Protocol and Statistical Analysis Plan Summary

A Phase 3, Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of VVZ-149 Injections for the Treatment of Postoperative Pain following Laparoscopic Colectomy

Investigational Product	**VVZ-149 Injections**
Protocol Number	**VVZ149-POP-P3-K301**
NCT Number	**NCT05764525**
Protocol/SAP Version	**Version 2.5/1.0**
Version Date	**January 27th, 2023**
Phase	**3**

Title:

A Phase 3, Multicenter, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of VVZ-149 injections for the Treatment of Postoperative Pain following Laparoscopic Colectomy

Protocol Number: VVZ149-POP-P3-K301

Inverstigational Product: VVZ-149 Injections

Phase: 3

Indication: Postoperative pain

Study Rationale:

VVZ-149 (Opiranserin, INN) is a dual antagonist of GlyT2 and 5HT2A, which plays an important role in modulating the induction and transmission of pain signals via the central and peripheral nervous systems. GlyT2 antagonists reduce the reuptake of glycine that inhibits pain signals at spinal synapses, which depresses the transmission of pain signals toward the brain. 5-HT2A is expressed in the termini of descending facilitatory projection neurons in the midbrain and involved in the amplification of pain signals in the spinal dorsal horn. 5HT2A is also expressed in the termini of peripheral nociceptive neurons (a start point of postoperative pain) and generates pain signals. Thus, 5-HT2A antagonists inhibit facilitatory pain signals and activation of nociceptive receptors, which reduces the sensation of pain. VVZ-149 has demonstrated comparable efficacy to morphine in well-controlled (blind, complete randomization with a positive control) animal studies using rat models of postoperative pain and formalin-induced pain.

Two Phase 1 studies (PT-VVZ149-01/02), five Phase 2 studies (PT-VVZ149-04/05, VVZ149-POP-P2-US001/US002/US004), and one Phase 3 study (VVZ149-POP-P3-US003) have been completed in Korea and the US to evaluate the efficacy, pharmacokinetics (PK) and safety of VVZ-149 Injections (Unafra, Brand name) for treating postoperative pain. Clinical trials with a continuous 8 to10-hours IV infusion of VVZ-149 Injections administered pre-, during-, and postoperatively demonstrated effective analgesia using VVZ-149 Injections with substantially reduced opioid consumption compared to the placebo. The most frequent adverse events (AEs) reported were nausea, vomiting, headache, dizziness, and somnolence, and to date, there have been no other clinically significant AEs, which indicates the excellence in safety and drug tolerance of VVZ-149 Injections.

OBJECTIVES:

Primary Objectives:

To make a pivotal assessment of the analgesic effects of VVZ-149 Injections (1000 mg VVZ-149 for 10 hours, administered as a loading dose of 160 mg for 30 minutes followed by a maintenance dose of 840 mg for 9.5 hours) for treating postoperative pain following laparoscopic colectomy.

Secondary Objectives :

To evaluate (1) the extended analgesic effects and reduced postoperative opioid requirements by VVZ-149 Injections, and (2) the safety and tolerability of VVZ-149 Injections up to 48 hours postdose

Subjects:

Adult men and women at least 18 years of age undergoing a planned laparoscopic colectomy
300 subjects who meet all of the inclusion and exclusion criteria
1:1 randomization to VVZ-149 Injections or placebo

Study Design:

This is a multicenter, randomized, double-blind, parallel group, placebo-controlled Phase 3 study in adults undergoing a planned laparoscopic colectomy to evaluate the efficacy and safety of VVZ-149 Injections on postoperative pain. The subjects who provide informed consent, meet all the inclusion/exclusion criteria from screening to post-surgery, and report the initial Numerical Rating Scale (NRS) of ≥ 5 measured immediately after regaining consciousness from anesthesia will be eligible for randomly assigned to the VVZ-149 treatment group or the placebo treatment group.

