# Clinical Study Protocol

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| **Protocol Title:** | A Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of SI-722 Intravesical Instillation in Interstitial Cystitis/Bladder Pain Syndrome Subjects |
| **Protocol Number:** | 722/1121 |
| **Study Phase:** | Phase 1/2 |
| **Investigational Product:** | SI-722 |
| **IND Number:** | 138170 |
| **Sponsor:** | Seikagaku Corporation<br>6-1, Marunouchi 1-chome<br>Chiyoda-ku, Tokyo 100-0005, Japan |
| **Date of Protocol:** | July 17, 2020 |
| **Version Number:** | 4.0 |

# LIST OF STUDY PERSONNEL

## Sponsor

| | |
|---|---|
| **Sponsor** | [redacted] |
| **Sponsor's Representative** | [redacted] |
| **Sponsor's Clinical Leader** | [redacted] |
| **Statistician** | [redacted] |
| **DM Manager** | [redacted] |
| **Medical Director** | [redacted] |

## Contract Research Organization

| | |
|---|---|
| **Contract Research Organization (Monitoring)** | [redacted] |
| **Contract Research Organization (DM, STAT)** | [redacted] |

# SIGNATURE PAGE

**Declaration of Sponsor**

**Title: A Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of SI-722 Intravesical Instillation in Interstitial Cystitis/Bladder Pain Syndrome Subjects**

*The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements.*

[redacted]

[redacted]

Date

**Declaration of the Investigator**

**Title: A Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of SI-722 Intravesical Instillation in Interstitial Cystitis/Bladder Pain Syndrome Subjects**

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, electronic Case Report Form, and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB, except where necessary to eliminate an immediate hazard to the subjects.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

**Responsible Investigator of the study site**

| | |
|---|---|
| Signature | Date |
| Name (block letters) | |
| Title (block letters) | |
| Institution (block letters) | |
| Phone number | |

# SYNOPSIS

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| **Protocol Title:** | A Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of SI-722 Intravesical Instillation in Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) Subjects |
| **Protocol Number:** | 722/1121 |
| **Investigational Product:** | SI-722 |
| **Study Phase:** | Phase 1/2 |
| **Objectives:** | Primary Objectives:<br>• To provide the Pharmacokinetics (PK) profiles of single intravesical instillations of SI-722 in IC/BPS subjects<br>• To assess the safety and tolerability of single intravesical instillations of SI-722 in IC/BPS subjects<br>Secondary Objective:<br>• To assess the preliminary efficacy of single intravesical instillations of SI-722 in IC/BPS subjects |
| **Planned Study Period:** | November 2019 through March 2021 |
| **Overall Study Design** | |
| **Study Design:** | This is a Phase 1/2, randomized, double-blind, placebo-controlled, single ascending dose study in IC/BPS subjects. |
| **Dosage/Dose Regimen:** | Eligible subjects will be assigned to one of four treatment cohorts of SI-722 or placebo in a 6:2 ratio:<br>• Cohort 1 = [redacted] of SI-722 or placebo [redacted]<br>• Cohort 2 = [redacted] of SI-722 or placebo [redacted]<br>• Cohort 3 = [redacted] of SI-722 or placebo [redacted]<br>• Cohort 4 = [redacted] of SI-722 or placebo [redacted] |
| **Duration of Treatment:** | Screening visit (assessment in site): Day -28 to Day -7<br>Screening period (assessment by subject daily diary): Day -7 to Day -1 |

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| | Investigational drug administration: Day 1<br>Follow-up and evaluation phase: Day 1 (post-dose) to Day 29 |
| **Planned Number of Subjects:** | A total 32 subjects (SI-722 group: 24 subjects, placebo group: 8 subjects) |
| **Study Population** | |
| **Inclusion Criteria:** | Subjects must meet all of the following criteria to be eligible for inclusion in the study:<br>1. Provide written informed consent form (ICF) which includes agreement for compliance with the requirements and restrictions listed in the ICF and in this protocol and the willingness and ability to comply with all aspects of the study requirements<br>2. Males or females, ≥18 and ≤80 years of age<br>3. Have symptoms of pelvic pain, pressure and/or discomfort perceived to be related to the urinary bladder, associated with lower urinary tract symptoms for greater than 6 months duration prior to the start date of Screening and continue to experience symptoms during the Screening period<br>4. A score of 19 or greater on the Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) at Screening visit<br>5. Must be capable of voiding without need for catheterization |

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| | 6. Ability and willingness to abstain from methylxanthine-containing products (eg, coffee, tea, cola drinks, chocolate and energy drinks) and alcohol from 24 hours prior to each visit and red wine, oranges, grapefruit (juice) from 7 days prior to Day 1 and 24 hours prior to each visit until after collection of the PK sample in each treatment period |
| **Exclusion Criteria:** | The presence of the following criteria excludes a subject from study enrollment:<br>1. Has a known allergy or contraindication to [redacted], chondroitin sulfate or acetaminophen<br>2. Urinary tract infection ≤30 days prior to date of first Screening visit and during the Screening period, or who have recurrent infections documented by positive urine culture (ie, >10,000 colony-forming units growth, <2 separate isolates recovered on culture) of >3 per 12 months in the last year<br>3. History of the following medical conditions or diseases:<br>• Chemical cystitis, urinary tuberculosis, or radiation cystitis<br>• Bladder cancer<br>• Female subjects: uterine, cervical, vaginal, urethral cancer or urethral diverticulum<br>• Male subjects: prostate cancer<br>4. Female subjects: Have gynecologic conditions that could reflect an etiology of their bladder pain at Screening visit<br>5. Male subjects: Have history of prostate surgery (transurethral resection of the prostate, transurethral incision of the prostate, transurethral needle ablation etc.) ≤6 months prior to date of first Screening visit and during the Screening period, or currently being treated for chronic bacterial prostatitis |

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| | 6. Have urinary incontinence due to urinary urgency ≤30 days prior to date of first Screening visit and during the Screening period<br>7. Has taken intramuscular injection and intraarticular injection of [redacted] ≤120 days prior to date of first Screening visit and during the Screening period, and any other route of [redacted] ≤30 days prior to date of first Screening visit and during the Screening period<br>8. Treatment with intravesical therapy ≤60 days prior to date of first Screening visit and during the Screening period<br>9. Treatment with any opioid therapy ≤7 days prior to date of first Screening visit and during the Screening period, and positive urine drug test at Screening visit<br>10. Has taken any of the following prohibited medications ≤1 day prior to date of first Screening visit and during the Screening period. Unless noted, these medications are prohibited in oral, injectable, and suppository forms, but they can be used in inhaled, nasal, or ophthalmic formulations, topical administration except for intravesical therapy<br>• Nonsteroidal anti-inflammatory drugs<br>• Any nonopioid analgesics<br>• Steroids (except for [redacted] and topical treatment)<br>• Any over the counter medications containing analgesic ingredients<br>11. Has taken any medications used for symptomatic relief of IC/BPS ≤1 day prior to date of first Screening visit and during the Screening period<br>12. Has taken any Cytochrome P450 3A4 (CYP3A4) inducers and inhibitors (eg. protease inhibitors, macrolides and barbiturates) ≤1 day prior to date of first Screening visit and during the Screening period<br>13. History of procedure(s) that has significantly affected bladder function, such as augmentation cystoplasty, cystectomy, cytolysis, or bladder catheterization |

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| | 14. InterStim placed, or botulinum toxin received ≤6 months prior to date of first Screening visit and during the Screening period or change in previously placed InterStim settings ≤3 months prior to date of first Screening visit and during the Screening period<br>15. History of bladder hydrodistension ≤3 months prior to date of first Screening visit and during the Screening period<br>16. Has the following exclusionary laboratory test results at Screening visit:<br>• Aspartate aminotransferase (AST) >1.5 times the upper limit of normal (ULN)<br>• Alanine aminotransferase (ALT) >2.5 times ULN<br>• Creatinine >1.5 times the ULN<br>• Positive human immunodeficiency virus (HIV) antibodies, hepatitis C (HCV) antibodies, or hepatitis B surface antigen (HBsAg)<br>• Positive tuberculosis (TB) blood test<br>17. Body mass index (BMI) ≥40 kg/$m^2$<br>18. Sexually active male or female subjects of childbearing potential who are not willing to use adequate contraceptive measures to avoid pregnancy. Adequate methods of birth control include hormonal contraception (female subjects), use of at least 1 acceptable double barrier method, vasectomy, intrauterine device, and/or exclusive sexual partner for whom 1 of the above acceptable methods applies. Acceptable double barrier methods include condoms (male or female) plus a spermicidal agent<br>19. Has cancer or a past history of any cancer ≤5 years prior to date of first Screening visit and during the Screening period<br>20. History of the following medical conditions or diseases:<br>• Chronic substance abuse (including alcohol), dependency or abuse of opiates, or other marijuana or other illicit drugs within the last 5 years prior to date of first Screening visit and during the Screening period |

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| | • Recurrent, severe allergic or immune-mediated reactions, or other autoimmune disorders<br>• Any clinically significant psychiatric disorder<br>21. Subjects who have been diagnosed with a sexually transmitted infection by the examination at the Screening visit; subject can be rescreened after documented test of cure<br>22. Subjects with diagnosed or suspected significant medical illness including (but not limited to) pulmonary, cardiovascular, cerebrovascular, renal, hepatic or hematological disease<br>23. Subjects who have difficulty receiving administration of investigational product (IP), or subjects with a tendency to bleed or with bleeding disorders such as (but not limited to) hemophilia, aplastic anemia, cirrhosis of the liver, leukemia, thrombocytopenia, and vitamin K deficiency. Subjects using medication for the purpose of anticoagulation, including heparin and warfarin, which cannot be reversed preoperatively will also be excluded<br>24. Is receiving worker's compensation or is currently involved in medical litigation<br>25. Have participated in a clinical study of an investigational drug, device, or biologics ≤90 days prior to date of informed consent<br>26. Any condition that, in the opinion of the Investigator, might interfere with the evaluation of the study objectives |
| **Criteria for Evaluation** | |
| **Pharmacokinetics Assessments:** | • Plasma [redacted] and SI-722 concentrations<br>• Plasma [redacted] and SI-722 PK parameters ($AUC_{0-t}$, $AUC_{0-last}$, $AUC_{0-\infty}$, $C_{max}$, $T_{max}$, $t_{1/2}$, $V_z/F$, CL/F)<br>• Urine [redacted] and SI-722 concentrations<br>• Urine [redacted] and SI-722 PK parameters (Ae) |
| **Safety Assessments:** | • Adverse events (AEs)<br>• Cystoscopy<br>• Vital signs<br>• Electrocardiograms (ECGs) |

