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A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Multi-Center Single Dose Study to Evaluate the Safety and Effectiveness of URG101 Compared with the Individual Components Lidocaine and Heparin in Subjects with Interstitial Cystitis/Bladder Pain Syndrome

(URG101-105, the ENGAGE-24 Study)

Clinical Protocol Version 5.0: 18-Apr-2017

1.0 TITLE PAGE

URG101

CLINICAL PROTOCOL

A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Multi-Center Single Dose Study to Evaluate the Safety and Effectiveness of URG101 Compared with the Individual Components Lidocaine and Heparin in Subjects with Interstitial Cystitis/Bladder Pain Syndrome (the ENGAGE-24 Study).

(Protocol URG101-105, the ENGAGE-24 Study)

Sponsor:	Urigen N.A., Inc. 675 US Hwy 1, STE B206 North Brunswick, NJ 08902 USA
Sponsor Contact:	[redacted]
Investigational Product:	URG101 (Alkalinized lidocaine and heparin)
Clinical Phase:	2a
Approval Date/Version:	18 April 2017; Version 5.0
Confidentiality Statement:	This protocol is a confidential communication and is the property of Urigen N.A., Inc. Acceptance implies an agreement not to disclose the information contained herein that is not otherwise publicly available, except for use by an institutional review board (IRB) for the purpose of obtaining approval to conduct the study. The IRB is requested and expected to maintain confidentiality. This document may not be used or published in whole or in part without the consent of Urigen N.A., Inc.

2.0 CLINICAL PROTOCOL SYNOPSIS

Name of Sponsor: **Name of Product:**	Urigen N.A., Inc. URG101
Protocol Title:	A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Multi-Center Single Dose Study to Evaluate the Safety and Effectiveness of URG101 Compared with the Individual Components Lidocaine and Heparin in Subjects with Interstitial Cystitis/Bladder Pain Syndrome (Protocol URG101-105, the ENGAGE-24 Study)
Clinical Phase	2a
Objectives:	**Primary Objective:** 1. To evaluate the change in sum of bladder pain intensity differences from baseline to 12 hours (SPID-12) after administration of URG101 compared with the SPID-12 after administration of lidocaine alone, heparin alone, and placebo as determined by using the 11-point NRS for bladder pain. **Secondary Objectives:** 1. To evaluate the change in bladder pain from baseline to 24 hours, using the sum of pain intensity differences (SPID-24) at defined time points, after administration of intravesical URG101 compared with alkalinized Lidocaine Hydrochloride Injection (20 mg/mL) alone, alkalinized Heparin Sodium Injection (5,000 USPU/mL) alone, and placebo [redacted]) 2. To evaluate the change in urgency from baseline to 12 and 24 hours, using the sum of urgency intensity differences (SUID) at defined time points, after administration of URG101 compared with alkalinized Lidocaine Hydrochloride Injection (20 mg/mL) alone, alkalinized Heparin Sodium Injection (5,000 USPU/mL) alone, and placebo ([redacted]) 3. To evaluate the absolute and percentage change in bladder pain and urgency intensity differences at 1, 12, and 24 hours after administration of URG101 compared with alkalinized Lidocaine Hydrochloride Injection USP (20 mg/mL) alone, alkalinized Heparin Sodium Injection USP (5,000 USPU/mL) alone, and placebo ([redacted]) 4. To evaluate the improvement of symptoms after treatment with URG101, measured using the Patient Global Assessment (question number 3) compared with alkalinized Lidocaine Hydrochloride Injection (20 mg/mL) alone, alkalinized Heparin Sodium Injection (5,000 USPU/mL) alone, and placebo ([redacted]) at 1, 12, and 24 hours after treatment 5. To evaluate the time to first administration of rescue medication for pain after treatment with URG101 compared to alkalinized Lidocaine Hydrochloride Injection (20 mg/mL) alone, alkalinized Heparin Sodium Injection (5,000 USPU/mL) alone, and placebo [redacted]) 6. To investigate the relationship of plasma lidocaine concentrations at 1 hour after study drug administration to bladder pain and urgency at 1 hour, and from baseline to 12 and 24 hours, using the sum of pain and urgency intensity differences at defined time points, after administration of URG101 compared with alkalinized Lidocaine Hydrochloride Injection (20 mg/mL) alone, alkalinized Heparin Sodium Injection (5,000 USPU/mL) alone, and placebo [redacted]) 7. To evaluate the safety and tolerability of intravesical administration of URG101
Study Design:	This is a Phase 2a, prospective, randomized, double-blind, placebo-controlled,