The VVZ-149 treatment group will receive a dosing regimen of a continuous IV infusion (1,000 mg of VVZ-149 mixed into a 500 mL saline bag; 160 mg as a loading dose will be administered for 30 minutes at the beginning of infusion followed by a maintenance dose of 840 mg for 9.5 hours) over 10 hours. The placebo group will be administered a placebo in the same way as the VVZ-149 treatment group over 10 hours. All subjects will be provided with a patient-controlled analgesia (PCA) pump upon emergence from anesthesia. After the start of the study drug infusion, subjects are allowed to self-administer IV PCA of fentanyl (5 μg IV bolus, 10 min lock-out) as needed to facilitate adequate pain relief. If the subject has been dosing with IV PCA of fentanyl but still reports the NRS score of ≥ 5 upon and requests additional pain medication, the subject will be given rescue medications. The efficacy, safety, and pharmacokinetics of the VVZ-149 Injections will be evaluated at scheduled time points for 48 hours from the start of the study drug infusion.

Inclusion and Exclusion Criteria:

Inclusion Criteria

Subjects who meet all of the following criteria will be eligible to participate in the study.

1. Men and women must be at least 18 years of age.
2. Female subjects who are not pregnant or breastfeeding.
3. Subjects must be undergoing a planned first laparoscopic colectomy.
4. Subjects classified in American Society Anesthesiologist (ASA) risk class of I or II.
5. Subjects who report the pain intensity ≥ 5 on the NRS (NRS: Numeric Rating Scale, 0~10) assessed after surgery.
6. Subjects must have the ability to understand study procedures and communicate clearly with the investigator and staff.
7. Subjects must have the ability to provide written informed consent.

Exclusion Criteria

A subject will be excluded from participation in the study if he/she met any of the following criteria:

Surgical Factors

8. Subjects undergoing emergency or unplanned surgery.
9. Subjects who had a previous laparoscopic colectomy or resection procedure.
10. Subjects with pre-existing conditions causing preoperative pain around the site of surgery

Subject Characteristics

11. Female subjects who are pregnant or breastfeeding.
12. Diagnosis of chronic pain (e.g., persistent pain with the intensity of NRS ≥ 5 at baseline)
13. Unstable or poorly controlled psychiatric conditions (e.g., post-traumatic stress disorder, anxiety, or depression). Antidepressant and antianxiety medication are allowed as long as the subject has been on a stable dose for at least 60 days prior to screening. Intraoperative antianxiety drugs are allowed.
14. Unstable, acute medical condition (e.g., unstable angina, congestive heart failure, renal failure, hepatic failure, or acquired immunodeficiency syndrome).
15. Clinically significant ECG findings as determined by the investigator at the screening visit: Prolonged QRS duration (> 200 msec), QTcF > 450 msec (male) or > 470 msec (female).
16. Body weight < 50 kg.

Drug, Alcohol, and Pharmacological Considerations

17. History of alcohol, opiate, or other drug abuse or dependence within 12 months prior to the Screening Visit.
18. Ongoing or recent (within 30 days prior to surgery) use of opioids.
19. History of opioid tolerance based on the patient report or investigator's judgment.
20. Alcohol consumption within 24 hours of surgery.
21. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) or non-opioid analgesics (including COX-2 inhibitors) within 24 hours of surgery.
22. Use of herbal medicine or dietary supplements (e.g., chaparral, comfrey, germander, jin bu huan, kava, pennyroyal, skullcap, St. John's wort, or valerian) within 7 days prior to surgery
23. Use of drugs that are known to increase the PR and QRS interval (Appendix 16.1) within 24 hours prior to surgery.
24. Use of weak/moderate/strong CYP3A inhibitors and inducers or the drugs that are known clinical substrates of renal transporters OCT2 and MATE1/2K (Appendix 16.1) within 24 hours prior to surgery.

Anesthetic and Other Exclusion Considerations

25. Use of any CNS drugs or local anesthetic wound infiltration.
26. Use of parenteral ketamine (any doses of), gabapentin, pregabalin, or lidocaine (> 1 mg/kg) intra- or peri-operatively, or within 24 hours of surgery.
27. Subjects with hypersensitivity to opioids.
28. Subjects who received another investigational drug within 30 days of the scheduled surgery..

Study Procedures:

Screening

Subjects will give informed consent and complete Screening Visit assessments to determine eligibility for the study.