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| | • Clinical laboratory assessments |
| **Efficacy Assessments:** | • Subject Daily diary<br>o Bladder pain (maximum and average bladder pain, bladder pain at that time)<br>o Symptoms of IC/BPS (pain, burning, discomfort, and pressure)<br>o Voiding frequency<br>▪ Diurnal (from the time of getting up to the time of going to bed)<br>▪ Nocturnal (overnight)<br>o Frequency of bladder pain (frequency of bladder pain when subjects urinate and frequency of voiding caused by bladder pain)<br>o Voiding volume<br>o Acetaminophen consumption (amount of acetaminophen, date and time of taking medicine and bladder pain at that time)<br>• Patient reported outcome (PRO) at the study site<br>o Interstitial Cystitis Symptom Index Score/Problem Index (ICSI/PI) score<br>o BPIC-SS<br>o Global Response Assessment (GRA)<br>• Voiding volume (during confinement)<br>• Inflammatory markers: Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) |
| **Statistical Methods:** | **Analysis populations**:<br>• The intention-to-treat (ITT) population includes all randomized subjects regardless of whether the subject received any IP or had any efficacy assessment collected.<br>• The Per-protocol (PP) population includes all ITT subjects without major protocol deviation.<br>• The safety population includes all randomized subjects who received IP. If a subject receives IP other than the subject's randomized treatment |

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| | assignment, then the subject is assigned to the treatment arm reflecting the treatment that the subject actually received during the study.<br>• The PK population includes all subjects who received SI-722 and who provided at least 1 evaluable PK sample.<br><br>**PK analysis**:<br>Plasma and urine concentrations of SI-722 and [redacted] will be determined for the safety population. The other PK analyses will be conducted based on the PK population. Pharmacokinetic profiles will be assessed by plasma SI-722 and [redacted] concentrations, urine SI-722 and [redacted] concentrations, and the corresponding PK parameters. Additional PK parameters will be estimated and analyzed for SI-722 and [redacted] if needed. PK data for SI-722 and [redacted] will be summarized using descriptive statistics based on the PK population.<br><br>**Safety analyses**:<br>All safety analyses will be conducted based on the safety population.<br>AEs will be analyzed in terms of treatment-emergent AE (TEAE) defined to be any event that begins or worsens in grade after the start of IP throughout of the study. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number of events and number (percentage) of subjects reporting TEAEs for each preferred term will be tabulated by system-organ class, by system-organ class and severity, and by system organ class and relationship to IP.<br>Safety endpoints of laboratory values, vital signs, ECGs and cystoscopy will be summarized by treatment group.<br><br>**Efficacy analyses**:<br>All efficacy analyses will be conducted based on the |

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| | ITT population. Each efficacy assessment will be summarized for all subjects by treatment group at each assessment visit. The assessments collected on daily diary will be calculated by average at each assessment visit. Efficacy assessments from the daily diary such as bladder pain and symptoms of IC/BPS will be summarized by study day in addition to the summary at each assessment visit. |

## Table 1 Time and Events Schedule

| Phase | Screenig | | Double-Blind Treatment Period | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | - | 2 | | | | | | | | | | 3 | 4 | 5 | 6 | 7 |
| Week | -4 to -1 | - | 0 | | | | | | | | | | | | 1 | 2 | 4 / Early Withdrawal |
| Day | -28 to -7 | -7 to 1 | 1 | | | | | | | | | 2 | 3 | 5 | 8 | 15 | 29 |
| Hour | | | Pre-dose | 0 | 0.25 | 0.5 | 1 | 2 | 4 | 6 | 8 | 12 | 24 | 48 | 96 | 168 | 336 | 672 |
| Window | | | | | +/- 3 min | +/- 3 min | +/- 5 min | +/- 5 min | +/- 5 min | +/- 5 min | +/- 5 min | +/- 5 min | +/- 5 min | +/- 6 h | +/- 1 D | +/- 1 D | +/- 3 D | +/- 3 D |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Outpatient visit | X | | | | | | | | | | | | X | X | X | X | X |
| Inpatient confinement | | | Day 1 through Day 2 | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | |
| IC/BPS history | X | | | | | | | | | | | | | | | | |
| Review of inclusion/exclusion criteria | X | | X | | | | | | | | | | | | | | |
| Physical examination | X | | X | | | | | | | | | X | X | X | X | X | X |
| Gynecologic examination | X | | | | | | | | | | | | | | | | |
| Height, Body weight, Demographics | X | | | | | | | | | | | | | | | | |
| Serology | X | | | | | | | | | | | | | | | | |
| TB blood test | X | | | | | | | | | | | | | | | | |
| NAAT | X | | | | | | | | | | | | | | | | |
| Urine drug screen | X | | | | | | | | | | | | | | | | |
| Hematology | X | | X | | | | | | | | | X | X | X | X | X | X |
| Coagulation | X | | X | | | | | | | | | X | X | X | X | X | X |
| Clinical chemistry | X | | X | | | | | | | | | X | X | X | X | X | X |
| Urinalysis | X | | X | | | | | | | | | X | X | X | X | X | X |
| Urine culture | X | | | | | | | | | | | | | | | | X |
| Serum pregnancy test | X | | | | | | | | | | | | | | | | |
| Urine pregnancy test | | | X | | | | | | | | | | | | | | X |
| Vital signs | X | | X | | | | X | | | | | X | X | X | X | X | X |
| 12-lead ECG | | | X | | | | X | | | | | X | | | | | |
| Cystoscopy | | | X | | | | | | | | | | | | X | | X |
| Distribute subject daily diary | X | | X | | | | | | | | | X | X | X | X | X | |
| Distribute acetaminophen | X | | X | | | | | | | | | X | X | X | X | X | |

| Phase | Screenig | | Double-Blind Treatment Period | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | - | 2 | | | | | | | | | | 3 | 4 | 5 | 6 | 7 |
| Week | -4 to -1 | - | 0 | | | | | | | | | | | | 1 | 2 | 4 / Early Withdrawal |
| Day | -28 to -7 | -7 to 1 | 1 | | | | | | | | | 2 | 3 | 5 | 8 | 15 | 29 |
| Hour | | | Pre-dose | 0 | 0.25 | 0.5 | 1 | 2 | 4 | 6 | 8 | 12 | 24 | 48 | 96 | 168 | 336 | 672 |
| Window | | | | | +/- 3 min | +/- 3 min | +/- 5 min | +/- 5 min | +/- 5 min | +/- 5 min | +/- 5 min | +/- 5 min | +/- 5 min | +/- 6 h | +/- 1 D | +/- 1 D | +/- 3 D | +/- 3 D |
| Randomization | | | X | | | | | | | | | | | | | | |
| IP administration | | | | X | | | | | | | | | | | | | |
| PK blood sample collection | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PK urine sample collection[a] | | | X | Continuous | | | | | | | | | X | X | X | X | X | X |
| Voiding volume record[b] | | X | Continuous | | | | | | | | | | | | X | X | X | X |
| Voiding time record[c] | | | | | | X | | | | | | | | | | | | |
| BPIC-SS | X | | X | | | | | | | | | | | | X | X | X | X |
| ICSI/PI | | | X | | | | | | | | | | | | | | | X |
| GRA | | | | | | | | | | | | | | | X | X | X | X |
| BS-POP | X | | | | | | | | | | | | | | | | | |
| Subject Daily Diary[d] | | Continuous | | | | | | | | | | | | | | | | |
| Adverse events | Continuous | | | | | | | | | | | | | | | | | |
| Concomitant medications | Continuous | | | | | | | | | | | | | | | | | |

[a] Urine void sample on Day 1 (pre-dose) will be collected at least once. Urine void samples within 30 minutes after study treatment instillation will be included. After each urine sample collection, voiding volume will be recorded.

[b] Voiding volume will be recorded in source documents by site staff during confinement. Except for that period, voiding volume will be recorded in subject daily diary by subjects. Volume will be measured at least 5 times within 7 days before Day 1, within 3 days before or after Day 8, Day 15, and within 5 days before Day 29 or early withdrawal.

[c] Thirty minutes after bladder instillation, the time of first voiding will be recorded.

[d] Subjects will be required to evaluate bladder pain using 11-points NRS pain scale and other assessments of diary in consecutive during 7 days prior to the Day 1. At least 5 days of bladder pain must be evaluated during 7 days.

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## LIST OF APPENDICES

# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| AUA | American Urological Association |
| BLQ | below the limit of quantification |
| BMI | body mass index |
| BPIC-SS | Bladder Pain/Interstitial Cystitis Symptom Score |
| BPS | Bladder Pain Syndrome |
| BS-POP | Brief Scale for Psychiatric Problem in Orthopaedic Patients |
| CFR | Code of Federal Regulations |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract reasearch organization |
| CRP | c-reactive protein |
| CS | chondroitin sulfate |
| CYP | cytochrome P450 |
| DMSO | dimethyl sulfoxide |
| ECG | electrocardiogram |
| ESR | erythrocyte sedimentation rate |
| FDA | the Food and Drug Administration |
| GCP | Good Clinical Practice |
| GRA | Global Response Assessment |
| HBsAg | Hepatitis B surface antigen |
| hCG | Human chorionic gonadotropin |
| HCV | Hepatitis C virus |
| HIV | human immunodeficiency virus |
| IB | investigator’s brochure |
| IC | interstitial cystitis |
| ICSI/PI | Interstitial Cystitis Symptom Index/Problem Index |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IP | investigational product |
| IRB | Institutional Review Board |
| ITT | intention-to-treat |

| Abbreviation | Definition |
|---|---|
| LC-MS/MS | liquid chromatography/tandem mass spectrometry |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NAAT | nucleic acid amplification testing |
| NRS | numerical rating scale |
| PK | pharmacokinetics |
| PP | per-protocol |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SRC | Safety Review Committee |
| [redacted] | [redacted] |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| [redacted] | [redacted] |
| ULN | upper limit of normal |
| VAS | visual analog scale |
| WOCBP | woman of childbearing potential |

# 1 INTRODUCTION

## 1.1 Background

Interstitial cystitis (IC)/bladder pain syndrome (BPS) is a chronic condition of unclear etiology involving bladder pain and usually urinary urgency, frequency, and nocturia. It is often misdiagnosed as a urinary tract infection or bacterial cystitis, but evidence of infections have not been found in patients with IC/BPS and antibiotics are generally ineffective.[1] IC/BPS is defined as "an unpleasant sensation (pain, pressure, and discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes." by the American Urological Association (AUA).[2]

[redacted]

Patients with IC/BPS have likely been treated with a variety of off-label therapies, but the standard treatment against which all therapies are measured is intravesical lavage. Dimethyl sulfoxide (DMSO) was approved in 1978 for the treatment of IC and is the only approved intravesical medication for this disorder by the Food and Drug Administration (FDA). Pentosan polysulfate sodium (brand name Elmiron®) was approved by the US FDA for the "relief of bladder pain or discomfort associated with IC" in 1996.[4] These are the only 2 drugs that have been approved by the FDA for this indication. In the worst cases, patients with IC/BPS may need to have their bladder removed. Therefore, more effective therapies are needed.[4]

Seikagaku Corporation (SKK) has developed the investigational product (IP) SI-722 for the treatment of IC/BPS. [redacted]

The first-in-human study of SI-722 performed in healthy United States subjects and healthy Japanese subjects has been completed. The study showed that single intravesical instillation of SI-722 were safe and well tolerated.