CLINICAL PROTOCOL SYNOPSIS (continued)

	multicenter, single-dose, pharmacokinetic study designed to test the efficacy and safety of the combination product (URG101) versus its alkalinized individual components (Heparin Sodium and Lidocaine Hydrochloride) and placebo [redacted]). A maximum of 300 subjects will be enrolled in Study URG101-105. In this study, alkalinized Lidocaine Hydrochloride Injection (20 mg/mL) and alkalinized Heparin Sodium Injection (5,000 USPU/mL) will be subsequently referred to by the drug names Lidocaine and Heparin. Eligible subjects exhibiting interstitial cystitis symptoms who have signed informed consent, will be screened and provisionally enrolled for intravesical treatment. Treatment may occur on the day of the Screening Visit (Visit 1) or any following day up to 1 week (Baseline and Drug Administration Visit 1a). If drug administration occurs on same day as screening then all assessments in Visit 1 and Visit 1a will be combined. If screening (V1), and baseline and drug administration (V1a) do not occur on same day, urine pregnancy test for women of childbearing potential and urine screen for drugs of abuse must be performed at both visits (V1 and V1a). Confirmation of symptom severity must be obtained before randomization: minimum pain score of 5 on the 11-point numerical rating scale [NRS] at Screening and 15 minutes (± 5 minutes) after voiding prior to study drug administration. Subjects will become fully enrolled upon receipt of acceptable qualifying laboratory evaluations (obtained via dipstick) and clinical assessments obtained before randomization. At the Screening Visit (V1), the following will be completed: medical history and demographics; medication history; the Pelvic Pain and Urgency/Frequency (PUF) questionnaire; 11-point NRS for bladder pain and urgency; a physical examination, including a pelvic examination to confirm lower urinary tract tenderness; vital signs; blood and urine samples for safety laboratory assessments (including urine hematuria analysis); urine pregnancy test for women of childbearing potential; urine screen for drugs of abuse; and concomitant medications. (Note: results from a pelvic examination performed within 7 days prior to the Screening Visit (V1) may replace a V1 pelvic examination.) [redacted] On the day of study drug administration (V1a), subjects will be randomized (2:1:2:1); URG101:placebo:lidocaine:heparin) and will receive a single administration of one of four intravesical treatments in a blinded fashion, based on random assignment: 1. Combination product, URG101 (buffered heparin-lidocaine) 2. Placebo: [redacted] 3. Lidocaine: [redacted] 4. Heparin: [redacted] Subjects will be monitored for 2 hours in the clinic after study drug administration.

CLINICAL PROTOCOL SYNOPSIS (continued)

	Subjects will maintain a urination log and symptom diary after discharge and will return to the clinic the following day to complete the in-clinic study procedures and collection of the study diary. The following will be completed according to the schedule of assessments over a 24-hour period after study drug administration: the 11-point NRS for bladder pain and urgency; the PORIS questionnaire; vital signs assessments; blood samples for safety laboratory assessments, i.e. blood coagulation (prothrombin time [INR] and activated partial thromboplastin time [aPTT]), and plasma lidocaine concentrations; adverse events; and concomitant medication assessments. Subjects will be contacted within 48 to 72 hours after the last study treatment to follow-up on any ongoing adverse events after the last clinic visit. The clinical study will plan to randomize 180 subjects. After 90 (50%) subjects have been enrolled and treated, the IDMC will examine the conditional power and determine if a modification to the sample size is required to yield an overall power of 90%. An adjustment to the type 1 error rate will not be necessary if the conditional power is >39% at the interim assessment. The IDMC will consist of 3 members: 1 physician expert in IC/BPS, 1 expert in clinical development, and a biostatistician. None of the IDMC members will be associated with study personnel; all communication between the IDMC and study personnel will be pre-defined and governed by the IDMC charter. The IDMC will have access to unblinded pain scores to perform their ranking of the pain endpoints and for assessment of conditional power.
Estimated Number of Subjects:	A target of 180 subjects subject to adjustment by the IDMC. A maximum of 300 subjects will be enrolled in Study URG101-105.
Number of Study Sites:	Up to 30 sites in the United States and Canada
Subject Population:	Adult subjects, aged ≥ 18 years, with Interstitial Cystitis who have moderate–to-severe symptoms of pain and/or urgency of bladder origin for at least 9 months, not currently taking narcotic pain medications, meeting the minimum screening scores.
Study Drug, Dose, Formulation, Method of Administration:	URG101: buffered lidocaine and heparin, instillation via urethral catheter. URG101 treatment comprises the following: • 18 mL containing Heparin Sodium [redacted] Placebo treatment comprises the following: • 18 mL [redacted] Heparin treatment comprises the following: • 12 mL Heparin Sodium [redacted], plus 6 mL 3X [redacted] buffer [redacted] Alkalinized Lidocaine treatment comprises the following: • 12 mL Lidocaine HCl ([redacted]), plus 6 mL 3X [redacted] buffer [redacted]
Criteria for Evaluation:	**Primary Endpoint:** 1. A measure of the sum of bladder pain intensity differences from baseline to

CLINICAL PROTOCOL SYNOPSIS (continued)