Anesthesia

Laparoscopic colectomy will be performed under general anesthesia induced with propofol 2 mg/kg, rocuronium 0.6 mg/kg, and remifentanil 0.05-0.1 μg/kg, while blood pressure, ECG, saturation levels (SpO2) will be monitored. Using a 50% oxygen-containing anesthetic ventilator, the following conditions will be maintained: The respiratory rate of 10-15 times per minute, the tidal volume of 8 mL/kg, the positive end-expiratory pressure of 5 cm H2O, the end-tidal CO2 (ETCO2) of 35-42 mmHg, and an I (inhalation): E (exhalation) ratio of 1:2. After the induction of anesthesia, an inhalational

anesthetic agent at a minimum alveolar concentration (MAC) of 0.6-1.0 will be used depending on age, and remifentanil of 0.03-0.1 μg/kg/min will be infused continuously to maintain anesthesia condition. In case of suturing the incision area, 30 μg of IV fentanyl and antiemetics will be provided. The mode/setting of ventilation and the types, or amounts of anesthetics/anti-emetics will be determined according to the condition of patients and clinical sites.

Randomization

Subjects who report the NRS score of ≥ 5 after emergence from anesthesia will be randomized in an 1:1 ratio. Subjects with the initial NRS of < 5 will be eligible for randomization if they report the NRS score of ≥ 5 when reassessed within 30 minutes after emergence from anesthesia.

Study Drug Administration

The VVZ-149 treatment group will receive a continuous IV infusion of VVZ-149 Injections as loading dose of 160 mg for 30 minutes followed by maintenance dose of 840 mg for 9.5 hours via an IV infusion pump. 100 mL of VVZ-149 (1,000 mg) will be mixed into 400-mL saline in a total 500-mL infusion bag. The placebo group will be administered with a placebo as in the VVZ-149 treatment group for 10 hours. The start of study drug infusion will be designated as Time 0 hour. Subjects will receive a full clinical supportive care for at least 2 hours until vital signs become stable after emergence from anesthesia according to the standard operating procedures at the post anesthesia care unit (PACU). Subjects will be encouraged to wait for at least 30 minutes after the start of the study drug infusion until they requests opiod analgesics by PCA or rescue medication. If the subject reports severe postoperative pain or requests additional pain medication, allowed rescue medications or administration of PCA will be provided.

PCA Opioid

After the emergence from anesthesia, subjects will report their pain intensity and will be provided with a PCA pump (Accumate 1200; WooYoung Medical, Seoul, Korea, etc.). After the start of the study drug infusion, subjects are allowed to self-administer PCA (fentanyl 5 μg IV bolus, 10-minute lock-out). For PCA administration, 2,000 μg of fentanyl and 0.3 mg of ramosetron (Nasea®, Astellas Pharma Korea, Seoul, Korea) mixed into 400-mL saline will be used (fentanyl 5 μg/mL).

Rescue medication

Allowed rescue medications will be provided if subjects report a pain intensity score of ≥ 5 on the NRS and require additional analgesia in addition to PCA. For the first 2 hours after the start of the study drug infusion, subjects will be allowed to receive IV fentanyl up to 2 doses in 1 hour with the first dose of 30 μg and the second dose of 20 μg at a 10-minute lockout interval. If subjects request additional rescue medications exceeding allowed fentanyl administrations for 1 hour, IV Oxycodone (Oxynorm, 2 mg, 2-hour lock-out) or Morphine (Morphine Sulfate Injection, 2 mg, 2-hour lock-out) will be given. After 2 hours from the start of the study drug infusion, IV pethidine (25 mg, 4-hour lock-out) in addition to PCA will be administered upon request in the ward. If subjects experience inadequate pain relief despite the use of PCA opioids and protocol-specified rescue medications, they will be provided appropriate pain medications at the investigator's discretion.

Pain Intensity Assessment

Pain intensity will be assessed using the NRS (0-10) at scheduled time points for 48 hours from the start of the study drug infusion. When a subject requests rescue medications, the corresponding pain

intensity score at the time of request will be recorded using the NRS, and the rescue medication will be administered.

Dropouts

Subjects are free to discontinue from the study at any time, without prejudice to future treatment. Reasons for withdrawal or discontinuation from the study may include the following and must be documented in the eCRF: a lack of efficacy, safety criteria (e.g., adverse events, unexpected drug reaction), pregnancy, protocol deviations, and sponsor/investigator decision. Once a subject is discontinued from the study, no data will be collected except for the safety data.

Safety Follow-Up

After discharge, subjects will be contacted for a follow-up phone interview. Subjects may visit the site at any time during the study for the postoperative care depending on the judgment of the investigator or the condition of a subject, but this follow-up visit is not included as part of this study. A total duration of the study is approximately 21 to 30 days including a safety follow-up.