Based on the Phase 1 study results, SKK plans to conduct Phase 1/2, randomized, double-blind, placebo-controlled, single ascending dose study (722/1121) to evaluate the pharmacokinetics (PK), safety, tolerability and exploratory efficacy of SI-722 when administered by intravesical instillation to patients with IC/BPS.

## 1.2 Nonclinical and Clinical Studies

A summary of nonclinical studies and prior clinical studies of SI-722 can be found in the current edition of the investigator's brochure (IB).

## 1.3 Summary of Possible Risk and Benefits to Subjects

### 1.3.1 Possible Risks

Safety data obtained from nonclinical and clinical studies indicated that there were no major safety concerns and SI-722 has an acceptable safety profile.

Based on the results of Phase1 study, dysuria, hematuria, and urethral irritation were identified as potential risks. No severe or serious events related to the urinary system were reported, but as a precaution, any changes of urinary function will be carefully monitored in the phase 1/2 clinical study.

### 1.3.2 Possible Benefits

This is the first clinical study to evaluate efficacy in subjects with IC/BPS. Based on the results of the cystitis model in rats, SI-722 at doses [redacted] is expected to improve urinary frequency and ameliorate symptoms of bladder pain in IC/BPS subjects. When [redacted] the SI-722 is instilled into the bladder, urinary frequency and bladder pain may be improved.

# 2 OBJECTIVES

Primary Objectives:

- To provide the PK profiles of single intravesical instillations of SI-722 in IC/BPS subjects
- To assess the safety and tolerability of single intravesical instillations of SI-722 in IC/BPS subjects

Secondary Objective:

- To assess the preliminary efficacy of single intravesical instillations of SI-722 in IC/BPS subjects

# 3 STUDY DESIGN AND PLAN

## 3.1 Study Design

This is a Phase 1/2, randomized, double-blind, placebo-controlled, single ascending dose study in IC/BPS subjects.

## 3.2 Dosage/Dose Regimen

Eligible subjects will be assigned to one of four treatment cohorts of SI-722 or placebo in a 6:2 ratio:

- Cohort 1 = [redacted] of SI-722 or placebo ([redacted])
- Cohort 2 = [redacted] of SI-722 or placebo ([redacted])
- Cohort 3 = [redacted] of SI-722 or placebo ([redacted])
- Cohort 4 = [redacted] of SI-722 or placebo ([redacted])

## 3.3 Duration of Study

Screening visit (assessment in site): Day -28 to Day -7

Screening period (assessment by subject daily diary): Day -7 to Day -1

Investigational drug administration: Day 1

Follow-up and evaluation phase: Day 1 (Post-dose) to Day 29

## 3.4 Planned Number of Subjects

A total 32 subjects (SI-722 group: 24 subjects, placebo group: 8 subjects)

[redacted]

## 3.5 Randomization

Randomization will be utilized to minimize bias in study evaluations. On Day 1, subjects will be randomized to SI-722 or placebo in a 6:2 ratio within four treatment cohorts. Cohorts will be filled sequentially as subjects are determined to be eligible during Screening. An unblinded Safety Review Committee (SRC) will evaluate the safety and tolerability of SI-722 1 week after administration for each cohort before advancing to the next higher dose.

# 4 STUDY POPULATION

## 4.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for inclusion in the study:

1. Provide written informed consent form (ICF) which includes agreement for compliance with the requirements and restrictions listed in the ICF and in this protocol and the willingness and ability to comply with all aspects of the study requirements
2. Males or females, ≥18 and ≤80 years of age
3. Have symptoms of pelvic pain, pressure and/or discomfort perceived to be related to the urinary bladder, associated with lower urinary tract symptoms for greater than 6 months duration prior to the start date of Screening and continue to experience symptoms during the Screening period
4. A score of 19 or greater on the Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) at Screening visit
5. Must be capable of voiding without need for catheterization
6. Ability and willingness to abstain from methylxanthine-containing products (eg, coffee, tea, cola drinks, chocolate and energy drinks) and alcohol from 24 hours prior to each visit and red wine, oranges and grapefruit (juice) from 7 days prior to Day 1 and 24 hours prior to each visit until after collection of the PK sample in each treatment period

## 4.2 Exclusion Criteria

The presence of the following criteria excludes a subject from study enrollment:

1. Has a known allergy or contraindication to [redacted] CS or acetaminophen
2. Urinary tract infection ≤30 days prior to date of first Screening visit and during the Screening period, or who have recurrent infections documented by positive urine culture (ie, >10,000 colony-forming units growth, <2 separate isolates recovered on culture) of >3 per 12 months in the last year
3. History of the following medical conditions or diseases:
   - Chemical cystitis, urinary tuberculosis, or radiation cystitis
   - Bladder cancer
   - Female subjects: uterine, cervical, vaginal, urethral cancer or urethral diverticulum
   - Male subjects: prostate cancer
4. Female subjects: Have gynecologic conditions that could reflect an etiology of their bladder pain at Screening visit
5. Male subjects: Have history of prostate surgery (transurethral resection of the prostate, transurethral incision of the prostate, transurethral needle ablation etc.) ≤6 months prior to date of first Screening visit and during the Screening period, or currently being treated for chronic bacterial prostatitis

6. Have urinary incontinence due to urinary urgency ≤30 days prior to date of first Screening visit and during the Screening period
7. Has taken intramuscular injection and intraarticular injection of [redacted] ≤120 days prior to date of first Screening visit and during the Screening period, and any other route of [redacted] ≤30 days prior to date of first Screening visit and during the Screening period
8. Treatment with intravesical therapy ≤60 days prior to date of first Screening visit and during the Screening period
9. Treatment with any opioid therapy ≤7 days prior to date of first Screening visit and during the Screening period, and positive urine drug test at Screening visit
10. Has taken any of the following prohibited medications ≤1 day prior to date of first Screening visit and during the Screening period. Unless noted, these medications are prohibited in oral, injectable, and suppository forms, but they can be used in inhaled, nasal, or ophthalmic formulations, topical administration except for intravesical therapy
    - Nonsteroidal anti-inflammatory drugs
    - Any nonopioid analgesics
    - Steroids (except for [redacted], and topical treatment)
    - Any over the counter medications containing analgesic ingredients
11. Has taken any medications used for symptomatic relief of IC/BPS ≤1 day prior to date of first Screening visit and during the Screening period
12. Has taken any Cytochrome P450 3A4 (CYP3A4) inducers and inhibitors (eg. protease inhibitors, macrolides and barbiturates) ≤1 day prior to date of first Screening visit and during the Screening period
13. History of procedure(s) that has significantly affected bladder function, such as augmentation cystoplasty, cystectomy, cytolysis, or bladder catheterization
14. InterStim placed, or botulinum toxin received ≤6 months prior to date of first Screening visit and during the Screening period or change in previously placed InterStim settings ≤3 months prior to date of first Screening visit and during the Screening period
15. History of bladder hydrodistension ≤3 months prior to date of first Screening visit and during the Screening period
16. Has the following exclusionary laboratory test results at Screening visit:
    - Aspartate aminotransferase (AST) >1.5 times the upper limit of normal (ULN)
    - Alanine aminotransferase (ALT) >2.5 times ULN
    - Creatinine >1.5 times the ULN
    - Positive human immunodeficiency virus (HIV) antibodies, hepatitis C antibodies (HCV), or hepatitis B surface antigen (HBsAg)
    - Positive tuberculosis (TB) blood test
17. Body mass index (BMI) ≥40 $kg/m^2$

18. Sexually active male or female subjects of childbearing potential who are not willing to use adequate contraceptive measures to avoid pregnancy. Adequate methods of birth control include hormonal contraception (female subjects), use of at least 1 acceptable double barrier method, vasectomy, intrauterine device, and/or exclusive sexual partner for whom 1 of the above acceptable methods applies. Acceptable double barrier methods include condoms (male or female) plus a spermicidal agent
19. Has cancer or a past history of any cancer ≤5 years prior to date of first Screening visit and during the Screening period
20. History of the following medical conditions or diseases:
    - Chronic substance abuse (including alcohol), dependency or abuse of opiates, or other marijuana or other illicit drugs within the last 5 years prior to date of first Screening visit and during the Screening period
    - Recurrent, severe allergic or immune-mediated reactions, or other autoimmune disorders
    - Any clinically significant psychiatric disorder
21. Subjects who have been diagnosed with a sexually transmitted infection by the examination at the Screening visit; subject can be rescreened after documented test of cure
22. Subjects with diagnosed or suspected significant medical illness including (but not limited to) pulmonary, cardiovascular, cerebrovascular, renal, hepatic or hematological disease
23. Subjects who have difficulty receiving administration of IP, or subjects with a tendency to bleed or with bleeding disorders such as (but not limited to) hemophilia, aplastic anemia, cirrhosis of the liver, leukemia, thrombocytopenia, and vitamin K deficiency. Subjects using medication for the purpose of anticoagulation, including heparin and warfarin, which cannot be reversed preoperatively will also be excluded
24. Is receiving worker's compensation or is currently involved in medical litigation
25. Have participated in a clinical study of an investigational drug, device, or biologics ≤90 days prior to date of informed consent
26. Any condition that, in the opinion of the Investigator, might interfere with the evaluation of the study objectives

# 5 SUBJECT WITHDRAWAL FROM THE STUDY

## 5.1 Criteria for Subject Withdrawal

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator or sponsor for safety, behavioral, compliance, or administrative reasons. Reasons for withdrawal may include, but are not limited to:

- Occurrence of a treatment-emergent AE (TEAE) that represents an unacceptable risk to the subject in the judgment of the Investigator
- The subject dies
- If the Investigator determines it would be impossible to continue the study because:
  - the subject won't comply with protocol requirements
  - the subject is lost to follow-up
  - there are technical issues at the site
- If a subject becomes pregnant
- The Investigator determines it is necessary to discontinue the study
- The subject withdraws his or her consent
- The Sponsor discontinues the study at a specific site
- The Sponsor prematurely terminates the study
- If a protocol deviation leads the investigator to judge it difficult for the subject to continue the study
- Any other reason documented by the investigator

## 5.2 Procedures for Subject Withdrawal

Subjects may withdraw from the entire study, including follow-up, at any time without penalty and for any reason without prejudice to his or her future medical care. In all cases, the reason(s) for withdrawal, including the primary reason, must be recorded on the electronic case report form (eCRF). If a subject is prematurely withdrawn from the study for any reason, the Investigator must make every effort to perform the evaluations described for the appropriate early withdrawal visit. If a subject withdraws consent and still agrees to undergo a final examination, this will be documented in the eCRF. A subject may also be withdrawn from the study by the Investigator, Sponsor, regulatory authority(ies), or an Institutional Review Board (IRB). Subjects will also be withdrawn if the entire study is terminated prematurely. Withdrawn subjects will not be replaced.