	12 hours (SPID-12) after administration of URG101 compared with the SPID-12 after administration of lidocaine alone, heparin alone, and placebo as determined by using the 11-point NRS for bladder pain **Secondary Endpoints:** 1. The sum of bladder pain intensity differences from baseline to 24 hours (SPID-24) after administration of URG101 compared with lidocaine alone, heparin alone, and placebo as determined by using the 11-point bladder pain NRS 2. The sum of urgency intensity differences from baseline to 12 and 24 hours (SUID-12 and SUID-24) after administration of URG101 compared with lidocaine alone, heparin alone, and placebo using the 11-point urgency NRS 3. Absolute and percentage change in bladder pain from baseline to 1, 12, and 24 hours after administration of URG101 compared with lidocaine alone, heparin alone, and placebo as determined by using the 11-point NRS for bladder pain 4. Absolute and percentage change in urgency intensity from baseline to 1, 12, and 24 hours after administration of URG101 compared with lidocaine alone, heparin alone, and placebo using the 11-point urgency NRS 5. Patient Global Assessment: Comparison of the percentage of subjects achieving ≥ 50% improvement in the PORIS questionnaire(Question 3), from baseline to 1, 12, and 24 hours after administration of URG101, lidocaine alone, heparin alone, and placebo 6. Time to first administration of rescue medication for pain after treatment with URG101 compared to alkalinized Lidocaine Hydrochloride Injection (20 mg/mL) alone, alkalinized Heparin Sodium Injection (5,000 USPU/mL) alone, and placebo [redacted]) 7. To evaluate the safety and tolerability of intravesical administration of URG101
	Pharmacokinetic Endpoints: 1. Comparison of plasma lidocaine concentrations at 1 hour post treatment with absolute and percentage change in pain using the 11-point NRS for bladder pain at 1, 12 and 24 hours after administration of URG101, lidocaine alone, heparin alone, and placebo 2. Comparison of plasma lidocaine concentrations at 1 hour post treatment with absolute and percentage change in urgency using the 11-point NRS for urgency, at 1, 12 and 24 hours after administration of URG101, lidocaine alone, heparin alone, and placebo 3. Comparison of plasma lidocaine concentrations at 1 hour post treatment with the sum of bladder pain intensity differences from baseline to 12 and 24 hours (SPID-12 and SPID-24) after administration of URG101 compared with lidocaine alone, heparin alone, and placebo as determined by using the 11-point bladder pain NRS 4. Comparison of plasma lidocaine concentrations at 1 hour post treatment with the sum of urgency intensity differences from baseline to 12 and 24 hours (SUID-12 and SUID-24) after administration of URG101compared with lidocaine alone, heparin alone, and placebo as determined by using the 11-point urgency NRS **Safety Endpoints:** 1. Change from baseline in INR at 1 hour after study drug administration

CLINICAL PROTOCOL SYNOPSIS (continued)

	2. Change from baseline in aPTT at the 1-hour post-study-drug time point 3. Adverse events **Pharmacokinetics:** Samples for peak plasma lidocaine concentrations will be collected at baseline and at 1 hour after study drug administration. **Efficacy:** • 11-point (i.e., 0 to 10) NRS bladder pain (numerical rating scale) • 11-point (i.e., 0 to 10) NRS urge (urgency intensity) to urinate (numerical rating scale) • PORIS questionnaire **Safety:** The following safety parameters will be evaluated: • Clinical laboratory tests • Vital sign measurements • Physical examination • Incidence of adverse events, serious adverse events • INR and aPTT Follow-up will occur for subjects with clinically significant, study drug–related abnormalities at the conclusion of the study termination visit, based on the investigators discretion.
Statistical Methods:	**Sample Size Estimate** Sample size estimates were based on a pilot trial of heparin-lidocaine versus lidocaine alone and a prior two-arm study of URG101 versus placebo. The primary efficacy endpoint is SPID-12. The sample size calculation is based on a one-way analysis of variance, comparing SPID-12 from four treatment groups. A target sample size of 180 subjects to be allocated unequally among the four treatment groups as follows: URG101:placebo:lidocaine: heparin at 2:1:2:1 (60 subjects per group and 30 subjects per group). This sample size is sufficient to achieve 90% power to detect a difference between the URG101 and lidocaine groups assuming a treatment effect size of 0.60. The study will also have 90% power to detect a difference between the URG101 and each of the placebo and heparin groups assuming an effect size for these comparisons of 0.75. Once 90 subjects have been enrolled, a blinded interim analysis will take place; and, if required, the number of subjects for the study increased to a maximum of 300 subjects. **Description of Analysis Sets:** All analyses of the efficacy of URG101 will be performed on the ITT set, which will include all randomized subjects from the investigative phase of the study who receive study drug. These efficacy analyses will compare the treatment groups on the basis of randomized treatment, regardless of the treatment actually received. Primary efficacy and key secondary efficacy analyses will also be conducted on a per protocol set, which will include all subjects in the ITT set who sufficiently comply with the protocol. Safety analyses will be based on the safety analysis set which will include all subjects who receive at least one dose of study drug and have at least one post dose safety assessment in both phases of the study. Safety summaries will be produced based on study treatment actually received.

