the dose selection for XG005 in the current study is based on the considerations to match the systemic exposures of an efficacious naproxen dose and pregabalin dose. The steady status C_{max} for naproxen and pregabalin resulted from XG005 oral dosing was lower than the C_{max} from combined dosing of naproxen and pregabalin, which may indicate potential advantage on reducing side effects from each drug when dosed combined.

4.3. Justification for Dose

In this study, the subjects will be randomized in a 1:1:1 ratio to receive one of two doses of XG005, or placebo. The two doses of XG005 are selected based on the plasma levels of naproxen and pregabalin previously associated with analgesic efficacy (Lyrica® (Pregabalin) Prescribing Information. (June 2011) Pfizer Inc., US.; Naprosyn® (naproxen sodium) Prescribing Information. (November 2017) Atnahs Pharma Australia Pty Ltd.; Bockbrader HN,

Wesche D, Miller R, et al. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet*. 2010;49(10):661-9.).

Naproxen is rapidly and completely absorbed from the GI tract with an *in vivo* bioavailability of 95%. The elimination half-life of naproxen ranges from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days. Following oral administration of naproxen 500 mg tablets, C_{max} of 71,100 ng/mL, T_{max} of 2.3 hours, and AUC_{0-t} of 1,218,000 ng.hr/mL were observed. Similar AUC and 30% lower C_{max} of naproxen were produced by oral administration of 1000 mg of XG005 tablet (4 × 250 mg XG005 tablets). In general, the clinical recommended dose ranges are 220 mg-1500 mg of naproxen for the various pain symptoms.

Two dose levels are planned in this study:

1) XG005 (low dose) with 750 mg XG005 BID which will deliver 375 mg BID of naproxen and 259 mg BID of pregabalin.

2) XG005 (high dose) with 1250 mg XG005 BID which will deliver 626 mg BID of naproxen and 433 mg BID of pregabalin.

Based on the PK modeling, 1250 mg XG005 BID will be equivalent to the exposure of naproxen at 490 mg BID and the exposure to pregabalin of 225 mg BID; 750 mg XG005 BID will result in bioequivalent to naproxen of 300 mg BID and pregabalin of 150 mg BID. So, the planned XG005 dose regimen would provide naproxen dose within the commonly prescribed dose for treating various pain indications. Pregabalin has been approved for maximum dose of 600 mg/day, though with 150 mg/day starting dose, in approved pain indications. Phase 1 studies in healthy volunteers from XG005 including dose of 1250 mg BID resulted in acceptable safety profile, with similar dizziness and somnolence incidences as reported in Lyrica label. Patient's safety will be carefully monitored in the study.

4.4. End of Study Definition

The end of study (EOS) is defined as the date on which the last subject completes the last visit (including the EOS and any additional follow-up).

The Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

5. STUDY POPULATION

5.1. Inclusion Criteria

A subject candidate must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Willing and able to sign the ICF approved by the IRB.
2. Male or female aged 18–80 years.
3. Scheduled to undergo unilateral first metatarsal bunionectomy.
4. Capable of undergoing a bunionectomy under anesthesia as described in the study surgical and anesthetic protocol.
5. Weight >40 kg and a BMI <39 kg/m^2.
6. No additional planned surgeries other than bunionectomy during the course of the study.
7. Have negative urine drug screen for drugs indicative of illicit drug use (unless results can be explained by a current prescription or acceptable OTC medication at Screening as determined by the Investigator) and no detectable results on the alcohol test (breath or saliva) indicative of alcohol abuse at Screening, and/or prior to surgery (may be repeated if the Investigator suspects a false-positive result).
   Note: *For those subjects who test positive for THC, if they are willing to abstain from use or consumption of THC-containing products from Screening through end of the subject's participation in the study, they may be allowed to participate in the study.*
8. Biological female subjects must be non-lactating. They must also be either sterile (bilateral tubal ligation, bilateral salpingectomy, or hysterectomy), post-menopausal for at least 1 year, have a partner who is sterile, be abstinent, have a same-sex partner, use a highly effective double-contraception method (hormonal protection is insufficient), or use an FDA-approved contraceptive for greater than 2 months prior to Screening visit and commit to an acceptable form of birth control for the duration of the study and for 30 days from completion of the study.
9. Willing and able to complete the study procedures and pain scales and to communicate meaningfully in English with study personnel.
10. Negative result of COVID-19 test within 3 days before Day 1 visit.

5.2. Exclusion Criteria

Any of the following criteria will exclude a subject from the study:

1. **Medical condition or history** that in the investigator's opinion could adversely impact the subject's participation or safety or the conduct of the study, or interfere with the pain assessments, including the following:

   a. Serious breathing difficulties or respiratory risk factors (including clinically significant use of opioid pain medicines and other drugs that depress the CNS) and conditions such as COPD that reduce lung function.

   b. Clinically unstable hypertension, cardiovascular disease, or history of cerebrovascular events. Hypertension must be stable without known end organ damage.

   c. Concurrent painful conditions that may require analgesic treatment during the study period.

   d. History of significantly reduced hepatic function (ALT, AST, or LDH ≥1.5 x ULN or renal function (creatinine ≥1.5 x ULN, angle closure glaucoma, or convulsive disorder.

   e. Recent history of urinary retention.

   f. History of gastrointestinal ulcer, bleeding, perforation, or recent surgery of gastrointestinal tract

   g. Subject is currently taking or has taken a chronic opioid at a dose greater than or equal to 20 mg hydrocodone per day ([≥20 MEQs] more than 30 consecutive days of daily use) for pain in the 2 months prior to surgery.

   h. Active cutaneous disease, or other disease, at the surgical site.

   i. Peripheral vascular disease, sickle cell disease, vascular grafts, or vasospastic disorders.

   j. Known bleeding disorder or is taking agents affecting coagulation preoperatively. DVT prophylaxis of the surgeon's choice is permitted postoperatively.

   k. Diabetes mellitus (uncontrolled). Diabetes must be controlled without known end organ damage (HgbA1c <7%).