## 5.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

# 6 STUDY METHOD AND PROCEDURES

## 6.1 Informed Consent

Before each subject is enrolled to the study, informed consent, using a form approved by the IRB responsible for that site, will be obtained from the subject according to the regulatory and legal requirements of the participating country/state. This consent form must be signed, dated, and retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. When consent is obtained must also be documented in the subject source record and eCRF.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IRB and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study, except for when the change is administrative or resigning is not required per the IRB. If the IB is updated during the study or new risks/information becomes available, ICF will need to be updated and new form signed by subjects still in study or entering study.

### 6.1.1 Subject Identification

At the screening visit, a unique subject number will be assigned consecutively for each subject after he or she signs the ICF. Subjects who drop out of the study before randomization will retain their unique subject number (ie, the subject number will not be reassigned). If a subject is rescreened after being designated as a screen failure, the subject will receive a new unique subject number upon rescreening.

## 6.2 Subject Entry

At the time of each subject's entry into the study, the investigator will perform all the examinations described in Table 1 and confirm that the subject is eligible for the study. Each subject who is judged as eligible for the study by the Investigator will be enrolled into the study.

## 6.3 Screen Failure

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics and reason for screen failure.

## 6.4 Re-screening

Re-screening of subjects may be allowed if the reason for screen failure is any of the following Inclusion and Exclusion Criteria:

Inclusion Criteria 3

Exclusion Criteria 2, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 17, 21 and 25

Additionally, re-screening of subjects who were screened but were not dosed because of cohort closing may be allowed.

## 6.5 Administration

Investigator will administer IP, SI-722 [redacted] or placebo [redacted] into the subject's bladder via catheter once.

## 6.6 Blinding

The Investigator, site personnel, and subjects will be blinded to the study treatment. Subjects will be randomly assigned in a 6:2 ratio to receive SI-722 or placebo, respectively. Investigators will remain blinded from each participant's assigned study treatment throughout the course of the study. In order to maintain this blind, the investigational drug will be prepared by an appropriate unblinded staff not otherwise involved in the study to ensure the blinding. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

## 6.7 Unblinding

All subjects, site personnel, and Investigators involved with the conduct of the study (except for an unblinded staff) will be blinded with regard to study treatment assignments. The blind may be broken in exceptional circumstances. In a medical emergency, when the management of a subject's condition requires knowledge of the treatment assignment, the Investigator, or designee, will obtain the study treatment assignment through Interactive Response Technology (IRT). The medical emergency should be discussed with the medical monitor prior to obtaining the treatment assignment, or as soon after as possible.

If the randomization code for a subject is broken, the Investigator will record the date and reason for breaking the blind for that subject in the source documents. Upon unblinding, the subject will be withdrawn from the study and should complete all follow-up procedures.

Unblinded study staff will examine and reconcile study medication orders, records of receipts, dispensing records, and inventory forms throughout the study.

## 6.8 Safety Review Committee

An unblinded SRC will evaluate the safety, tolerability and PK of SI-722 1 week after administration for each cohort before advancing to the next higher dose.

After administration for each cohort is completed, the SRC will review and assess (at a minimum) safety, tolerability and PK data through Day 8 prior to dose escalation for the next cohort of subjects. The SRC will carefully evaluate the propriety of continuing to focus on urologic-related adverse events (AEs). Prior to each SRC meeting, an interim blinded safety report will be prepared for that cohort presenting the relevant safety and tolerability findings.

## 6.9 Concomitant Medications

Any medication or vaccine (including over-the-counter or prescription medicines) that the subject is receiving from time of informed consent until Day 29 or study discontinuation must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

### 6.9.1 Prohibited Concomitant Medications

The following medications are prohibited for the periods specified prior to the start date of Screening and through study completion.

- 120 days prior to the start date of Screening: Any [redacted] are prohibited by intramuscular injection and intraarticular injection
- 60 days prior to the start date of Screening: Any bladder instillation medication (ex. DMSO, cocktail, etc.)
- 30 days prior to the start date of Screening: Any route of [redacted] are prohibited (except for intramuscular injection and intraarticular injection)
- 7 days prior to the start date of Screening: Any opioids are prohibited by any route of administration
- 1 day prior to the start date of Screening: Nonsteroidal anti-inflammatory drugs, any nonopioid analgesics and steroids (except for [redacted], and topical treatment)*
- 1 day prior to the start date of Screening: Any over the counter medication containing the analgesic ingredient*
- 1 day prior to the start date of Screening: Any other medications used for symptomatic relief of IC/BPS
- 1 day prior to the start date of Screening: Any CYP3A4 inducers and inhibitors (eg. protease inhibitors, macrolides, and barbiturates)

*** Unless noted, these medications are prohibited in oral, injectable, and suppository forms, but they can be used in inhaled, nasal, ophthalmic formulations, or topical administration except for intravesical therapy.**

### 6.9.2 Restricted Concomitant Medications

The following medications are allowed to be used during the study if the subjects have been on a stable dosage for 3 months prior to the start date of Screening.

- Elmiron® (pentosan polysulfate sodium)
- Tricyclic antidepressants (eg, amitriptyline, nortriptyline)

### 6.9.3 Rescue Medication

Acetaminophen will be provided to subjects as a rescue medication for relief of the bladder pain. Subjects will be required to use only the provided acetaminophen to treat breakthrough pain in the bladder. Acetaminophen will be used only if subjects feel the need to use rescue medication and will not be used excursively. The usage of subject's acetaminophen is 1 or 2 caplets at 1 time and the limitation is up to 3,000 mg/day. An interval between doses of at least 4 hours is recommended.

Subjects will be recommended not to use other medications that contain acetaminophen, such as cold medicine which may cause the subject to consume more than 3,000 mg of acetaminophen in 1 day.

## 6.10 Concomitant Therapies

Investigators will record the information for therapies used concomitantly from time of informed consent until Day 29 or study discontinuation whichever occurs first.

### 6.10.1 Prohibited Concomitant Therapies

History of augmentation cystoplasty, cystectomy, cytolysis, bladder catheterization and other procedures significantly affecting bladder function are prohibited.

Placing InterStim and receiving botulinum toxin are prohibited for 6 months prior to the start date of Screening and during Screening period. Change in InterStim and bladder hydrodistention are prohibited for 3 months prior to the start date of Screening and during the Screening period.

### 6.10.2 Restricted Concomitant Therapies

Subjects can remain on stable frequency of therapies performed for treatments of IC/BPS (stable defined as continuous treatment for 30 days prior to the start date of Screening).

## 6.11 Lifestyle Restrictions

### 6.11.1 Meals and Dietary Restrictions

Refrain from consumption of red wine, oranges, grapefruit or grapefruit juice (pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices) from 7 days prior to Day 1 until after the collection of the 48 hour PK sample. Subjects are asked to refrain from such products for 24 hours prior to their next scheduled visit.

### 6.11.2 Caffeine and Alcohol

Ingesting methylxanthine-containing products (eg, coffee, tea, cola drinks, chocolate and energy drinks) and alcohol will be prohibited for 24 hours before study treatment administration until after the collection of the 48 hour PK sample. Subjects are asked to refrain from such products for 24 hours prior to their next scheduled visit.

### 6.11.3 Ingesting Water

Ingesting any water over 250 mL will be prohibited from morning on Day 1 until study treatment administration.

# 7 INVESTIGATIONAL PRODUCT

## 7.1 Identity of Investigational Products

[redacted]

### 7.1.1 Investigational Product

The complete statement of the components and quantitative composition of SI-722 drug product and SI-722 diluent are shown in Table 2 and Table 3, respectively.

**Table 2 Composition of SI-722 Drug Product**

| Component | Quantity (/Vial) | Function |
|---|---|---|
| SI-722 drug substance | [redacted] | Active ingredient |
| Placebo* | - | - |

Note: Filling amounts are [redacted] to permit withdrawal and administration of the labeled amounts [redacted]
*Placebo is the SI-722 diluent (Table 3) without SI-722.

**Table 3 Composition of SI-722 Diluent**

| Component | Quantity (/Vial) | Function |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

[redacted]

## 7.2 Treatment Administered

1. The Investigator will receive the prefilled syringe with SI-722 or placebo prepared by the unblinded staff
2. Under sterile aseptic conditions, Investigator introduces an appropriately sized catheter with lubricant into the bladder and remove residual urine
3. A catheter adapter will be attached to the end of the syringe
4. The solution will be instilled into the empty bladder through the catheter.

5. The actual amount instilled will be documented, and the time of instillation will be recorded on the source documents and eCRF
6. The catheter will be removed
7. The solution will remain in the bladder for 30 minutes. Subject should make an effort not to void within 30 minutes after study treatment administration. During the 30 minutes immediately following bladder instillation subjects should be instructed to switch positions from supine, to alternating lateral sides every five minutes for 30 minutes (eg, supine, right lateral, left lateral, supine, etc.).

### 7.3 Packaging and Labeling

SI-722 and SI-722 diluent will be packaged separately in single-dose vials and will be labeled appropriately as IP for this study according to regulatory requirements. SI-722 will be supplied in a carton containing 1 bottle of SI-722 and 1 bottle of solution.

### 7.4 Preparation, Handling, Storage, and Accountability

Information on the preparation, handling, storage, and accountability of SI-722 can be found in the pharmacy manual.

# 8 STUDY ASSESSMENTS

## 8.1 Pharmacokinetics Assessments

### 8.1.1 Plasma Pharmacokinetics Assessments

Blood samples of approximately 10 mL each will be collected for measurement of SI-722 and [redacted] concentrations. SI-722 and [redacted] concentrations in plasma will be measured using a validated high-performance liquid chromatography/tandem mass spectrometry (LC-MS/MS) method. Plasma PK parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, $C_{max}$, $T_{max}$, $t_{1/2}$, $V_z/F$, $CL/F$) for SI-722 and [redacted] will be estimated. PK blood sampling will occur pre-dose and 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 96, 168, 336 and 672 hours post-dose. Additional samples may be collected at additional time points during the study if warranted by the Investigator. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each blood sample collected will be recorded in the CRF.

### 8.1.2 Urine Pharmacokinetics Assessment

Urine samples of approximately 8 mL will be collected for measurement of SI-722 and [redacted] concentrations. SI-722 and [redacted] concentrations in urine will be measured using a validated LC-MS/MS method. Urine PK parameters (Ae) for SI-722 and [redacted] will be estimated. PK urine sample will be collected pre-dose (at least once) and 0 to 24 hours post-dose. Urine sample will be also collected on Day 2, Day 3, Day 5, Day 8, Day 15 and Day 29, and these samples will be used for measurement of SI-722 and [redacted] concentrations if needed. After each urine sample collection, voiding volume will be measured. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each urine sample collected will be recorded in the CRF.