CLINICAL PROTOCOL SYNOPSIS (continued)

	Primary Efficacy Determination: The primary efficacy endpoint will be compared between the URG101 and the lidocaine, heparin, and placebo groups using an analysis of covariance model which will include factors for treatment and baseline pain values. Pairwise comparisons of least squares means between URG101 and each of the other treatment arms will be performed. If the p-value associated with these comparisons is < 0.05 in favor of URG101, the primary aim of the trial will be confirmed. Missing data for efficacy values will be imputed by the last observation carried forward method. **Secondary Efficacy Determinations:** Analyses of secondary endpoints relating to changes in the NRSs for pain and urgency will be performed using analysis of covariance models similar to that used for the primary efficacy endpoint. Nonparametric methodology in exploratory analyses may be used to supplement the parametric analyses. Treatment group comparisons relative to improvement on the PORIS questionnaire, (Question 3), will be made with standard contingency table techniques. **Pharmacokinetic Determinations:** A comparison of pain and urgency assessments as measured by 11-point NRS to plasma lidocaine concentrations at 1 hour after study drug administration will be made for the PK set.
	Safety Determinations: All safety analyses will be performed on the safety analysis set. The change in INR and aPTT at baseline and 1 hour will be compared for the various treatment groups using descriptive statistics. **Other Determinations:** Demographic and disposition data, randomization, drug administration, medical history, prior and concomitant medications, adverse events, clinical laboratory measurements, vital signs, physical examination findings, and all other safety data will be listed by subject and time point. Descriptive statistics will be tabulated for change from baseline in the vital signs. In addition to clinical and laboratory assessments, subject safety will be monitored by recording adverse events and serious adverse events throughout the study. Any pregnancy that occurs during the study will be promptly reported to the sponsor, but will not be considered a serious adverse event. Treatment-emergent adverse events will be summarized by type, frequency, severity, relationship to study drug, and number of subjects per treatment. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities.
Duration of Treatment:	Each study subject will receive a single dose of URG101, placebo ([redacted]), alkalinized Lidocaine, or alkalinized Heparin by random assignment. The randomization ratio will be 2:1:2:1, respectively.

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4.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
aPTT	activated partial thromboplastin time
AUC	area under the concentration-time curve
β-hCG	beta human chorionic gonadotropin
BPS	bladder pain syndrome
CRA	clinical research associate
CRF	case report form
DMSO	dimethyl sulfoxide
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	hydrochloride
IC	interstitial cystitis
IC/BPS	Interstitial cystitis/bladder pain syndrome
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IxRS	interactive voice or web response system
MedDRA	Medical Dictionary for Regulatory Activities
NRS	numerical rating scale
PORIS	Patient Overall Rating of Improvement of Symptoms
PT	prothrombin time
PUF	Pelvic Pain and Urgency/Frequency
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SPID-12	sum of pain intensity differences from baseline to 12 hours
SPID-24	sum of pain intensity differences from baseline to 24 hours
SUID-12	sum of urgency intensity differences from baseline to 12 hours
SUID-24	sum of urgency intensity differences from baseline to 24 hours
TEAE	treatment emergent adverse event
USP	United States Pharmacopeia
WBC	white blood cell

5.0 ETHICS

This study will be conducted in compliance with the following: the protocol; Food and Drug Administration (FDA) regulations; International Conference on Harmonisation (ICH) E6, Guideline for Good Clinical Practice; and all other applicable local laws and regulatory requirements. Each study site will seek approval by an institutional review board (IRB) or according to regional requirements. The IRB will evaluate the ethical, scientific and medical appropriateness of the study. Furthermore, in preparing and handling case report forms (CRFs), the investigator, subinvestigator, and the site staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identification code will be used to identify each subject.

5.1 INFORMED CONSENT

All subjects will have the purpose of the study, study interventions and evaluations, and the potential risks and benefits of participation explained to them and any questions will be answered. If a subject consents to participation in this study, the subject will review and sign the informed consent form (ICF).

Written informed consent will be obtained from all subjects (or their guardian or legal representative, as applicable for local laws). Consent will be documented on a written ICF. The ICF will be approved by the same IRB that approves this protocol. Each ICF will comply with the following: the FDA regulations in Title 21 Code of Federal Regulations, Part 50; ICH; Good Clinical Practice (GCP); and local regulatory requirements. The investigator agrees to obtain approval from the sponsor of any written ICF used in the study, prior to submission to the IRB.