Efficacy Endpoints:

The primary efficacy endpoint

Time-weighted Sum of Pain Intensity Difference (SPID) from baseline over 12 hours after the start of the study drug infusion (i.e., post-dose).

The secondary efficacy endpoints

- Total number of PCA requests for 12 hours post-dose
- Total amount of PCA and rescue medication consumption for 12 hours post-dose
- Proportion of subjects with ≥ 40% decrease in pain area at 6 hours post-dose compared to the maximum pain area with the pre-dose pain intensity
- Time-weighted SPID for 24 hours post-dose (SPID 24)

Exploratory endpoints

- Time-weighted SPID for 6 hours post-dose (SPID 6)
- Total number of PCA requests for 24 and 48 hours post-dose
- Total amount of PCA and rescue medication consumption for 24 and 48 hours post-dose
- Population of subjects with ≥40%, ≥60%, and ≥80% decrease in pain area at 12, 24, and 48 hours post-dose compared to the maximum pain area with the pre-dose pain intensity
- Proportion of subjects who have not requested any rescue medication between 0-2, 2-6, 6-12, 12-24, and 24-48 hours post-dose
- Time to the first and the second rescue medication requested by subject
- Pharmacokinetic (PK) profile of VVZ-149 Injections

Safety Endpoints:

Postoperative nausea and vomiting, 12-lead electrocardiograms (ECGs), vital signs, clinical laboratory evaluation (blood chemistry, hematology, blood coagulation, and thyroid testing), oxygen saturation, physical examination, and adverse events reported during the study.

Statistical Analysis:

The primary objective is to evaluate a pivotal assessment of the analgesic effects of VVZ-149 Injections in subjects with moderate to severe postoperative pain following laparoscopic colectomy. The secondary objectives include the extended analgesic efficacy, safety and PK of VVZ-149 Injections.

General Statistical Considerations

Statistical analyses will be performed using SAS® Enterprise Guide (version 9.4) 64 bit (SAS Institute Inc., Cary, NC, USA) or higher.

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, median, standard deviation (STD), minimum and maximum. The mean and median will be reported to an additional level of precision than the original observation in its rawest form (i.e., electronic case report form, eCRF), and the STD and other measures of variability (e.g., standard error) will be reported to two additional levels of precision than the original observations. The minimum and maximum will be the same precision as the original data.

Categorical variables will be summarized using counts of subjects (n) and percentages (%) and will be presented in the form "n (xx.x)". Percentages will be rounded to one decimal place. If counts of subjects is zero (0), then percentage will not be displayed. To ensure completeness, summaries for categorical variables will include all categories, even if no subjects had a response in a particular category. Unless otherwise specified, the denominator for each percentage will be based on the number of subjects with available data in the population being summarized.

Unless otherwise specified, all statistical tests will be 2-sided using α=0.05. Estimates and confidence intervals will be reported to 1 more decimal than the original data. P-values will be reported to 4 decimal places. Pvalues less than 0.0001 will be displayed as "< 0.0001"; p-values greater than 0.9999 will be displayed "> 0.9999". Summary tables will be summarized by treatment and overall, as appropriate. All data, including those derived, will be presented in individual subject data listings.

Demographic Data Analysis

The Modified Intent-to-Treat (mITT) population will be used for the analysis of demographic variables. Age, height, body weight and body mass index (BMI) will be summarized using descriptive statistics. Age group, sex, race and American Society of Anesthesiologists (ASA) risk classification will be summarized with the number and percentage of subjects in each parameter category.

Subjects who have not initiated the study drug infusion, or who do not have a baseline pain intensity score nor any post-dose pain intensity score will be excluded from the mITT population.

Descriptive statistics will be performed in all subjects and by treatment group. Continuous variables will be summarized using descriptive statistics (sample size, mean, standard deviation, minimum, median, and maximum values). Categorical variables will be summarized using the number and percentage of subjects.

Safety Analyses

- The Safety Population who have initiated study drug infusion will be used for all safety analyses. The occurrence, the number of subjects, severity, and relatedness will be summarized for adverse events (AEs) and serious adverse events (SAEs) using descriptive statistics.
- Vital signs, 12-lead ECGs, and clinical laboratory evaluations per group will be summarized using descriptive statistics, and further statistical analyses will be performed regarding indices considered clinically significant as necessary.

Efficacy Analyses

- The Modified Intent-to-Treat (mITT) population will be used for the efficacy analyses.