   l. History of malignancy in the past 2 years with the exception of squamous cell or basal cell carcinoma.

   m. Prior bunionectomy on the index foot or other foot surgery on the index foot that could impact the surgery or data collection endpoints.

   n. Presence of, history of or family history of keloid and/or hypertrophic scar

2. **Use of disallowed medications** at the window specified below and planned to use throughout the study period, including the following:

a. Pain medication (opioids, NSAIDs, COX-2 inhibitors, tramadol, ketamine, clonidine, gabapentin, pregabalin, or cannabinoids) within 2 days prior to Day -1.

b. CNS active drugs such as benzodiazepines, tricyclic antidepressants, Serotonin, and norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), or any other serotonergic medications within 7 days prior to Day -1. The use of lorazepam and other sleep medications, except those containing analgesic properties, is permitted.

c. Use of parenteral or oral corticosteroid(s) within 14 days prior to Day -1.

d. Antihypertensive agent or diabetic regimen at a dose that has not been stable for at least 30 days, or which is not expected to remain stable throughout the study.

e. Digoxin, warfarin lithium, theophylline preparations, aminoglycosides, and all antiarrhythmics except beta-blockers within 7 days prior to Day -1 and throughout the study.

f. Current use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days.

3. Positive results for hepatitis B surface antigen (HbsAg) and/or hepatitis B anti-core antibody (anti-HBc) but negative results for anti-surface antibody (anti-HBs) at the Screening Visit.

4. Positive results for hepatitis C antibody unless patient received curative therapy and a negative viral load is documented.

5. Human immunodeficiency virus (HIV) infection or positive HIV serology at the Screening Visit.

6. Known positive COVID-19 viral test during screening or suspected COVID-19 infection at the Day 1 Visit

7. History of illicit drug use, or prescription medicine or alcohol abuse within the past 2 years.

8. History of opioid dependence.

9. History of NSAID-induced bronchospasm or presence of nasal polyps, history of asthma or chronic rhinitis.

10. Significant history of allergic reactions or known intolerance to naproxen, pregabalin or any gabapentinoid, or to any rescue medication used in the study, or any medication used in the surgical and anesthetic protocol.

11. Biological female subjects who are pregnant or lactating, who plan to get pregnant, or who have a positive serum pregnancy test at Screening and/or Day 1 (prior to surgery).

12. Participated in another clinical trial within 30 days, or previously participated in a clinical study with a similar investigational product.

13. Presence of severe depression as indicated by Patient Health Questionnaire (PHQ-9) total score of ≥20 or item 9 score >0 at the Screening Visit (see Appendix H: Patient Health Questionnaire-9 (PHQ-9)).

14. Presence of severe anxiety as indicated by General Anxiety Disorder (GAD-7) score of ≥15 at the Screening Visit (see Appendix I General Anxiety Disorder (GAD-7)).

15. Presence of history of suicidal behavior or ideation as indicated by the Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening Version at Screening Visit. (See Appendix J Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening Version)

All Inclusion and Exclusion criteria must be verified by the Investigator or designee at Screening (Day -28 to Day -1) and Pre-Surgery (Day 1).

5.3. Screen Failure

A screen failure is defined as any subject who fails Screening assessments or is ineligible based on inclusion/exclusion criteria during Screening or on the Day 1 Pre-operative assessment.

5.4. Replacement of Subjects

Any subject who is withdrawn or discontinued from the study after receiving study drug will not be replaced. Subjects who withdraw consent before dosing may be replaced.

5.5. Number of Subjects and Centers

This study will be conducted at a minimum of 3 study sites in the US. A total of 450 subjects will be randomized (150 per arm) to achieve 130 evaluable subjects per treatment group. An evaluable subject is defined as one who receives study drug, completes surgery, and has at least 2 post-operative pain assessments.

A PK subgroup of 90 subjects (approximately 30 subjects per study arm) will be assessed at 1 site only.

6. STUDY TREATMENT

All subjects will be randomized to receive either low-dose XG005, high-dose XG005, or placebo.

XG005 [750 mg Q12 hours]

XG005 [1250 mg Q12 hours]

Placebo [matching tablets Q12 hours]

6.1. Description

XG005 drug product is formulated as tablets containing 250 mg of XG005.

Placebo tablets of XG005 are identical in appearance to their respective active drug tablets.

Each treatment group will be administered a total of 5 tablets to maintain the blind and administered as 5 identical blue tablets (low or high XG005 or its placebo) every 12 hours.

6.2. Dosing and Administration

Study drug (XG005 low or high dose, or placebo) will be administered as an oral dose 60 minutes prior to surgery on Day 1 then every 12 hours for 72 hours after the time of first dose. The number and strength of active drug tablets to be administered at each dose level is shown in Table 1. Subjects randomized to placebo will receive the corresponding number of placebo tablets.

Table 1 Dose and Pill Relationship

Study Arms	**1**	**2**	**3**
Dose Strength	**Placebo**	**XG005 (low dose)**	**XG005 (high dose)**
Dose Levels	No Drug	750 mg	1250 mg
Number of Tablets	5 × XG005 placebo tablets	3 × 250 mg XG005 tablets + 2 × XG005 placebo tablets	5 × 250 mg XG005 tablets

6.3. Preparation/Handling/Storage/Accountability

6.3.1. Acquisition and Accountability

The Sponsor will provide adequate quantities of the study drug kits which will include XG005 and matching placebo to each study site.

6.3.2. Product Storage and Stability

All study drugs must be stored at controlled room temperature (20° to 25°C or 68°to 77°F; excursions are permitted between 15° and 30°C [59°and 86°F]) in a secure cabinet or room with

access restricted to necessary clinic personnel. The site will be required to keep a temperature log to establish a record of compliance with storage conditions.

6.3.3. Packaging and Labeling

Sufficient quantities of XG005 tablets and matching placebo tablets will be supplied by the Sponsor or its designee in high density polyethylene (HDPE) sealed bottles with polypropylene child resistant (PPCR) cap with an induction seal liner. In order to maintain the blinding, study drug kits will be provided with appropriate labeling to meet regulatory requirements.