Investigators may discuss study availability and the possibility for entry with a potential subject without first obtaining informed consent. However, informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for this study, including withdrawal from current medication(s).

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator or by a qualified designee, the IRB-approved written ICF will be signed and dated by both the subject and the person

obtaining consent (investigator or designee), as well as by any other parties required by the IRB. The subject will receive a copy of the signed ICF; the original will be kept on file by the investigator.

6.0 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Urigen N.A, Inc. (Urigen), at approximately 30 investigational sites in the United States and Canada.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) are included in the Investigator Study Files provided to each site.

7.0 INTRODUCTION

7.1 BACKGROUND

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a disease considered rare as late as 1990. The hallmarks of the disease are frequency and urgency of urination, and bladder pain of simply pelvic origin. As knowledge of the disease and its symptomology increase, the reported prevalence increases. In 1990 it was thought that 60,000 to 80,000 women in the United States had IC[1]. In 1997, it was thought to be approximately 500,000 to 1,000,000[4]. Estimates as high as one in four women can be made when utilizing a questionnaire that encompasses a more complete battery of IC symptoms[1,7]. This increase in reported prevalence is primarily due to a change in awareness of the disease. Traditionally, IC was diagnosed only in severe patients with a destroyed bladder, and considered to be relatively rare. It is currently widely accepted that IC includes many patients with mild, intermittent, and severe forms of the disease[7,8]. Most patients with IC have low-grade bladder symptoms (3 on a scale of 0 to 10) punctuated by intense flares of 8 to 10 out of 10 that last from 3 days to 3 weeks and may occur infrequently or as often as five to eight times per year. These flares are often incorrectly diagnosed.

Currently, since many of these IC flares are misdiagnosed as urinary infections in women and often as prostatitis in men, several billion dollars in treatments are inappropriately prescribed to these patients that offer no relief.

For the unfortunate patient with severe disease living daily with pain scores of 8, 9, or 10 out of 10, there is little or no relief or effective therapy available to relieve these intense symptom flares. Drugs such as pyridium and urelle offer minimal urinary analgesia. Anticholinergic and antimuscarinic compounds have limited or no success in the treatment of pain in IC/BPS.

Opiates have been utilized but have limited success and are not optimum drugs to employ. Because opiates can, in time, upregulate sensory nerves due to dependency, the patient's pain will become resistant relatively quickly as tolerance to the drug grows; the patient will become addicted to the medications. In addition, opiates can significantly impair a patient's mental faculties, and overall functioning will be markedly affected. Neural stimulators such as Interstim® might help temporarily with frequency and urgency, but have little or no activity on small unmyelinated C fibers

(pain fibers) because they do not originate in the sacral nerves being stimulated. Patients who are considered to be surviving this disease have a quality of life reported to be worse than that of dialysis patients and unfortunately many have committed suicide[16].

There are currently two FDA-approved therapies for the symptoms of bladder pain of IC: oral Elmiron® capsules (pentosan polysulfate sodium) and intravesical RIMSO®-50 and its generics (50% dimethyl sulfoxide [DMSO]).

Elmiron is a synthetic heparinoid-like molecule that is thought to work by augmenting the mucus layer with heparin and, thus may provide a physicochemical barrier to the penetration of the urinary solutes to the bladder wall[21]. According to the product label, the efficacy of Elmiron was evaluable at 3 months, with 38% of patients achieving greater than 50% improvement in bladder pain versus 18% for placebo-treated patients. In a dose-ranging study of Elmiron, Nickel et al.[1] observed a response rate of about 20% at 1 month of treatment that increased to approximately 60% at 8 months, resulting in their conclusion that chronic duration of therapy is more important than dosage.

Intravesical treatment with RIMSO-50 (50% DMSO) was approved by the FDA in 1978 for symptomatic treatment of IC. Its exact mechanism of action is unclear, and six to eight weekly bladder instillations are required. After each instillation, patients exhibit an unpleasant garlic-like odor, and the majority of patients complain of significant discomfort both during and after each treatment (RIMSO-50 product label). Perez-Marrero et al.[11] conducted a placebo-controlled study of 50% DMSO for IC, during which subjects received intravesical instillations of study drug or saline placebo every 2 weeks for two sessions of four treatments each. A total of 53% of DMSO treated patients exhibited "marked improvement" versus 18% for placebo treated patients. Nevertheless, most urologists view current IC treatment options as unsatisfactory, as exemplified by the Mayer et al.[2] statement: "Effective medical treatment for patients with moderate to severe IC remains elusive."