Participants who have not initiated the study drug infusion, or who do not have a baseline pain intensity score nor any post-dose pain intensity score will be excluded from the mITT population.

- To assess the robustness of the efficacy analyses, additional sensitivity analyses will be performed for the Per-Protocol (PP) population who completed at least 6 hours of study drug infusion, who have safety and efficacy data at least until Time 6 hours, and do not have any significant protocol deviations and for the Full Analysis Set (FAS) population who meet major inclusion/exclusion criteria, who have initiated study drug infusion, and who have any efficacy data after randomization.
- The primary efficacy endpoint is the time-weighted Sum of Pain Intensity Difference (SPID) for the first 12 hours postdose. The SPID for 12 hours postdose (SPID 12) will be estimated using the lineartrapezoidal rule (L x Hour) with the PI scores assigned from Time 0 to Time 12 hours postdose. SPID 12 will be summarized using descriptive statistics by treatment group, and analyzed using an analysis of variance (ANOVA) model with treatment as a main effect. The treatment effect will be tested at a two-sided alpha=0.05 level of significance. The means, standard error (SE), two-sided 95% confidence interval, and two-sided p-value from the ANOVA model will be presented. If the normality assumption is not met using Shapiro-Wilk test, a ranked ANOVA will be used to analyze the primary efficacy endpoint. The rank of the SPID 12 ranked across both treatment arms will be analyzed using a ranked ANOVA model with treatment as the main effect.
- All secondary efficacy analyses will be carried out using two-sided tests at the alpha = 0.05 level of significance. The total number of PCA requests and the total amount of opioid consumption by PCA and/or rescue medication at pre-defined time intervals until 12 hours postdose will be summarized and analyzed using a repeated-measures ANOVA. The main effects of treatment and time and their interaction (treatment x time) will be evaluated. The proportion of subjects with ≥ 40% decrease in pain area at 6 hours post-dose compared to the maximum decrease in pain area with the pre-dose pain intensity will be summarized and analyzed by treatment group using Chi-square test (or Fisher's test if the expected cell counts with less than 5 is greater than 20%). The same method described for the primary efficacy endpoint (ANOVA) will be used to analyze the time-weighted SPID for 24 hours postdose (SPID 24).
- All exploratory efficacy analyses will be carried out using two-sided tests at the alpha = 0.05 level of significance. SPID 6 will be analyzed using an ANOVA model with treatment as the main effect. The total number of PCA requests and the total amount of opioid consumption by PCA and rescue medication for 24 (at a 6-h interval) and 48 hours (at a 12-h interval) post-dose will be analyzed using a separate repeated measures ANOVA with the main effects of treatment and time and their interaction (treatment x time).

  Proportion endpoints measured per time interval will be analyzed by treatment group using Chi-square test (or Fisher's test). Additional analysis will performed using a generalized linear model with repeated measures using a logit link.

  The time-to-event exploratory endpoints (time to first and second rescue medications requested by subject) will be analyzed based on the Kaplan-Meier (KM) estimate of median time (in minutes) with log-rank test and Cox proportional hazard model with treatment as a factor.

Schedule of Assessments

Period	Screen	Baseline		Treatment Dosing and Assessment															F/U[q]
Visit	1	2																	3
Study Day	-30to-1	1											2				2 to 3		21
Time Point		Pre op	Pre dose	0h[a]	0.5h	1h	2h	4h	6h	8h	10h	12h	18h	24h	30h	36h	42h	48h / ET	
Time Point Window					±5 m	±10 m		±15 m			-30 m	±15m	±1 h						+7 d
Informed consent	X																		
Inclusion exclusion criteria	X	X[b]	X[b]																
Demographics	X																		
HADS/PCS[r]		X																	
Weight and height	X																		
Medical/ medication history	X																		
Physical Examination[c]	X	X																X	
Pregnancy test[d]	X	X																	
Clinical laboratory evaluations[e,g]	X													X					
Vital signs[f,g]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[g]	X		X								X			X					
Pain intensity (NRS)[h,g]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK sampling[i,g]					X[j]	X					X[k]								
Randomization[l]			X[l]																
Study drug infusion[m]				X															
PCA Infusion[n]				X															
Rescue medication[o]				X															
Nausea/vomiting assessment				X															
Pulse oximetry[g]				X															
AE[p] and ConMeds		X																	X