All collected urine samples are used for further analysis of metabolites which might be conducted separately from this study. A portion of plasma samples as well as urine samples from this study will be saved for the metabolite analysis study.

## 8.2 Safety Assessments

### 8.2.1 Adverse Events

- Assessment Points: AE will be reported from Informed Consent to Day 29 or an early withdrawal visit.
- Method: See Section 10.4 for collecting AE information

### 8.2.2 Cystoscopy

- Assessment Points: Cystoscopy will be performed on Day 1 (pre-dose) to identify presence or absence of Hunner's leasion as well as Day 8, and Day 29 or an early withdrawal visit to evaluate abnormal change from Day 1.
- Method: Subjects must fully void their bladders after the cystoscopy procedure in preparation for the IP instillation. About five photographs inside the bladder will be printed and filed with each subject's source document.

### 8.2.3 Physical Examination

- Assessment Points: Screening, Day 1 (pre-dose), Day 2, Day 3, Day 5, Day 8, Day 15 and Day 29 or an early withdrawal visit.
- Method: Physical examination will be performed to identify presence or absence of any abnormality. At Screening, gynecological examination will be performed to exclude subjects with gynecologic conditions that could reflect an etiology of their bladder pain (see Section 4.2). It is not necessary to exclude subjects with any abnormal gynecologic conditions if these conditions do not reflect an etiology of their bladder pain.

### 8.2.4 Vital Signs

- Assessment Points: Screening, Day 1 (pre-dose, and 1 hour post dosing), Day 2, Day 3, Day 5, Day 8, Day 15 and Day 29 or an early withdrawal visit.
- Method: Vital signs (to be taken before blood collection) will be measured and will include body temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate. A completely automated device will be used. Manual techniques will be used only if an automated device is not available.

### 8.2.5 Electrocardiograms

- Assessment Points: Day 1 (pre-dose; and 1 hour post dosing), Day 2.
- Method: Using an electrocardiogram (ECG) machine that automatically measures PR, QRS, QT, and QTc intervals.

### 8.2.6 Clinical Laboratory Assessments

- Assessment Points: Blood and urine samples for clinical laboratory tests (blood: hematology, coagulation and clinical chemistry, urine: urinalysis) will be collected at Screening, pre-dose on Day 1, Day 2, Day 3, Day 5, Day 8, Day 15 and Day 29 or early withdrawal.

  Serology (HIV antibodies, HBsAg, and HCV antibody), TB blood test, Nucleic acid amplification testing (NAAT) for *Neisseria. gonorrhoeae and Chlamydia. trachomatis* and Urine drug screen will be done at Screening only.

  Pregnancy tests will be done at Screening (serum), pre-dose on Day 1 (urine), and on Day 29 or early withdrawal (urine). Urine culture will be done at Screening, and on Day 29 or early withdrawal.

- Method: The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section in the eCRF. The laboratory reports must be filed with the source documents. All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline, or are no longer considered clinically significant by the Investigator, or are otherwise explained and any appropriate action taken.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

- All protocol-required laboratory assessments, as defined in Appendix 1, must be conducted in accordance with the laboratory manual and the Schedule of Activities (see Table 1).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, serious AE [SAE], AE, or dose modification), then the results must be recorded in the eCRF.

Immediate safety concerns should be discussed with the medical monitor upon occurrence or awareness to determine if the subject should discontinue study treatment (See Appendix 1).

## 8.3 Efficacy Assessments

### 8.3.1 Daily Diary

#### 8.3.1.1 Bladder Pain

- Assessment Points: Daily from Day -7 until Day 29. Bladder pain assessment must be taken at least 5 days in a week prior to Day 1.
- Item: Daily bladder pain score using a standardized 11-points numerical rating scale (NRS) pain scale in subject daily diary (See Appendix 2).
- Method: Subjects will record daily maximum and average bladder pain over the last 24 hours and bladder pain at that time, basically before going to bed.

#### 8.3.1.2 Symptoms of IC/BPS (Pain, Burning, Discomfort, and Pressure)

- Assessment Points: Daily from Day -7 until Day 29. This assessment must be taken at least 5 days in a week prior to Day 1.
- Item: See Appendix 3
- Method: Subjects will record maximum daily symptoms of pain, burning, discomfort, and pressure over the last 24 hours, basically before going to bed.

#### 8.3.1.3 Voiding Frequency

- Assessment Points: Daily from Day -7 until Day 29. This assessment must be taken at least 5 days in a week prior to Day 1.
- Item: See Appendix 4
- Method: Subjects will record the number of times of the diurnal (from the time of getting up to the time of going to bed) and nocturnal (overnight) urination.

#### 8.3.1.4 Frequency of Bladder Pain

- Assessment Points: Daily from Day -7 until Day 29. This assessment must be taken at least 5 days in a week prior to Day 1.
- Item: See Appendix 5
- Method: Subjects will record daily frequency of bladder pain when they urinate and frequency of voiding caused by bladder pain, basically before going to bed.

#### 8.3.1.5 Voiding Volume

- Assessment Points: One day within 7 days before Day 1, within 3 days before or after Day 8 and Day 15, and within 5 days before Day 29.
- Item: See Appendix 6
- Method: Subjects will measure voiding volume at least 5 times in a day preferably including the first and last urine.

#### 8.3.1.6 Acetaminophen Consumption and Pain

- Assessment Points: Daily from Day -7 until Day 29.
- Item: See Appendix 7
- Method: Subjects will record daily amount of acetaminophen (rescue medication), date and time of taking medicine over the last 24 hours (from the time of going to bed to the time of next going to bed), and bladder pain at that time when subject takes acetaminophen.

### 8.3.2 Patient Reported Outcomes at the Study Site

#### 8.3.2.1 Interstitial Cystitis Symptom Index Score/Problem Index

- Assessment Points: Day 1 (pre-dose) and Day 29 or an early withdrawal visit.
- Item: See Appendix 8
- Method: The Interstitial Cystitis Symptom Index/Problem Index (ICSI/PI) questionnaire will be administered to the subjects at each listed visit.

#### 8.3.2.2 Bladder Pain/Interstitial Cystitis Symptom Score

- Assessment Points: Screening, Day 1 (pre-dose), Day 8, Day 15 and Day 29 or an early withdrawal visit.
- Item: See Appendix 9
- Method: The BPIC-SS questionnaire will be administered to the subjects at each listed visit.

#### 8.3.2.3 Global Response Assessment

- Assessment Points: Day 8, Day 15 and Day 29 or an early withdrawal visit.
- Item: See Appendix 10
- Method: The Global Response Assessment (GRA) questionnaire will be administered to subjects at each listed visit.

### 8.3.3 Voiding Volume (During confinement)

- Assessment Points: Day 1 to Day 2 (during confinement).
- Item: Not applicable
- Method: Subjects collect urine void sample with container and voiding volume will be measured by site staff.

### 8.3.4 Inflammatory Markers

- Assessment Points: Screening, Day 1 (pre-dose), Day 2, Day 3, Day 5, Day 8, Day 15 and Day 29 or an early withdrawal visit
- Method: Erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) blood markers testing will be performed by collecting the blood samples

## 8.4 Other Assessments

### 8.4.1 BS-POP

- Assessment Points: Screening
- Item: BS-POP (See Appendix 11)
- Method: The subjects will answer the BS-POP questionnaire (Appendix 11.1) at Screening visit. Investigator will answer the BS-POP questionnaire (Appendix 11.2) at Screening visit.

# 9 STUDY SCHEDULE AND VARIABLES

Adherence to the study design requirements is essential and required for study conduct. Study procedures and schedule are listed below and summarized in the Time and Events Schedule (See Table 1).

**Study procedures**:

Each subject will be asked to complete 7 study visits:

- Screening visit (Visit 1)
- Randomization and IP administration at Day 1 and confinement for assessment of PK and safety until Day 2 (Visit 2)
- Follow-up visits at Day 3, Day 5, Day 8, Day 15 and Day 29

Subjects who discontinued the study in mid-course will be asked to complete an early withdrawal visit.

Study procedures to be performed at each respective visit is provided in detail below.

## 9.1 Visit 1: Screening Period (Day -28 to Day 1 [pre-dose])

The following procedures will be performed at Screening visit (Visit 1) or during the Screening period (Day -28 to Day 1 [pre-dose]).

Before performing any screening procedures:

- Obtain written informed consent

After informed consent is obtained:

- Perform eligibility check in accordance with study protocol inclusion/exclusion criteria
- Perform physical examination
- Perform gynecological examination
- Collect demographics and baseline characteristics (eg, physical examination, height, body weight)
- Collect medical history
- Collect IC/BPS history and treatment history
- Perform urine drug screen test
- Collect blood sample for laboratory tests (hematology, coagulation, chemistry, Serology, TB blood test)
- Collect urine samples for urinalysis and urine culture
- Collect sample for NAAT
- Collect sample for serum β human chorionic gonadotropin (β-hCG) pregnancy test
- Record vital signs

- Distribute acetaminophen as rescue medication
- Record Patient Reported Outcome (PRO) assessments (BPIC-SS and BS-POP)
- Record AEs
- Collect concomitant medication and therapy information:
  1. Confirm use and amount of concomitant medication(s)/therapy(ies)
  2. Assess use of restricted medication(s)/therapy(ies)
  3. Assess washout of prohibited medication(s)/therapy(ies)
- Provide instructions for refraining from any water over 250 mL from morning on Day 1 until study treatment administration.