6.3.4. Randomization

The randomization schedule for each treatment group will be generated by Lotus Clinical Research, LLC (Lotus). Subjects who meet all entry criteria will be randomized before pre-surgery dosing on Day 1 by the IXR system.

Study drug kits will be dispensed by the clinical site pharmacist at each study site according to the randomization schedule.

6.4. Blinding

6.4.1. Blinding Procedures

This is a double-blind study. Neither the subjects nor the investigator will be aware of the treatment assignment. Blinding will be maintained throughout the study by using active and placebo dosage forms of identical appearance. Access to the randomization code will be strictly controlled according to the standard operating procedures of the CRO.

6.4.2. Breaking the Blind

A subject or subjects may be unblinded in the event of a SAE, or other event, or if there is a medical emergency where the identity of the drug must be known to properly treat a subject. If a subject becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the administered study drug will affect that subject's treatment options. In the event of a medical emergency requiring identification of the study drug administered to an individual subject, the investigator will make every attempt to contact the independent medical monitor to explain the need for opening the code within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

6.4.3. Study Treatment Compliance

All doses of study drug will be administered in the clinical unit under direct observation of clinic personnel and will be recorded in the eCRF. Clinic personnel will confirm that the subject has received the entire dose of study drug.

The date and time of study drug dosing will be recorded on the appropriate page of the eCRF. If a subject is not administered study drug, the reason for the missed dose will be recorded.

6.5. Prior and Concomitant Medications

Restrictions for prior and concomitant medications and therapies are described in Section 5.1.

6.5.1. Prior Medication

All prior medications received by the subject within 30 days before signing the ICF should be recorded in the subject's eCRF.

6.5.2. Rescue Medication

During the domiciling period, subjects may be administered IV acetaminophen 1 g, Q 6 hours, PRN, up to 4 g in 24 hours. If a patient is unable to tolerate acetaminophen or if there is insufficient pain relief, 50 mg tramadol will be administered Q 4 hours, PRN, up to 300 mg in 24 hours. Intravenous acetaminophen should always be the first rescue medication administered with tramadol being used as the second option.

Prior to receiving any rescue medication, an NPRS assessment must be performed immediately before administering any rescue medication.

6.5.3. Concomitant Medication

Any other concomitant medication deemed necessary for the welfare of the subject (except prohibited medications) during the study may be given at the discretion of the investigator. If a concomitant medication is taken, except for those specified in the protocol, a joint decision will be made by the investigator and the sponsor to continue or discontinue the subject based on the time the medication was administered, its pharmacology and PK, and whether the use of the medication will compromise the safety of the subject or the interpretation of the data. The investigator is responsible for ensuring that details regarding the medication are adequately recorded in the eCRF.

6.5.4. Permitted Medications

Only the protocol-defined rescue medication is permitted in the study. All other analgesics administered will result in a subject terminating early from the study.

No pretreatment for potential nausea and vomiting is permitted. Administration of antiemetic medications are limited to subjects with active vomiting, subjects with a score ≥5 on the NNRS, or by subject request only.

6.5.5. Surgery and Anesthesia

Subjects will undergo primary, unilateral, first metatarsal Austin bunionectomy. The surgical procedure should be limited to a maximum duration of 90 minutes. End of surgery will be defined as completion of the last suture.

The surgery will be performed under regional anesthesia via a local Mayo block using lidocaine (20 mL, 2.0%) without epinephrine, with IV propofol for sedation.

Propofol induction (dose per discretion of anesthesiologist) will be given as an initial bolus followed by a continuous infusion of up to 250 µg/kg/min for intraoperative sedation.

A small dose of lidocaine (up to 5 mL of 1% lidocaine without epinephrine) may be administered to reduce vein irritation at the infusion site.

Intraoperatively, all subjects will be given 50 µg of fentanyl IV around the time of induction with propofol.

Once sedated, a Mayo block of the first metatarsal will be induced using lidocaine (20 mL, 2.0%) without epinephrine.

Midazolam 1 mg IV may be administered preoperatively for anxiolysis.

A pneumatic ankle tourniquet inflated between 150 and 250 mmHg will be applied to achieve homeostasis.

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Study Stopping Criteria

The following criteria will determine whether to stop study drug dosing. The Investigator and the Sponsor may decide to stop drug administration based on other safety signals not described in the following criteria:

- One drug-related SAE without a clear alternative etiology, or
- Two or more subjects develop a severe adverse event (Grade 3 or above, based on FDA Guidance Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, see Appendix L) possibly related or related to the study drug of the same preferred term or same symptom, or
- Greater than 25% of subjects develop any severe adverse event (Grade 3 or above, based on FDA Guidance Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, see Appendix L) possibly related or related to the study drug.

If one of the above stopping criteria is met, dosing will be stopped and unblinded assessment will be conducted for further decision making.

So far, there have been no identified adverse events of special interests (AESIs) for XG005 in the three completed phase 1 trials, which showed good tolerability and an acceptable safety profile.

7.2. Discontinuation of Study Treatment

Subjects can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment.

The investigator may withdraw a subject from the study if the subject meets any of the following criteria:

- Is noncompliant with the protocol
- Experiences an SAE or intolerable AE(s) that, in the investigator's opinion, requires withdrawal from the study
- Has laboratory safety assessments that reveal clinically significant hematologic or biochemical changes from baseline values
- Develops symptoms or conditions that are listed in the exclusion criteria during study
- Requires a medication prohibited by the protocol (including receiving rescue medication beyond what is allowed per protocol)

- Requests early discontinuation for any reason.

The investigator can also withdraw a subject upon the request of the sponsor, or if the sponsor terminates the study. If withdrawal is considered because of an SAE or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an AE, the event will be followed until it is resolved, stable, or judged by the investigator to be not clinically significant.

7.3. Participant Discontinuation/Withdrawal

When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the eCRF. Any subject who fails to return for final assessments will be contacted by the site in a reasonable attempt to have them comply with the protocol. The status of subjects who fail to complete final assessments will be documented in the eCRF.