Buffered lidocaine-heparin (intravesical instillation) URG 101, is proposed as an investigational new drug for the treatment of pelvic pain and urgency of bladder origin. All components of the investigational solution are currently FDA approved for other indications. Lidocaine Hydrochloride (HCl) is a local anesthesia for pain control during surgical procedures and for topical applications. Heparin sodium is an

anticoagulant for the prevention and treatment of thrombotic conditions such as pulmonary embolism and arteriovenous thrombosis. The proposed use of buffered lidocaine-heparin is based on both open-label clinical experience[12,13], and on Urigen's double-blind placebo-controlled study, URG101-101, in subjects with symptoms of pelvic pain and urgency. In this study, subjects experienced immediate symptom relief; improvement in urgency for drug versus placebo achieved statistical significance ($p = 0.006$) and trended to improvement in pain ($p = 0.093$). A recent, multisite, double-blind study using a single dose of URG101 versus placebo showed a significant reduction in pain and urgency ($p = 0.03$)[20].

URG101 (alkalinized lidocaine-heparin) is a combination therapy for relief of symptoms of pain and urgency associated with interstitial cystitis/bladder pain syndrome. The formulation is instilled directly into the bladder, with the lidocaine modulating bladder neural hyperactivity that is often associated with bladder pain and urgency, urge, and muscle spasms. Heparin (chemically similar to Elmiron, which is approved for IC) augments natural heparinoids on the surface of the urothelium to limit urinary potassium and other urinary toxins from penetrating to the underlying tissues.

Since the two FDA-approved therapeutics, RIMSO-50 and Elmiron, require chronic administration for any benefit to develop, there is no treatment for pain other than narcotics. Consequently, alkalinized lidocaine-heparin provides relief over both a short-term and medium-term time period, for which there is no current FDA-approved therapy. URG101 offers the first relief that is effective and that downregulates sensory nerves without rebound[13].

We propose that URG101 will meet a serious need in this patient population for the following reasons: (1) the millions of people afflicted with IC; (2) no effective therapy for severe symptom flares; (3) reduced quality of life; (4) the wasted use of antibiotics to treat nonexistent infections; and (5) very real suicide threat in patients with severe symptoms.

7.2 URG101

The individual components of this combination therapy, Lidocaine HCl and heparin sodium, are FDA-approved products for use as a local anesthetic and an anticoagulant, respectively. It was demonstrated that when these components were mixed together and buffered by the addition of sodium bicarbonate, the resultant solution reduced symptoms of pelvic pain and urgency upon instillation into a subject's bladder[12]. Most subjects exhibit both an acute benefit as well as sustained benefit from single and multiple treatments[13,20]. This multimodal therapy achieves acute benefit for subjects who have no standard acute treatment for pelvic pain and urgency of bladder origin.

The rationale for this combination therapy is twofold. Lidocaine, a local anesthetic, traverses the urothelium when uncharged at alkaline pH, reversing the local neural hyperactivity of the bladder neurons and, thereby reducing the sensations of pain and urge, and also reducing muscle spasms. Heparin, a glycosaminoglycan, augments natural heparinoids that may be deficient on the surface of the urothelium. Heparinoids are part of the mucus layer of the urothelium and help to limit urinary solutes such as urea and potassium from penetrating to the underlying tissues thereby preventing pain, tissue inflammation, and muscle spasms[21].

7.3 CLINICAL EXPERIENCE WITH URG101

Previously, URG101 was studied in open-label clinical studies at the University of California – San Diego[13] and in a controlled Phase 2 multicenter trial sponsored by Urigen. These studies demonstrated that URG101 was safe and well tolerated. No serious adverse events (SAEs) or unexpected adverse events (AEs) or significant changes in blood coagulation were observed, demonstrating that heparin in the bladder does not appreciably enter into systemic circulation.

[redacted]

In the URG101-104 study, a multicenter, single-dose, cross-over, double-blind, placebo-controlled study, followed by one open label treatment, a total of 28 subjects were enrolled[20]. The study was terminated early due to a recall of heparin with no suitable replacement, and the planned interim analysis became the final unblinded analysis. Statistical significance was achieved for the primary endpoint (i.e., average percentage change in pain from 0.5 to 12 hours), was 42% on URG101 compared with 21% on placebo ($p = 0.03$). Similar results were seen with the secondary endpoints of ≥ 50% overall improvement ($p = 0.01$) and average percentage change in pain plus urge and urge alone ($p = 0.03$).

7.4 RISKS AND BENEFITS

The study drug components (Lidocaine Hydrochloride and Heparin Sodium) both have extensive previous human experience since their United States approvals in 1948 and 1939, respectively. Additionally, both of these drugs are normally administered via parenteral injection, whereas intravesical alkalinized lidocaine-heparin is administered into the lumen of the bladder and only comes into contact with the urothelium.

Lidocaine is a well-characterized small molecule drug used for local anesthesia. The uncharged form of lidocaine is able to traverse membranes and enter into systemic circulation. AEs are primarily dose-related upon reaching a 6-µg/mL serum lidocaine concentration. The maximum recommended intravenous dose for adults is 300 mg, which is well above the 200 mg lidocaine dose in URG101. Additionally, intravenous lidocaine is also a class I antiarrhythmic and is often used simultaneously with intravenous heparin in the acute care setting after myocardial infarction. Heparin (a large, naturally sulfated polysaccharide) is an intravenous anticoagulant used for the prophylaxis and treatment of arterial or venous thrombosis and coagulopathies. Heparin's large size prevents it from being absorbed across epithelial surfaces.