At least 7 days prior to randomization date, sites should:

- Distribute subject daily diary
- Provide instructions for recording subject daily diary which must be taken at least 5 days in a week prior to the start date of IP administration
- Provide subject education and materials on accurate pain reporting
- Provide instructions and containers with scale for recording voiding volume by subject daily diary which must be measured at least 5 times in a day within 7 days before Day 1

## 9.2 Visit 2: Treatment with inpatient (Day 1)

Pre-dose:

- Perform eligibility check in accordance with study protocol inclusion/exclusion criteria
- Perform physical examination
- Collect concomitant medication and therapy information
- Review of subject daily diary
- Record PRO assessments (BPIC-SS and ICSI/PI)
- Record vital signs
- 12-lead ECG
- Record AEs
- Collect blood sample for laboratory tests (hematology, chemistry and coagulation) and PK
- Collect urine sample for urinalysis and PK
- Perform urine pregnancy test
- Record urine volume
- Distribute subject daily diary
- Distribute acetaminophen, if necessary
- Perform cystoscopy

- Randomization

IP administration (0 hour)

- IP administration

Post-dose:

- Record the time of first voiding
- Record urine volume
- Collect blood sample for PK at 0.25, 0.5, 1, 2, 4, 6, 8, 12 hours after administration
- Collect urine sample for PK over interval of 0 to 24 hours after administration
- Record vital signs at 1 hour after administration
- 12-lead ECG at 1 hour after administration
- Record AEs

### 9.3 Visit 2: Follow-up and Evaluation Period with Inpatient (Day 2)

- Perform physical examination
- Record vital signs
- 12-lead ECG
- Collect blood sample for laboratory tests (hematology, chemistry and coagulation) and PK
- Collect urine sample for urinalysis and PK
- Distribute subject daily diary
- Distribute acetaminophen, if necessary
- Record urine volume
- Collect concomitant medication and therapy information
- Review subject daily diary
- Record AEs

### 9.4 Visit 3: Follow-up and Evaluation Period (Day 3 [Week 0])

- Perform physical examination
- Record vital signs
- Collect blood sample for laboratory tests (hematology, chemistry and coagulation) and PK
- Collect urine sample for urinalysis and PK
- Distribute subject daily diary
- Distribute acetaminophen, if necessary
- Collect concomitant medication and therapy information
- Review subject daily diary

- Record AEs

### 9.5 Visit 4: Follow-up and Evaluation Period (Day 5 ± 1 day)

- Perform physical examination
- Record vital signs
- Collect blood sample for laboratory tests (hematology, chemistry and coagulation) and PK
- Collect urine sample for urinalysis and PK
- Distribute subject daily diary
- Distribute acetaminophen, if necessary
- Provide instructions and containers with scale for recording voiding volume by subject daily diary which must be measured at least 5 times in a day within 3 days before or after Day 8
- Collect concomitant medication and therapy information
- Review subject daily diary
- Record AEs

### 9.6 Visit 5: Follow-up and Evaluation Period (Day 8 ± 3 days)

- Perform physical examination
- Record vital signs
- Collect blood sample for laboratory tests (hematology, chemistry and coagulation) and PK
- Collect urine sample for urinalysis and PK
- Perform cystoscopy
- Distribute subject daily diary
- Distribute acetaminophen, if necessary
- Provide instructions and containers with scale for recording voiding volume by subject daily diary which must be measured at least 5 times in a day within 3 days before or after Day 15
- Record PRO assessments (BPIC-SS and GRA)
- Collect concomitant medication and therapy information
- Review subject daily diary
- Record AEs

### 9.7 Visit 6: Follow-up and Evaluation Period (Day 15 ± 3 days [Week 2])

- Perform physical examination
- Record vital signs

- Collect blood sample for laboratory tests (hematology, chemistry and coagulation) and PK
- Collect urine sample for urinalysis and PK
- Distribute subject daily diary
- Distribute acetaminophen, if necessary
- Provide instructions and containers with scale for recording voiding volume by subject daily diary which must be measured at least 5 times in a day within 5 days before Day 29
- Record PRO assessment (BPIC-SS and GRA)
- Collect concomitant medication and therapy information
- Review of subject daily diary
- Record AEs

### 9.8 Visit 7: Follow-up and Evaluation Period (Day 29 ± 5 days [Week 4])

- Perform physical examination
- Record vital signs
- Collect blood sample for laboratory tests (hematology, chemistry and coagulation) and PK
- Collect urine sample for urinalysis, urine culture, and PK
- Perform urine pregnancy test
- Perform cystoscopy
- Record PRO assessments (BPIC-SS, ICSI/PI, and GRA)
- Collect concomitant medication and therapy information
- Review of subject daily diary
- Record AEs

### 9.9 An Early Withdrawal Visit

Subjects who discontinue early from the study will be asked to complete an early withdrawal visit. The following activities will be performed at the early withdrawal visit:

- Perform physical examination
- Record vital signs
- Collect blood sample for laboratory tests (hematology, chemistry and coagulation) and PK
- Collect urine sample for urinalysis, urine culture, and PK
- Perform urine pregnancy test
- Perform cystoscopy
- Record PRO assessments (BPIC-SS, ICSI/PI, and GRA)

- Collect concomitant medication and therapy information
- Review of subject daily diary
- Record AEs

## 9.10 Unscheduled Visit

In the event the Investigator needs to conduct follow-up assessments to evaluate an AE, the following safety assessments may be performed on an unscheduled visit:

- Physical examination
- Record vital signs
- Collect blood sample for laboratory tests (hematology and chemistry) and PK if considered appropriate
- Perform cystoscopy, if necessary

# 10 ADVERSE EVENTS

## 10.1 Adverse Events

An AE is any untoward medical occurrence that occurs in a subject administered with IP, and that does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings and the cystoscopy), symptom, or disease temporally associated with the use of IP, whether or not considered related to the product.

All AEs occurring after obtaining written informed consent will be documented in the subject source record and eCRF. Concomitant illnesses that existed before entry into the study will not be considered AEs unless they worsen after IP administration. All AEs, regardless of the source of identification (eg, laboratory assessments, cystoscopy findings, subject reports) must be documented.

Pre-existing conditions will be recorded in the subject source record and eCRF on the medical history or appropriate page.

TEAE will be defined as an AE that begins or that worsens in severity after IP has been administered.

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology.

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the subject to discontinue the study treatment (see Section 5.1 and 5.2).

## 10.2 Serious Adverse Events

An SAE is defined as any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening, meaning that the subject is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

AEs reported from clinical studies and associated with hospitalization or prolonged hospitalization are considered serious. Any hospitalization except observational admissions of less than 24 hours for logistical reasons meets these criteria. This category also includes transfer within the hospital to an acute/intensive care unit (eg, from a standard-of-care unit to an acute/intensive care unit).

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities, or respite care (eg, caregiver relief)
- Nursing homes or skilled nursing facilities
- Emergency room visits
- Same-day surgeries (such as outpatient/same day/ambulatory procedures)
- <24-hour admissions for observation or evaluation for logistical reasons

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include the following:

- Admission for treatment of a pre-existing condition that did not worsen
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures, which should be noted in the baseline documentation for the individual subject

### 10.3 Cystoscopy, Vital Signs, Electrocardiograms and Laboratory Tests

If an abnormal findings of cystoscopy, vital signs, ECGs or laboratory tests are observed, the Investigator should judge whether it is an AE or not by referring to the following criteria:

- When any medical intervention such as pharmacotherapy or surgical care is performed in order to improve the abnormality
- Other than case above, when investigator judges that the abnormality is medically important and should be considered an AE

### 10.4 Process for Collecting Adverse Events and Serious Adverse Events Information

All AEs and SAEs will be collected from the signing of the ICF continuously until Day 29 as specified in the Schedule of Activities (See Table 1).

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the medical history/current medical conditions section in the eCRF not the AE section.

All SAEs during study treatment period will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 12.

The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.

Investigator will conduct physical examination to collect on Screening, Day 1 (pre-dose), Day 2, Day 3, Day 5, Day 8, Day 15 and Day 29 or an early withdrawal visit. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Investigators are not obligated to actively seek AE or SAE reports from former study subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 12.

### 10.5 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

### 10.6 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 5.3). Further information on follow-up procedures is given in Appendix 12.

### 10.7 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (within 24 hours) by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

### 10.8 Pregnancy

Details of all pregnancies in female subjects and, if indicated, female partners of male subjects which occur during the study, will be collected.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

# 11 STATISTICAL METHODS

While key analyses are described in this section, additional analyses, including supportive analysis, sensitivity analysis, and subgroup analysis, and details such as data handling will be specified in the statistical analysis plan (SAP).

The impact of COVID-19 will be evaluated i.e. based on the missing data, and if deemed necessary appropriate sensitivity analyses will be performed and documented.

## 11.1 Analysis Populations

### 11.1.1 Intention-to-treat Population

The intention-to-treat (ITT) population includes all randomized subjects regardless of whether the subject received any IP or had any efficacy assessment collected.

### 11.1.2 Per Protocol Population

The Per-protocol (PP) population includes all ITT subjects without major protocol deviation.

### 11.1.3 Safety Population

The safety population includes all randomized subjects who received IP. If a subject receives IP other than the subject's randomized treatment assignment, then the subject is assigned to the treatment arm reflecting the treatment that the subject actually received during the study.

### 11.1.4 Pharmacokinetic Population

The PK population includes all subjects who received SI-722 and who provided at least 1 evaluable PK sample.

## 11.2 Demographics, Baseline Characteristics, Medical History, and Concomitant Medications

Subjects' age, height, weight, and other continuous baseline characteristics will be summarized using descriptive statistics, while sex, race, and other categorical variables will be provided using frequency tabulations. Medical history and concomitant medications will be summarized using frequency tabulations by system organ class and preferred term of the MedDRA and Anatomical Therapeutic Chemical class and standardized drug name of WHO Drug Global, respectively.

## 11.3 Pharmacokinetic Analyses

Plasma and urine concentrations of SI-722 and [redacted] will be determined for the safety population. The other PK analyses will be determined based on the PK population.

Pharmacokinetic profiles will be assessed by plasma SI-722 and [redacted] concentrations, urine SI-722 and [redacted] concentrations, and the corresponding PK parameters.

The following PK parameters for SI-722 and [redacted] will be estimated, where possible, using Phoenix WinNonlin v8.0 software (or higher) and actual blood sample collection times:

Plasma PK parameter

$C_{max}$ maximum concentration after dosing

$t_{max}$ time to reach the maximum plasma concentration

$AUC_{0-t}$ area under the plasma concentration-time curve from time 0 to t hours after dosing, in which time t is the last time at which the concentration can be observed in all cohorts.

$AUC_{0-last}$ area under the concentration-time curve from time 0 to time the last quantifiable concentration

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time 0 to infinite time, calculated as the sum of $AUC_{last}$ and $C_{last}/\lambda_z$, in which $C_{last}$ is the last observed quantifiable concentrations

$t_{1/2}$ terminal half-life

$V_z/F$ apparent volume of distribution

CL/F apparent total plasma clearance

Urine PK parameter

Ae cumulative amount of excreted in urine

Details will be outlined in the SAP. Additional PK parameters will be estimated and analyzed if needed.

### 11.4 Safety Analyses

All safety analyses will be conducted based on the safety population.

#### 11.4.1 Adverse Events

AEs will be analyzed in terms of TEAEs, defined to be any event that begins or worsens in grade after the start of IP throughout of the study. All AEs will be coded using MedDRA.

The number of events and number (percentage) of subjects reporting TEAEs for each preferred term will be tabulated by system-organ class, by system-organ class and severity, and by system-organ class and relationship to IP. If more than 1 event occurred with the same preferred term for the same patient, the subject will be counted only once for that referred term using the most severe or related occurrence for the summary by severity, or relationship to IP, respectively.

#### 11.4.2 Laboratory Tests

Laboratory values will be summarized by treatment group, including changes from baseline at each time point. The number (percentage) of subject with abnormal will be summarized and the shift tables will be tabulated by treatment group and time points.

#### 11.4.3 Vital Signs

Vital sign measurements will be summarized by treatment group, including changes from baseline at each time point.