7.4. Early Termination

Whenever possible, any subject who prematurely withdraws from the study will undergo all EOS assessments per the Schedule of Assessments (Section 1.2) and the Early Termination assessments that include NPRS, PGA, SIS, RSS and NNRS. Subjects who terminate early from the study will be requested to remain in the clinic for the full 72 hours for continued collection of safety assessments only (vital signs, ECGs, laboratory testing, AE monitoring, and concomitant medications).

8. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential subjects will sign an ICF as outlined in Section 10.2.

All assessments and procedural details during Screening (Day -28 to Day -1), Pre-surgery/Surgery (Day 1), the Treatment Period (hours post end of surgery), and EOS/ET are described in the Schedule of Assessments (Section 1.2).

All efficacy, safety, and PK assessments are anchored to time at end of surgery (last suture).

Pharmacokinetic (PK) sampling timepoints correlate with the collection of the 11-pt Numeric Pain Rating Scale (NPRS) efficacy assessments when they overlap.

8.1. Efficacy Assessments

Study staff will record subject-reported pain assessments via a standard 11-point NPRS at the following time points post-end of surgery: 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours within a ±10-minute window (Appendix C). NPRS will be collected prior to PK sampling and administration of rescue medication.

Study staff will record subject-reported PGA of pain control using a 5-point scale (poor, fair, good, very good, excellent) at the following time points post-end of surgery: 24, 48, and 72 hours within a ±10-minute window and just prior to receiving a dose of rescue medication (Appendix D).

Study staff will record the time and the dose of rescue medication administered on the rescue medication form. NPRS and PK sampling will be collected immediately prior to administering rescue medication.

Nausea will be self-assessed using an 11-point NNRS at the following time points post-end of surgery: 1, 4, 8, 12, 24, 48, 72 hours within a ±10-minute window (Appendix E). Additional NNRS assessments will be collected when an AE of nausea or vomiting is reported or prior to any rescue antiemetic administration. Subject will report Sleep Interference Score (SIS) using an 11-point NRS scale (0-10) at 24, 48 and 72 hours post-end of surgery within a ±15minute window (Appendix F)

8.2. Safety Assessments

The timing and frequency of all safety assessments are provided in the SOA (Section 1.2). Safety endpoints include monitoring and recording of AEs and SAEs, clinical laboratory results (serum chemistry, hematology, coagulation, and urinalysis), 12-lead ECG results, and vital signs measurements (blood pressure [systolic and diastolic], heart rate, respiratory rate, oral body temperature, and continuous pulse oximetry), and recording of relevant safety data.

Trained staff on hand in the research unit will monitor respiratory safety via respiration rate, continuous pulse oximetry and oxygen saturation (SpO_2) checks every 12 hours post-end of surgery within a ±10-minute window, and somnolence if observed by Staff at times other than

when a formal assessment of somnolence is scheduled. The Ramsay Sedation Scale (RSS, Appendix G) will be used as an assessment of sedation (somnolence) with the same time sequence as the NPRS determination, but with a window of ±15 minutes. A Columbia-Suicide Severity Rating Scale since last visit (Appendix K) will be administered at 72 hours post treatment and at the follow-up visit and at the end of study visit/early termination visit.

For all safety assessments, the investigator will determine whether results are clinically significant, which is defined as any variation in a result that has medical relevance and that may result in an alteration in medical care (e.g., active observation, diagnostic measures, or therapeutic measures). If clinical significance is noted, the result and reason for significance will be documented and an AE reported on the AE page of the subject's electronic case report form (eCRF). The investigator will monitor the subject until the result has reached the reference range or the result at Screening, or until the investigator determines that follow-up is no longer medically necessary.

8.2.1. Reporting Adverse Events and Serious Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the sponsor, regardless of their relationship to study drug or clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

8.2.1.1. Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product, whether or not there is a causal relationship suspected between the product and the event. An AE can therefore be any unfavorable and unintended sign, symptom or disease that is temporally associated with the use of the pharmaceutical product.

An AE includes any untoward medical occurrence in a subject or clinical trial participant administered a pharmaceutical product, whether or not there is a causal relationship suspected between the product and the event. An AE can therefore be any unfavorable and unintended sign, symptom, or disease that is temporally associated with the use of the pharmaceutical product.

A treatment emergent adverse event (TEAE) is defined as any event that was not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the study drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

An adverse reaction is any AE caused by a study drug. Adverse reactions belong to a subset of all suspected adverse reactions and indicate that there are reasons to conclude that the study drug caused the event.

8.2.1.2. Definition of Serious Adverse Event

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
- Life-threatening AE (i.e., immediate risk of death from the event as it occurred; this does not include an AE that, had it occurred in a more serious form, might have caused death).
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacitation
- Congenital anomaly

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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical 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.

8.2.1.3. Assessment of Severity

The severity (or intensity) of an AE will be assessed based on FDA Guidance Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix L). The investigator will assess the intensity of each AE/SAE based on his/her clinical judgment.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed as severe.

Changes in the severity of an AE should be documented to allow the duration of the event at each level of intensity to be assessed. An AE characterized as intermittent does not require documentation of the onset and duration of each episode.

8.2.1.4. Assessment of Relationship to Study Drug

The investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (i.e., whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be classified as follows:

- Not related: There is not a reasonable possibility of relationship to study drug. The AE does not follow a reasonable temporal sequence from study drug administration or can be

reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

- Unlikely Related: when the temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE

- Possibly Related: when the AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions

- Related: There is a reasonable possibility of relationship to study drug. The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications), represents a known reaction to the study drug or other drugs in its class, is consistent with the known pharmacologic properties of the study drug, and/or resolves with discontinuation of the study drug (and/or recurs with re-challenge, if applicable).

8.2.1.5. Assessment of Expectedness

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or package inserts of the individual components of the IMP, or if it occurs with specificity or severity that has not been previously observed with the study drug being tested; or, if an investigator brochure is not required or available, the AE or suspected adverse reaction is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacologic properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

8.2.1.6. Adverse Event Reporting and Follow-up Period

The AE reporting period begins at the time of first dose of study drug and ends 30 days after the last dose of study drug.