ET = Early Termination

a. The start time of the study drug (VVZ-149 Injections or placebo) infusion will be designated as Time 0 hour.

b. Randomization will be performed only for the subjects who met all inclusion/exclusion criteria.

c. A full physical examination (General condition, nutritional status, Skin/Mucosa, eyes (except impaired vision), ear, nose, throat, thyroid, lungs, cardiovascular system, abdomen, kidney/urogenital system, neuropsychiatric system, spinal/limbs/tumor, peripheral circulation, endocrine system, others) will be performed. Any abnormal symptoms or signs will be recorded.

d. Pregnancy test will be performed for all female subjects at the screening visit and prior to surgery, except for those who are in menopause. The serum β-HCG and urine tests will be performed at screening and pre-op, respectively.

e. Clinical laboratory evaluations will be performed on empty stomach (fasting for 8 hours) at screening, including blood chemistry, hematology, blood coagulation, and thyroid testing. If the same clinical laboratory evaluation is performed within 30 days of screening, the test result can be used alternatively. A serology test will be performed only at screening, and the results performed within 60 days of screening can be used.

* It is allowed to confirm results of partial laboratory tests performed at screening (e.g., thyroid, serum, and blood chemistry) before randomization, depending on study site circumstances.

f. Vital signs (pulse rate, respiration rate, blood pressure, and temperature measured from tympanum) will be collected after the subject had been in the supine or semi-fowler position for at least 5 minutes.

g. When scheduled for the same time point, assessments will be recommended to be performed in the following order: NRS – Vital signs – Oxygen saturation via pulse oximetry – 12-lead ECG – PK sampling – Blood sampling for clinical laboratory evaluations. The order of study assessments is allowed to make changes depending on study site circumstances.
* It is allowed to use 12-lead electrocardiogram results within 30 days in the absence of medical history.
* It is allowed to perform the electrocardiogram and oxygen saturation at Time 10 hours within ± 2 hours of the scheduled time point.

h. Pain intensity (NRS, 0-10) will be assessed for 48 hours postdose. Additional pain intensity will be assessed immediately before administration of any rescue medication, and both the NRS and corresponding time will be recorded.

i. Pharmacokinetic (PK) samples will be collected from the opposite arm to the study drug infusion. If the blood sampling is not available from the opposite arm, the venipuncture is performed from other body parts except for the infusion arm.

j. A PK sample at Time 0.5 h will be collected before the completion of the loading dose infusion (-5 minutes).

k. A PK sample at Time 10 h will be collected before the completion of the maintenance dose infusion (-15 minutes). If the total duration of the study drug infusion is less or more than 10 hours, PK sampling at Time 10 h will be performed within 15 minutes before the completion of the infusion. Additional PK samples will be collected 30 minutes after termination of the study drug infusion (±5 minutes).

l. Subjects with pain intensity scores of ≥5 on the NRS upon emergence from anesthesia will be randomly assigned to either the VVZ-149 or placebo group (1:1 ratio). Subjects with the initial NRS of <5 will be eligible for randomization once they report the NRS score of ≥5 within 30 minutes after emergence from anesthesia.

m. Randomized subject will be assigned with a study drug number and and the corresponding study drug will be administered. A continuous IV infusion of VVZ-149 (1,000 mg) or a placebo over 10 hours will be administered as a loading dose of 160 mg for 30 minutes followed by a maintenance dose of 840 mg for 9.5 hours.

n. Subjects will be provided with a PCA pump for fentanyl IV infusion upon emergence from anesthesia. Once the study drug infusion has been initiated, subjects may self-administer fentanyl (5 μg IV bolus, 10-min lock-out) by pushing a button of the PCA pump for pain control.

o. If subjects request additional rescue medications in addition to the PCA opioid, the pain intensity and corresponding time will be recorded. Upon confirming the criteria for rescue medication administration, subjects will be provided with rescue opioid within 15 minutes of the pain intensity assessment using the NRS.

p. Adverse events identified before the study drug infusion will be documented as medical history.

q. Safety follow-up will be conducted over the phone. If clinically significant adverse events are reported at the safety follow-up, subjects will be allowed to return to the site for the postoperative standard of care follow-up as necessary and will receive clinical laboratory evaluations, physical examination, and/or vital signs examination.

r. The HADS and PCS questionnaires can be performed on the day before surgery (Day-1) depending on study site.