### 11.4.4 Electrocardiograms

ECGs will be summarized by treatment group, including changes from baseline at each time point.

### 11.4.5 Cystoscopy

The number (percentage) of subjects with abnormal cystoscopy will be summarized by treatment group.

## 11.5 Efficacy Analyses

All efficacy analysis will be conducted based on the ITT population.

Each efficacy assessment will be summarized for all subjects by treatment group at each assessment visit. The assessments collected on daily diary will be calculated by average at each assessment visit. Efficacy assessments from the daily diary such as bladder pain and symptoms of IC/BPS will be summarized by study day in addition to the summary at each assessment visit.

## 11.6 General Considerations

Placebo group will be combined regardless of planned volume. All study-collected data will be summarized by treatment group using descriptive statistics, graphs, and/or data listings. Unless otherwise specified, descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), median, and minimum (min) and maximum (max) values, and analysis of categorical variables will include number of patients (n) and percentage.

### 11.6.1 Visit Window and Unscheduled Assessments

The data collected during follow-up time point will be displayed and analyzed according to the actual visit date in the eCRF. Assessments taken outside of protocol-allowable windows will be displayed according to the eCRF assessment recorded by the Investigator. Unscheduled assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in investigating or managing AEs) will be included in listings but not summaries of the data.

### 11.6.2 Significance Level and Confidence Coefficient

A two-sided 5% significance level will be used, and a two-sided 95% confidence coefficient will be used for interval estimation.

### 11.6.3 Missing Data

Missing data will not be imputed and will be excluded from the analysis.

# 12 ETHICAL CONSIDERATION

## 12.1 Good Clinical Practice Compliance

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

## 12.2 Institutional Review Board Approval

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of Title 21 of the Code of Federal Regulations (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

## 12.3 Informed Consent

The Investigator or his/her representative will explain the nature of the study to the subjects and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB or study center.

The medical record must include a statement that written informed consent was obtained and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subjects.

## 12.4 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

## 12.5 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

# 13 PROCEDURE FOR COMPLETION AND CORRECTION OF THE CASE REPORT FORM

The procedures for completion of the eCRFs and reconciliation of data queries will be provided in the CRF Completion Guidelines .

# 14 DIRECT ACCESS TO SOURCE DATA

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

# 15 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

# 16 ARCHIVING OF SOURCE DATA AND OTHER RECORDS

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuation of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

# 17 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings by the Sponsor. The results of and data from this study belong to the Sponsor. No individual subject will be identified in any publication.

The Sponsor will comply with the requirements for publication of study results.

# 18 COVID-19 PANDEMIC AND SUGGESTED MEASURES

This section is provided in response to the "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic" issued by the FDA on March 2020. Taking the COVID-19 impact into account, this section provides guidance to Investigators and their site staff to mitigate risks and suggested measures to modify operations. Each Investigator may choose to implement different measures according to their sites' operations; which may include, but are not limited to the following items.

## 18.1 Screening Questions to Identify Potential COVID-19 Exposure

When scheduling an on-site visit for subjects, consider asking the subjects a few, short questions regarding potential exposure to COVID-19 before their on-site visit (in-person interactions). For example:

1. Have you had any of the following symptoms in the past 14 days without confirmation of etiology such as a positive flu test, existing chronic medical condition, etc.
   - Fever greater than 100.4 dgrees Fahrenheit
   - Cough
   - Difficulty breathing
   - Sore throat
2. In the last 14 days, have you lived with, visited, cared for, or been in a room for a prolonged period of time with someone who is under investigation or has been confirmed for COVID-19?

## 18.2 Screening Window

If a subject has completed all Screening Visit procedures and is eligible to proceed to Study Day 1 but cannot do so within the allotted timeframe of 28 days, it will be considered to extend the visit window on a case by case basis. The BPIC/SS questionnaire must be repeated to ensure it is valid and within 28 days of dosing, but further consultation is necessary with Contract Research Organization (CRO) and may necessitate approval by the study's Medical Monitor and Sponsor.

## 18.3 Follow-Up Visit by Phone

Should a subject not be able to complete a study visit in-person, the following procedures will be completed via phone, as necessary by the schedule of events according to the protocol:

1. Medical history
2. IC/BPS history and treatment history
3. Concomitant medication and therapy information
4. Adverse events
5. PRO questionnaires (BPIC-SS, ICSI/PI and GRA)

Site staff will capture the above in the source documents and promptly notify CRO and Clinical Research Associate (CRA) of the partial phone visit as soon as possible. All missing data, and the phone visit itself, will be considered protocol deviations. Site staff will need to complete additional forms for IRB submission and state "COVID-19" in the comment column of the deviation log.

### 18.4 Remote Monitoring

Due to travel restrictions, shelter in place or stay at home mandates, sites' change in operations, and a number of other reasons to try to contain the spread of the virus and minimize exposure, it is reasonable to conduct monitoring visits remotely, instead of in-person, whenever feasible. Site staff/Investigator will work with CRO and the assigned CRA to define and understand the logistics of the remote visit such as source data verification.

### 18.5 Data Management

In order to confirm the effect of COVID-19 on this study, the following information will be captured in eCRF.

- Missed visit due to COVID-19
- Missed assessment due to COVID-19
- Screen failed subject due to COVID-19
- Early discontinuation due to COVID-19
- AE related to COVID-19

# 19 REFERENCES

1. Nickel JC, Egerdie B, Davis E, Evans R, Mackenzie L, Shrewsbury SB. A Phase II study of the efficacy and safety of the novel oral SHIP1 activator AQX-1125 in subjects with moderate to severe interstitial cystitis/bladder pain syndrome. J Urol. 2016;196:747-754.
2. Hanno PM, Erickson D, Moldwin R, Faraday MM. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. J Urol. 2015;193:1545-1553.
[redacted]
4. Hanno PM, Nordling J, Staskin DR, Wein AJ, Wyndaele JJ. Bladder Pain Syndrome - An Evolution. 2nd ed. Cham: Springer International Publishing; 2018.
[redacted]

# Appendix 1 Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by central clinical laboratories.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 4.1 and Section 4.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

**Table 4 Protocol-required Safety Laboratory Assessments**

| Laboratory Assessments | Parameters | |
|---|---|---|
| Hematology | Platelet count<br>Red blood cell (RBC) count<br>Hemoglobin<br>Hematocrit | White blood cell (WBC) count with differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils |
| Coagulation | partial thromboplastin time (PTT)<br>prothrombin time/international normalized ration (PT/INR) | |
| Clinical chemistry | Blood urea nitrogen<br>Potassium<br>Creatinine<br>Sodium<br>Glucose<br>Calcium<br>Total and direct bilirubin<br>Total protein<br>Total cholesterol<br>HDL-cholesterol<br>LDL-cholesterol<br>Triglyceride | Alanine Aminotransferase (AST)<br>Aspartate Aminotransferase (ALT)<br>Alkaline phosphatase (ALP)<br>Hypothalamic-pituitary-adrenal axis evaluation:<br>adrenocorticotropic hormone (ACTH)<br>Cortisol<br>Inflammatory markers:<br>Erythrocyte sedimentation rate (ESR)<br>C-reactive protein (CRP) |

| | |
|---|---|
| Routine urinalysis | • Specific gravity<br>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick<br>• Microscopic examination (if blood or protein is abnormal) |
| Urine culture | • Urine culture will be performed at Screening and on Day 29 or early withdrawal |
| Other screening tests | • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)<br>• Serum β-human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential [WOCBP]) at Screening<br>• Urine pregnancy tests (pre-dose on Day 1, and Day 29 or early withdrawal)<br>• Serology (HIV antibody, HBsAg, and HCV antibody)<br>• TB blood tests<br>• NAAT for *Neisseria. gonorrhoeae and Chlamydia. trachomatis* |

Investigators must document their review of each laboratory safety report.

# Appendix 2 Pain Score 0-10 Numerical Rating Scale

The NRS is a unidimensional measure of pain intensity in adults, including those with chronic pain due to rheumatic diseases.

The NRS is a segmented numeric version of the visual analog scale (VAS) in which a respondent selects a whole number (0–10 integers) that best reflects the intensity of his/her pain. Respondents are most commonly asked to report pain intensity "in the last 24 hours" or an average pain intensity. The common format is a horizontal bar or line. Similar to the VAS, the NRS is anchored by terms describing pain severity extremes.

The 11-point NRS ranges from '0' representing 1 pain extreme (eg, "no pain") to '10' representing the other pain extreme (eg, "pain as bad as you can imagine" or "worst pain imaginable").

Subjects will select the level that best describes their maximum and average bladder pain over the last 24 hours, and their bladder pain at the moment, respectively.

**PAIN SCORE 0-10 NUMERICAL RATING**

| ☐0 | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 | ☐7 | ☐8 | ☐9 | ☐10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No pain | | | | | Moderate pain | | | | | Worst possible pain |

# Appendix 3 Symptoms of Interstitial Cystitis/Bladder Pain Syndrome

Subjects will select the level that best describes the severity of other symptom from their bladder over the last 24 hours.

| | Not at all | Mild | Moderate | Severe |
|---|---|---|---|---|
| Pain | ☐ | ☐ | ☐ | ☐ |
| Burning | ☐ | ☐ | ☐ | ☐ |
| Discomfort | ☐ | ☐ | ☐ | ☐ |
| Pressure | ☐ | ☐ | ☐ | ☐ |

# Appendix 4 Voiding Frequency

Subject will record their responses to the following items every day.