During the treatment period of the study, participants will be asked about AEs. All AEs that occur during the course of the study must be collected, documented, and reported to the principal investigator. The occurrence of AEs will be assessed at baseline and daily while in the clinical research unit and at each follow-up clinic visit.

Subjects will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have used any new medications or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to subject observations, AEs will be documented from any data collected on the AE page of the eCRF (eg, laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

All AEs and SAEs observed while a subject is receiving study drug should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

8.2.1.7. Recording of Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes dose level, type and frequency of event, date and time of onset, investigator-specified assessment of severity and relationship to study drug, date, and time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Any AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. MedDRA (version 23.0 or higher) will be used to code all AEs.

8.2.1.8. Serious Adverse Event Reporting

Any AE that is considered serious by the investigator or which meets SAE criteria (Section 8.1.1.2) must be reported to the sponsor immediately (after the investigator has confirmed the occurrence of the SAE). The investigator and the study medical monitors will assess whether there is a reasonable possibility that the study drug caused the SAE. The sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in US Title 21 Code of Federal Regulations (CFR) Parts 312 and 320. The investigator is responsible for notifying the IRB directly.

For this study, the following contact information is to be used for SAE reporting:

Lotus Medical Monitor: [redacted]

24/7 SAE and medical question hotline: [redacted]

SAE email: [redacted]

Sponsor Medical Monitor: [redacted]

Xgene Pharmaceutical Inc.

Email: [redacted]

Telephone: [redacted]

8.2.1.9. Reporting of Pregnancy

Pregnancy diagnosed during the study, or that occurs within 30 days after stopping study medication, must be reported immediately to the Investigator. Pregnancy, in and of itself, is not regarded as an adverse event, unless there is suspicion that study medication may have interfered with the effectiveness of a contraceptive medication. If the subject becomes pregnant while on-study, the study drug must be immediately discontinued. Pregnancy information about a female subject or a female partner of a male subject should be reported immediately from the time the Investigator first becomes aware of a pregnancy or its outcome. This will be performed by the Investigator completing a Pregnancy Form.

Any pregnancy complication, spontaneous abortion, elective termination of a pregnancy for medical reasons, outcome of stillbirth, congenital anomaly/birth defect, or serious adverse event in the mother will be recorded as an SAE and will be reported as described in Section 8.2.1.8.

8.2.2. Clinical Laboratory Assessments

Clinical laboratory samples will be analyzed at the central laboratory.

Blood and urinalysis samples will be collected. The following standard clinical laboratory assessments will be performed at the time points indicated in the SOA (Section 1.2).

Hematology:	Complete blood count including hemoglobin, hematocrit, RBC count, RBC indices, MCH, MCHC, platelet count, and WBC count including differential. HbA1c will be assessed at Screening only.
Coagulation:	PT, PTT, and fibrinogen
Serum Chemistry:	Albumin, total bilirubin, total protein, calcium, ALP, ALT, AST, BUN, creatinine, glucose, sodium, potassium, chloride, bicarbonate, LDH, and uric acid. Creatinine clearance will be calculated by the Cockcroft/Gault formula (Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16: 31-41.)
Urinalysis:	pH, specific gravity, blood and leukocyte esterase, glucose, protein, and ketones
Serology:	Hepatitis B virus surface antigen, hepatitis B anti-core antibody (anti-HBc) and anti-surface antibody, hepatitis C virus antibody, and HIV antibody types 1 and 2 (Screening only)

All subjects will undergo a urine drug screen (amphetamines, barbiturates, benzodiazepines, cocaine, opiates [including heroin, codeine, and oxycodone], phencyclidine [PCP], THC, methamphetamines, methadone, and ecstasy), and alcohol screen at Screening only.

A serum pregnancy test will be performed at Screening and a urine pregnancy test on Day 1 prior to dosing only in premenopausal women of childbearing potential or women who are not surgically sterile. Results must be available before surgery.

Clinical laboratory tests may be repeated at the discretion of the investigator, if necessary, for assessment of inclusion and exclusion criteria or evaluation of clinical laboratory abnormalities.

8.3. Pharmacokinetic Assessments

8.3.1. Pharmacokinetic Sampling and Analysis

Blood draws will always be performed after each NPRS, nausea, SIS and/or PGA assessment, when applicable, and prior to the first administration of rescue medication. The PK sampling plan uses the post-end-of-surgery schedule to be consistent with the efficacy assessment schedule.

Each subject in the PK subgroup (one site only) will have blood samples drawn for PK assessments at the following time points: prior to the first dose (pre-dose), and post end of surgery at 1, 2, 3, 4, 6, 8, 10, 12, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours within a ±15-minute window. The actual clock time when the PK sample is collected will be recorded, and the post-dose time for PK analysis will be calculated based on the recorded clock time.

The timing and frequency of PK sample collection is listed in the SOA (Section 1.2).

Details for the collection, processing, storage, and shipping of PK samples will be provided to the clinical unit separately.

Pharmacokinetic samples will be analyzed using a validated liquid chromatography coupled with tandem mass spectrometry assay for XG005 in human plasma. Assay details, results, and validation will be provided in a separate bioanalytical report.

9. STATISTICAL METHODS AND DATA ANALYSIS

Full details of the statistical analysis methodology will be provided in a separate Statistical Analysis Plan (SAP). A separate PK analysis plan will also be prepared.

A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.1. Statistical Hypotheses

This primary efficacy endpoint is to test the mean difference of summed pain intensity from end of surgery to 48 hours post-surgery (SPI48) between high dose XG005 and Placebo groups.

The study null hypothesis is XG005 high dose and placebo have the same effect. And the alternative hypothesis is XG005 high dose and placebo have different effect. These will be tested at a two-tailed alpha of 0.05, and the Null hypothesis will be rejected if p-value < 0.05.