The previous human experience of intravesical buffered lidocaine-heparin in the URG101-101 study involved 43 subjects on active drug. The intravesical instillation of buffered lidocaine-heparin (160 mg lidocaine, 40,000 units heparin, pH 7.8) did not alter the prothrombin time (PT) and activated partial thromboplastin time (aPTT) of these subjects, consistent with the heparin component not entering systemic circulation. Monitoring of serum lidocaine concentrations at 1 hour demonstrated

that the serum lidocaine concentrations were < 1.0 µg/mL for most subjects (32 of 43), with only 11 subjects with serum lidocaine concentrations > 1.0 µg/mL, and the highest concentration of 1.5 µg/mL. In the URG101-104 study serum levels of lidocaine ranged from 0.24 to 2.0 µg/mL, with an average of 0.51 µg/mL, and neither the aPTT nor the PT was altered in any subject[20]. These serum lidocaine concentrations are well below the toxic 6-µg/mL concentration for lidocaine and changes in bleeding parameters have not been seen; therefore, the lidocaine and heparin in URG101 do not pose an unacceptable safety risk.

In summary, buffered lidocaine-heparin provides relief of bladder pain and urgency over both short-term and medium-term time periods, for which there is no currently FDA-approved therapy, and thus may be beneficial for individuals with chronic pelvic pain of bladder origin.

7.5 STUDY RATIONALE

7.5.1 Rationale for Dose

Intravesically administered heparin is safe because it is a large molecule, will not penetrate the bladder epithelium, and will not be observed systemically; therefore, it is in essence, a topical therapy. This was substantiated by the two Phase 2 clinical trials previously conducted by Urigen. A total of 90 subjects received a dose of 40,000 units of heparin, and 28 subjects received a total of 51 exposures to 50,000 units of heparin. Plasma INR and aPTT were unchanged after administration of drug in all subjects. In extensive experience at University of California – San Diego, the higher doses of heparin were more effective than the lower doses.

Unlike intravesically instilled heparin, lidocaine has potential toxicity if the serum concentrations exceed 6 µg/mL. In one reported trial[17], up to 6 mg lidocaine (approximately 300 to 400 mg total dose) per kg of body weight was given to 12 subjects. Serum lidocaine concentrations were measured for 3 hours after administration. The highest serum concentration observed was 1.7 µg/mL, which was well below the level where symptoms may occur. In the Urigen Phase 2 studies, the highest lidocaine dose administered was 200 mg. In all subjects receiving the drug, lidocaine concentrations were < 2.0 µg/mL which were well below the concentrations that are associated with safety issues. In the Urigen URG101-104 study, 50% of subjects experienced relief of symptoms (i.e., 50% reduction overall)

after a single administration of URG101 containing 50,000 units of heparin and 200 mg lidocaine[20]. The placebo arm showed only an 11% reduction in symptoms. These data revealed the greatest difference in relief of symptoms between drug and placebo for any therapeutic trial conducted in IC. As a result of these data, 50,000 units of heparin combined with 200 mg lidocaine is the proposed dose for the Phase 2a URG101-105 study since excellent efficacy is seen at this dose, along with very safe serum lidocaine concentrations, no changes in bleeding parameters, and no significant symptoms or toxicities.

7.5.2 Rationale for Single Dose

The Urigen Study URG101-101 revealed a 51% placebo response rate. This was seen throughout the study, with the exception of one study site. This site enrolled subjects with severe IC/BPS, where the placebo response was 20% in keeping with prior studies with subjects with severe disease. [redacted] There is currently no effective therapy to relieve these intense symptom flares.

It is proposed, therefore, to perform a single-dose study to document the effectiveness of URG101 in relieving the intense flare in subjects with IC.

7.5.3 Rationale for Study Endpoint

Pain and urgency analog scales were used in the clinical trials that were the basis of the Elmiron approval and were reliable outcome measures[16]. The global assessment of symptoms (also known as the Patient Overall Rating of Improvement in Symptoms [PORIS] questionnaire) was also part of the basis for the ultimate FDA approval of Elmiron for sale in the United States. This endpoint was validated statistically[19] and was found to be a sensitive and reliable outcome measure. This endpoint was also used for several therapeutic trials conducted by the National Institute of Diabetes and Digestive and Kidney Diseases clinical trials collaborative group[11]. Both the analog scales and the PORIS questionnaire were utilized in Study URG101-104 with successful outcomes. For the proposed Phase 2a (Study URG101-105) clinical trial with URG101, the numerical rating scales (NRSs) for bladder pain will be employed

as the basis for the primary outcome measure, and the urgency NRS, the PORIS questionnaire and frequency will be used for secondary endpoints. Urination diaries will be collected for information purposes.