Daytime urine: _____

Night time urine (urination wake you up from sleeping): _____

# Appendix 5 Frequency of Bladder Pain

Subject will select the level that the best describes frequency of bladder pain when they urinate and voiding frequency caused by bladder pain.

| Never | Rarely | Sometimes | Always |
|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ |

# Appendix 6 Voiding Volume

Subject will record 5 times of voiding volume with the time in a day. First voiding in the morning and before you go to bed are preferable.

| | | |
|---|---|---|
| | **Time (24-hour notation)** | **Volume** |
| | | *Record by container with scale*<br>*Select BLQ if less than the minimum scale* |
| **1** | **Time (24-hour notation)** | **Volume** |
| | : | mL/ BLQ |
| **2** | **Time (24-hour notation)** | **Volume** |
| | : | mL/ BLQ |
| **3** | **Time (24-hour notation)** | **Volume** |
| | : | mL/ BLQ |
| **4** | **Time (24-hour notation)** | **Volume** |
| | : | mL/ BLQ |
| **5** | **Time (24-hour notation)** | **Volume** |
| | : | mL/ BLQ |

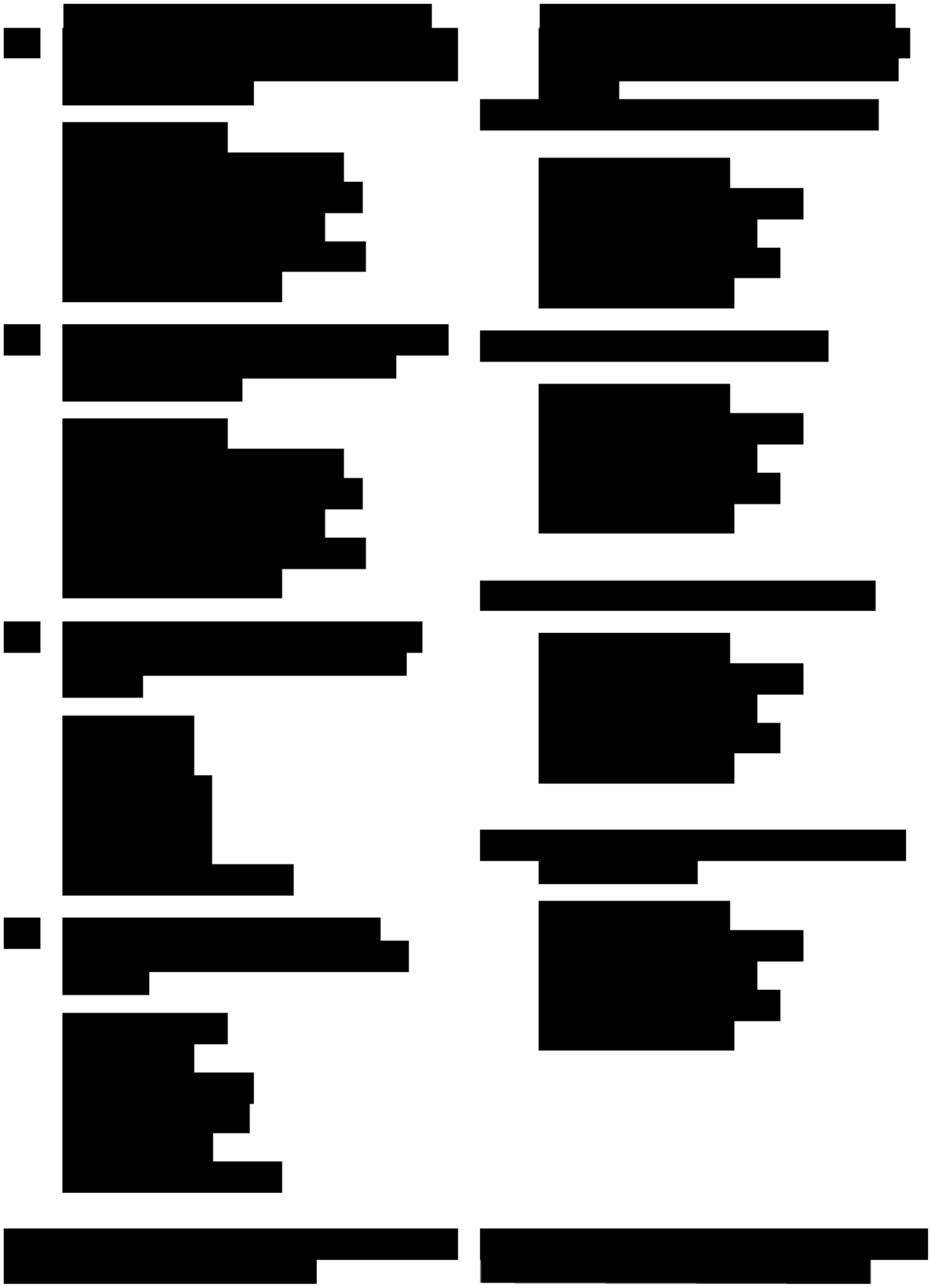
# Appendix 7 Acetaminophen Consumption

Please record the time, the number of tablets and bladder pain when you take rescue medicine.

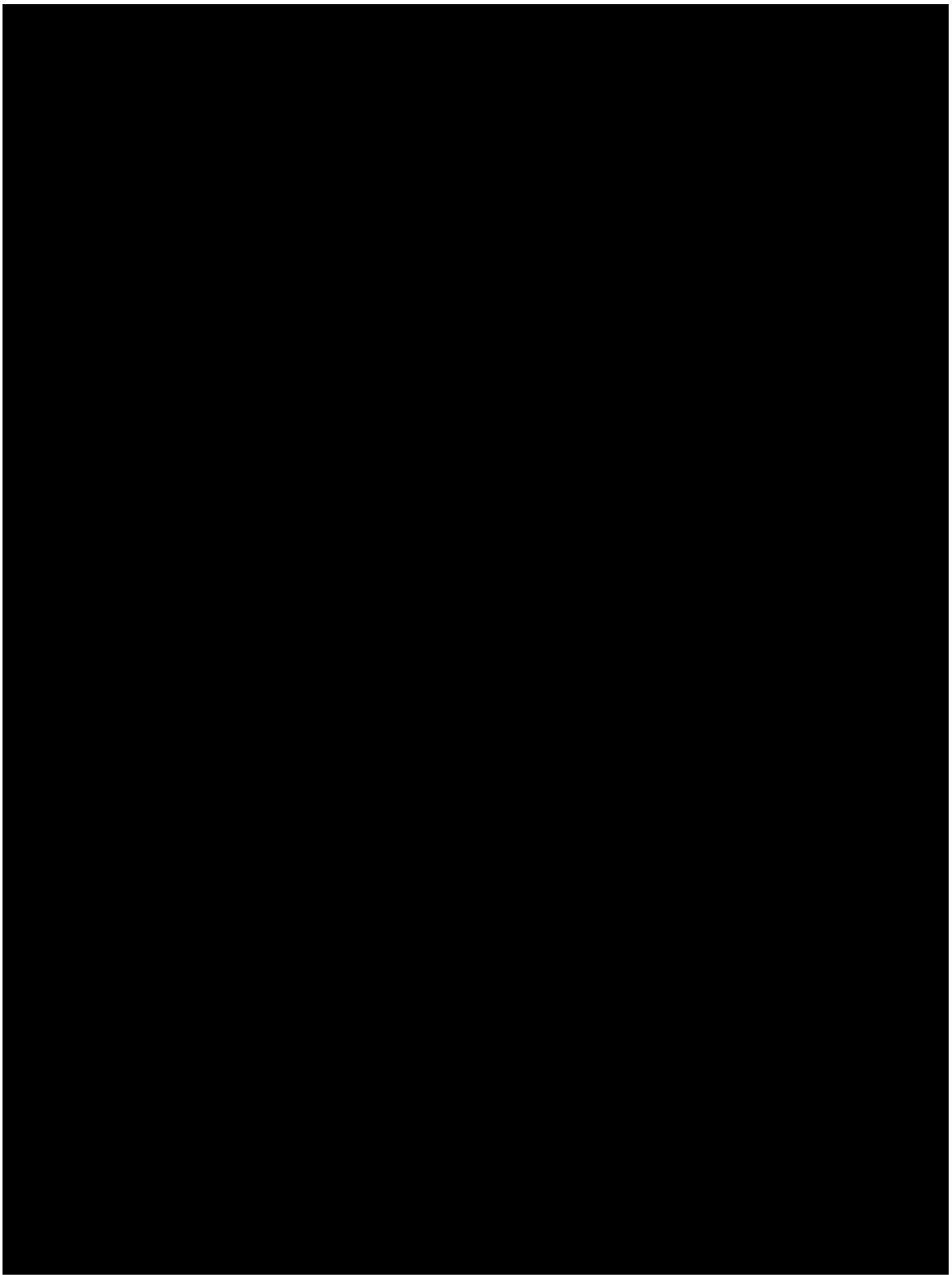
| | | | | |
|---|---|---|---|---|
| | **Time** **(24-hour notation)** | *Please fill in from getting up to getting up the next day* | **Number of tablets** | *Please fill in the number of tablets taken* |
| | **Pain score** | *Each time you took acetaminophen, select the level of your bladder pain from 1 – 10** | | |
| **1** | **Time** **(24-hour notation)** | : | **Number of tablets** | |
| | **Pain score** | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 | | |
| **2** | **Time** **(24-hour notation)** | : | **Number of tablets** | |
| | **Pain score** | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 | | |
| **3** | **Time** **(24-hour notation)** | : | **Number of tablets** | |
| | **Pain score** | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 | | |
| **4** | **Time** **(24-hour notation)** | : | **Number of tablets** | |
| | **Pain score** | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 | | |
| **5** | **Time** **(24-hour notation)** | : | **Number of tablets** | |
| | **Pain score** | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 | | |
| **6** | **Time** **(24-hour notation)** | : | **Number of tablets** | |
| | **Pain score** | ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 | | |

** 0: No pain, 5: Moderate pain, 10: Worst possible pain*

# Appendix 8 Interstitial Cystitis Symptom/Problem Index



# Appendix 9 Bladder Pain Interstitial Cystitis Symptom Score



# Appendix 10 Global Response Assessment

**Global Response Assessment**

As compared to when you started the study, how would you rate your overall symptoms now?

- ☐ Markedly worse
- ☐ Moderately worse
- ☐ Slightly worse
- ☐ No change
- ☐ Slightly improved
- ☐ Moderately improved
- ☐ Markedly improved

# Appendix 11 Brief Scale for Psychiatric Problem in Orthopaedic Patients

## Appendix 11.1 Questionnaire for medical personnel

## Appendix 11.2 Questionnaire for patients

# Appendix 12 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## Definition of AE

| AE Definition |
| --- |
| • An AE is any untoward medical occurrence in a subject or clinical study subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment.<br>• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment. |

| Events Meeting the AE Definition |
| --- |
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.<br>• The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE. |

| **Events NOT Meeting the AE Definition** |
|---|
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.<br>• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.<br>• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. |

**Definition of SAE**

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

| **A SAE is defined as any untoward medical occurrence that, at any dose:** |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br>The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br>In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. |

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

**d. Results in persistent disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

**f. Other situations:**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

**Recording and AE and/or SAE**

**AE and SAE Recording**

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the medical monitor or Sponsor in lieu of completion of the AE/SAE eCRF page.

- There may be instances when copies of medical records for certain cases are requested by the medical monitor or Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the medical monitor or Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Intensity**

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

**Assessment of Causality**

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship, either as not related or related.

  Not Related: There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Related: The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the medical monitor or Sponsor . However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** the medical monitor or Sponsor**.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AEs and SAEs**

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the medical monitor or Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.

- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

**Reporting of SAEs**

**SAE Reporting via an Electronic Data Collection Tool**

- The primary mechanism for reporting an SAE to the medical monitor or Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor or Sponsor by telephone.

In case of an SAE, the Principal Investigator will send a report within 24 hours of notification to the Sponsor. Reporting guidance will be provided separately.

**SAE Reporting via Paper CRF**

- Facsimile transmission of the SAE paper eCRF is the preferred method to transmit this information to the medical monitor or Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE eCRF pages within the designated reporting time frames.