9.2. Sample Size Determination

One hundred thirty (130) evaluable subjects per study arm will yield 90% power to detect a standardized effect size of 40% (Wang 2010; Wu J, Jiang J, Wei W. Confidence intervals of effect size in randomized comparative parallel-group studies. *Stat Med*. 2006;25(4):639-51.; Vevea J, Woods CM. Publication bias in research synthesis: sensitivity analysis using A priori weight functions. *Psychological Methods*. 2005;10(4):428–43.; Singla NK, Chelly JE, Lionberger DR, et al. Pregabalin for the treatment of postoperative pain: results from three controlled trials using different surgical models. *J Pain Res*. 2015;8:9-20.) at a two-tailed a= 0.05 for the familywise type one error. Recruitment goals will be 150 subjects per arm or N=450 total.

Randomization Strata: Study Site

9.3. Multiplicity Adjustment

A serial gatekeeping procedure will be used to control the overall type-1 error rate at 0.05 for primary and secondary endpoints. If the primary endpoint is not significant at a two-tailed alpha of 0.05, there is no testing on secondary endpoints. If the primary endpoint is significant at a two-tailed alpha of 0.05, the secondary endpoints will be tested following the hierarchy testing procedure with a pre-specified order as Section 3. If any secondary endpoint is not significant, the successive secondary endpoints will not be tested.

9.4. Populations

- The Intent-to-Treat (ITT) population is defined as all randomized subjects. Subjects will be analyzed according to the treatment group to which they were randomized.
- The Safety Population is defined as all subjects who receive study medication. Subjects will be analyzed according to the actual treatment they receive.

- The modified Intent-to-Treat (mITT) Population is defined as all ITT subjects who received at least one dose of study medication and have at least 2 NPRS assessments post-end of surgery.
- The Per-Protocol Population is defined as all mITT subjects who have no major protocol violations which may potentially bias efficacy analysis of the study.

9.5. Statistical Analyses

9.5.1. General Approach

All data collected will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings, but not included in the calculation of summary statistics.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation (SD), minimum and maximum).

Baseline demographic and background variables will be summarized overall for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

9.5.2. Efficacy Analyses

The primary endpoint of the comparison of summed pain intensity (SPI) from end of surgery to 48 hours post-surgery (SPI48) for high dose XG005 vs placebo will analyzed, using analysis of covariance (ANCOVA) model. The model will use treatment as main effect, and study site as a covariate. More details for efficacy analyses will be specified in SAP.

9.5.3. Safety Analyses

Adverse events will be coded by preferred term and system organ class (SOC) using the latest version of MedDRA (version 23 or higher). All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized by treatment and overall, as well as by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be presented in the data listings and summarized by treatment and overall.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Physical examination findings will be presented in a data listing.

9.5.4. Pharmacokinetic Analyses

PK analyses will be addressed in a separate PK Analysis Plan.

Individual plasma concentrations of naproxen, pregabalin and XG005 (and/or other metabolites as appropriate) will be listed by subject and summarized by gender, dose, and nominal time point using descriptive statistics (i.e., N, arithmetic mean, SD, percent coefficient of variation [CV%], median, minimum, maximum, and geometric mean).

The PK parameters of XG005 will be analyzed based on the actual sampling times. All parameters will be calculated using the latest version of Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) or SAS® (SAS Institute Inc., Cary, North Carolina). Pharmacokinetic parameters will be summarized by time point for each dose level using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum). Geometric means will be reported for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}48}$, and C_{max}.

9.5.5. Handling of Missing Data

For the PK analysis, concentrations that are below the limit of quantification (BLQ) will be treated as zero for descriptive statistics with the exception that a BLQ value between two quantifiable concentrations will be set as missing. Missing concentrations will be treated as missing from the PK parameter calculations. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

For efficacy analyses, when rescue medication is used, the last pain intensity measure prior to the use of rescue medication will be used (imputed) for the subsequent protocol-specified time points for measurement of pain intensity after the time of the rescue medication.
Missing data as a result of discontinuation due to adverse event or due to lack of efficacy will be imputed with worst observation carry forward (WOCF) method.

For safety analyses, missing data will not be imputed in general, otherwise specified.

More detail will be described in the SAP.

9.5.6. Interim Analysis

No formal interim analysis will be performed in this study.

9.5.7. Protocol Deviations and Violations

Protocol deviations will be identified on an ongoing basis by the clinical study team.

9.5.8. Subgroup Analyses

Analyses by subgroup may be further described in the SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Good Clinical Practice

The investigator agrees to conduct the study as outlined in this protocol, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki; ICH E6(R2): Good Clinical Practice; the protocol; and all national, state, and local laws or regulations.

10.2. Informed Consent Process

Written informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each subject before he or she enters the study or before performing any unusual or nonroutine procedure that involves risk to the subject. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study.

Before recruitment and randomization, each prospective subject or his/her legal guardian will be given a full explanation of the study and will be allowed to read the approved ICF. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give his or her consent to participate in the study by signing the ICF. A copy of the ICF will be provided to the subject/legal guardian.

10.3. Institutional Review

Federal regulations and ICH guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study that is to be provided to the subject or the subject's legal guardian must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH E6(R2): Good Clinical Practice will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

10.4. Confidentiality and Privacy

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the FDA, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished,

confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.5. Study Management

10.5.1. Clinical Monitoring

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and standard operating procedures.

Monitoring for this study will be performed by Lotus. The clinical monitor, as a representative of the sponsor will visit the investigator and study site at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

Details of clinical site monitoring are documented in the Clinical Monitoring Plan (CMP).

10.5.2. Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, their representatives, the FDA, or other regulatory agencies access to all study records.

The investigator should promptly notify the sponsor and study site(s) of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.5.3. Data Quality Insurance

This study will be conducted using the quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with current International Council for Harmonization (ICH) guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current Good Clinical Practice, the protocol, and standard operating procedures.

Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and any subsequent investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Site personnel will maintain source documentation, enter subject data into the eCRF as accurately as possible, and will rapidly respond to any reported discrepancies.

Paper copies of the eCRFs and other database reports may be printed and signed by the investigator. This system provides site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information.

10.5.4. Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor. The sponsor is responsible for informing the investigator/institution when these documents no longer need to be retained.

10.5.5. Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important deviation (sometimes referred to as a major or significant deviation) is a subset of protocol deviations that leads to a subject being discontinued from the study, or significantly affects the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH E6(R2) guidelines.

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations, if appropriate, in a timely manner.

10.5.5.1. Unavoidable Protocol Deviations Related to COVID-19

Unavoidable protocol deviations involving study procedure scheduling delays, early or missed visits, and missing information might occur due to the COVID-19 situation. In general, if a study procedure is completed, it might not be considered a protocol deviation, even if it is completed

remotely, out-of-window, or using alternative methods. If a procedure cannot be completed and results in missing data, it might be considered a protocol deviation. COVID-19 related Protocol deviations are to be documented, and specific information that explains the basis of missing data including relationship to COVID-19 must be captured in the CSR. Missing data related to COVID-19 will be treated as non-COVID-19 related missing data. Any causal relationship between the study drug and an SAE in a trial participant diagnosed with CoVID-19 must be submitted to the FDA. The sponsors and investigators are required to document how restrictions related to CoVID-19 led to changes in study conduct, duration of those changes, which trial participants were impacted and how they were impacted.

10.6. Publications

The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR § 50.25I. After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for determining how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and any other related issues. The sponsor has final approval authority over all such matters.

Data are the property of the sponsor and cannot be published without their prior authorization, but data and any permission for publication thereof will not be unduly withheld.

11. LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve, extrapolated to infinity
$AUC_{0\text{-}t}$	area under the concentration-time curve from time 0 to the last measurable concentration timepoint
BID	twice daily
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
C-SSRS	Columbia-Suicide Severity Rating Scale
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
C_{max}	maximum concentration
$C_{max, ss}$	maximum concentration at steady state
C_{min}	minimum concentration
CrCL	creatinine clearance
CRF	case report form
CRO	Clinical research organization
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
GI	Gastrointestinal
h	Hour
HBsAg	surface antigen of Hepatitis-B-Virus
HCV	hepatitis C virus
HDPE	high density polyethylene
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
LDH	lactic dehydrogenase
MAD	multiple ascending dose
MAOI	monoamine oxidase inhibitor
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume

MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mmHg	millimeters of mercury
NSAIDs	non-steroidal anti-inflammatory drugs
PE	physical examination
PK	Pharmacokinetic
PPI	proton pump inhibitor
PT	preferred term; prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell (count)
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOA	Schedule of Assessments
SOC	system organ class
SOP	standard operating procedure
TEAEs	treatment-emergent adverse events
T_{max}	time to maximum concentration
US	United States
WBC	white blood cell (count)
WOCBP	women of childbearing potential

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APPENDIX A: INVESTIGATOR'S SIGNATURE

***S*tudy Title:**	A Randomized, Double-Blind, Placebo -Controlled Trial to Evaluate the Safety and efficacy of XG005 Tablets in Subjects Undergoing Bunionectomy
Study Number:	PR-XG005-02-BUN-01
Study Version:	Version 5.0
Protocol Date:	15 Nov 2022

I have read the attached protocol entitled "A Randomized, Double-Blind, Placebo Controlled Trial to Evaluate the Safety and efficacy of XG005 Tablets in Subjects Undergoing Bunionectomy" and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice, The Declaration of Helsinki (2004), and applicable FDA regulations/ guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Xgene Pharmaceuticals, Inc.

Clinical Site:

Principal Investigator or Investigator:

Name

Role

Affiliation

City, State

Investigator's Signature	**Date**

APPENDIX B: PRE-STUDY PERSONALITY QUESTIONNAIRE

Pre-Study Personality Questionnaire

A. *Please answer the following questions about yourself by indicating the extent of your agreement using the following scale:*

Strongly	Disagree	Neutral	Agree	Strongly Agree
1	**2**	**3**	**4**	**5**

1. In uncertain times, I usually expect the best _____
2. It's easy for me to relax. _____
3. If something can go wrong for me, it will. _____
4. I'm always optimistic about my future. _____
5. I enjoy my friends a lot. _____
6. It's important for me to keep busy. _____
7. I hardly ever expect things to go my way. _____
8. I don't get upset too easily. _____
9. I rarely count on good things happening to me. _____
10. Overall, I expect more good things to happen to me than bad. _____

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Pre-Study Personality Questionnaire

B. *Here are a number of characteristics that may or may not apply to you. For example, do you agree that you are someone who likes to spend time with others? Please write a number next to each statement to indicate the extent to which you agree or disagree with that statement.*

Disagree strongly	Disagree a little	Neither agree nor disagree	Agree a little	Agree Strongly
1	**2**	**3**	**4**	**5**

I see Myself as Someone Who

1. Is original, comes up with new ideas _____
2. Is curious about many different things _____
3. Is ingenious, a deep thinker _____
4. Has an active imagination _____
5. Is inventive _____
6. Values artistic, aesthetic experiences _____
7. Prefers work that is routine _____
8. Likes to reflect, play with ideas _____
9. Has few artistic interests _____
10. Is sophisticated in art, music, or literature _____

C. *Please indicate how often each statement applies to you generally in daily life.*

Never					*Always*
0	***1***	***2***	***3***	***4***	***5***

1. I do not notice (I ignore) physical tension or discomfort until they become more severe. _____
2. I distract myself from sensations of discomfort. _____
3. When I feel pain or discomfort, I try to power through it. _____

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Pre-Study Personality Questionnaire

D. *Please indicate how often each statement applies to you generally in daily life.*

Never					*Always*
0	***1***	***2***	***3***	***4***	***5***

1. I can pay attention to my breath without being distracted by things happening around me. _____
2. I can maintain awareness of my inner bodily sensations even when there is a lot going on around me. _____
3. When I am in conversation with someone, I can pay attention to my posture._____
4. I can return awareness to my body if I am distracted. _____
5. I can refocus my attention from thinking to sensing my body. _____
6. I can maintain awareness of my whole body even when a part of me is in pain or discomfort. _____
7. I am able to consciously focus on my body as a whole. _____

E. *Please indicate how often each statement applies to you generally in daily life.*

Never					*Always*
0	***1***	***2***	***3***	***4***	***5***

1. I notice how my body changes when I am angry. _____
2. When something is wrong in my life, I can feel it in my body. _____
3. I notice that my body feels different after a peaceful experience. _____
4. I notice that my breathing becomes free and easy when I feel comfortable. _____
5. I notice how my body changes when I feel happy / joyful. _____

F. *Please indicate how often each statement applies to you generally in daily life.*

Never					*Always*
0	***1***	***2***	***3***	***4***	***5***

1. When I feel overwhelmed, I can find a calm place inside. _____
2. When I bring awareness to my body, I feel a sense of calm. _____
3. I can use my breath to reduce tension. _____
4. When I am caught up in thoughts, I can calm my mind by focusing on my body/breathing.

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Pre-Study Personality Questionnaire

STUDY STAFF USE ONLY

For all items, higher score predicts greater placebo response

A. OPTIMISM

Source: Revised Life Orientation Test (LOT-R). ***Reverse score items 3, 7 and 9. Items 2, 5, 6, and 8 are filler items, do not score.***
(Geers, 2005: "Dispositional optimism was related to less cold pressor pain in the placebo condition as compared with the control condition.")

B. OPENNESS

Source: The Big Five Inventory (BFI). ***Reverse score items 7 and 9.***

C. NOT DISTRACTING

Source: Multidimensional Assessment of Interoceptive Awareness (MAIA)
Not-Distracting: Tendency not to ignore or distract oneself from sensations of pain or discomfort
(Note: original instructions are to reverse score all 3 items, resulting in a "not distracting" score
negatively correlated with placebo response. For our purposes we will not reverse score; higher score predicts higher placebo response).

D. ATTENTION REGULATION

Source: Multidimensional Assessment of Interoceptive Awareness (MAIA)
Attention Regulation: Ability to sustain and control attention to body sensations

E. EMOTIONAL AWARENESS

Source: Multidimensional Assessment of Interoceptive Awareness (MAIA)
Emotional Awareness: Awareness of the connection between body sensations and emotional states

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STUDY STAFF USE ONLY

Pre-Study Personality Questionnaire

F. SELF-REGULATION

Source: Multidimensional Assessment of Interoceptive Awareness (MAIA)
Self-Regulation: Ability to regulate distress by attention to body sensations

(Vachon-Presseau, 2018: "... openness (from the big 5 personality dimensions) and 4 out of 8 subscales from the Multidimensional Assessment of Interoceptive Awareness (MAIA)- Not Distracting (maia/nd), Attention Regulation (maia/a), Emotional Awareness (maia/e), and Self-Regulation (maia/sr)- correlated with the magnitude of response after correcting for multiple comparisons ($p < 0.0013$) ...
Patients with increased emotional awareness experience greater placebo analgesia… whereas patients who tend not to ignore or distract themselves from discomfort experience less placebo analgesia (Mais/nd displayed in e) … In our patients, placebo pill response was driven primarily by a combination of a greater openness to experience, increased emotional awareness, decreased distraction about pain and discomfort, augmented capabilities in describing inner experiences, and higher sensitivity to non-painful situations.")

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APPENDIX C: NUMERIC PAIN RATING SCALE

On a scale of 0-10, please rate your pain by marking an "X" in the appropriate box that best describes your pain level NOW.

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
No Pain										***Worst pain imaginable***

The NPRS should also be administered prior to administration of any per protocol rescue medication.

APPENDIX D: PATIENT GLOBAL ASSESSMENT

5-Point PGA of Pain Control

"Overall, please rate how well your pain has been controlled during the last 24 (48, 72) hours since you received study medication?"

☐ Poor (0)
☐ Fair (1)
☐ Good (2)
☐ Very Good (3)
☐ Excellent (4)

APPENDIX E: NUMERIC NAUSEA RATING SCALE

On a scale of 0-10, please rate your nausea by marking an "X" in the appropriate box that best describes your nausea level NOW.

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
No nausea										***Worst nausea imaginable***

APPENDIX F: SLEEP INTERFERENCE SCORE

On a scale of 0-10, please rate how the pain at the operation site has interfered with your sleep during the last 24 hours (0=no interference, 10=worst interference imaginable).

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
No interference										***Worst interference imaginable***

APPENDIX G: RAMSAY SEDATION SCALE

Performed using a series of steps: observation of behavior (score 1 or 2), followed (if necessary) by assessment of response to voice (score 3), followed (if necessary) by assessment of response to loud auditory stimulus or light glabellar tap (score 4 to 6)

Score	Definition
1	Anxious and agitated or restless or both
2	Cooperative, oriented, and tranquil
3	Responds to commands only
4	Brisk response to a light glabellar tap or loud auditory stimulus
5	Sluggish response to a light glabellar tap or loud auditory stimulus
6	No response to a light glabellar tap or loud auditory stimulus

APPENDIX H: PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

APPENDIX I GENERAL ANXIETY DISORDER (GAD-7)

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

(For office coding: Total Score T____ = ____ + ____ + ____)

APPENDIX J COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) BASELINE/SCREENING VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation*** Past X Months - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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APPENDIX K COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) SINCE LAST VISIT VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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APPENDIX L TOXICITY GRADING SCALE TABLES

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illnes	Mild (Grade 1)	(Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

APPENDIX M SUMMARY OF CHANGES

Version 4.0 to Version 5.0

Additions to text are noted by underlining and deletions are noted by cross-out.

Section and/or page number	Changes from previous version	Justification
Section 7.1	Revision of Stopping Criteria	Per FDA's recommendation
Section 8.2.1.3	Revision of assessment of severity	Per FDA's recommendation
Appendix L	Inserted Toxicity Grading Scale Tables for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials	Per FDA's recommendation
Section 12	Addition of Guidance (toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials) in Reference list.	Per FDA's recommendation