8.0 STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective of the study is as follows:

1. To evaluate the change in sum of bladder pain intensity differences from baseline to 12 hours (SPID-12) after administration of URG101 compared with the SPID-12 after administration of lidocaine alone, heparin alone, and placebo as determined by using the 11-point NRS for bladder pain. The IDMC will establish the exact primary endpoint based on the data recorded during the run-in phase of the study. The SPID score that is not determined by the IDMC as the primary endpoint will be considered the first secondary endpoint.

8.2 SECONDARY OBJECTIVES

The secondary objectives of the study are as follows:

1. To evaluate the change in bladder pain from baseline to 24 hours, using the sum of pain intensity differences (SPID-24) at defined time points, after administration of intravesical URG101 compared with alkalinized Lidocaine Hydrochloride Injection (20 mg/mL) alone, alkalinized Heparin Sodium Injection (5,000 USPU/mL) alone, and placebo [redacted]

2. To evaluate the change in urgency from baseline to 12 and 24 hours, using the sum of urgency intensity differences (SUID) at defined time points, after administration of URG101 compared with alkalinized Lidocaine Hydrochloride Injection (20 mg/mL) alone, alkalinized Heparin Sodium Injection (5,000 USPU/mL) alone, and placebo [redacted]

3. To evaluate the absolute and percentage change in bladder pain and urgency intensity differences at 1, 12, and 24 hours after administration of URG101 compared with alkalinized Lidocaine Hydrochloride Injection USP (20 mg/mL) alone, alkalinized Heparin Sodium Injection USP (5,000 USPU/mL) alone, and placebo ([redacted])

4. To evaluate the change in improvement of symptoms using the Patient Global Assessment (question number 3) after treatment with URG101 compared with alkalinized Lidocaine Hydrochloride Injection (20 mg/mL) alone, alkalinized

Heparin Sodium Injection (5,000 USPU/mL) alone, and placebo ([redacted]) at 1, 12, and 24 hours

5. To evaluate the time to first administration of rescue medication for pain after treatment with URG101 compared to alkalinized Lidocaine Hydrochloride Injection (20 mg/mL) alone, alkalinized Heparin Sodium Injection (5,000 USPU/mL) alone, and placebo ([redacted])
6. To investigate the relationship of plasma lidocaine concentrations at 1 hour after study drug administration to bladder pain and urgency at 1 hour, and from baseline to 12 and 24 hours, using the sum of pain and urgency intensity differences at defined time points, after treatment with URG101compared with alkalinized Lidocaine Hydrochloride Injection USP (20 mg/mL) alone, alkalinized Heparin Sodium Injection USP (5,000 USPU/mL) alone, and placebo ([redacted])
7. To evaluate the safety and tolerability of intravesical administration of URG101

9.0 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN

This is a phase 2a, prospective, randomized, double-blind, placebo-controlled, multicenter, single-dose, pharmacokinetic study designed to determine the efficacy and safety of the combination product (URG101) versus its alkalinized individual components (Heparin Sodium and Lidocaine Hydrochloride) and placebo [redacted].

In this study, alkalinized Lidocaine Hydrochloride Injection (20 mg/mL) and alkalinized Heparin Sodium Injection (5,000 USP U/mL) will be subsequently referred to by the drug names alkalinized Lidocaine and alkalinized Heparin.

Eligible subjects exhibiting interstitial cystitis symptoms who have signed informed consent, will be screened and provisionally enrolled for intravesical treatment. Treatment may occur on the day of the Screening Visit (Visit 1) or any following day up to 1 week (Baseline and Drug Administration, Visit 1a). **If drug administration occurs on same day as screening then all assessments in Visit 1 and Visit 1a will be combined.** Confirmation of symptom severity must be obtained before randomization: minimum pain score of 5 on the 11-point numerical rating scale [NRS] at Screening and 15 minutes (± 5 minutes) after voiding prior to study drug administration. There is no minimum score requirement for the urgency NRS scales for patients to enter the study. Subjects will become fully enrolled upon receipt of acceptable qualifying laboratory evaluations and clinical assessments obtained before randomization.

On the day of study drug administration (V1a), subjects will be randomized (2:1:2:1; URG101:placebo:lidocaine:heparin) and will receive a single administration of one of four intravesical treatments in a blinded fashion, based on random assignment:

1. URG101 (buffered lidocaine-heparin)
2. Placebo: [redacted]
3. Lidocaine alone: [redacted]
4. Heparin alone: [redacted]

During the study, subjects will be allowed to take their protocol-allowed medications at their ususal doses. Additionally, they may use only a short acting non-steroidal anti-inflammatory drugs (NSAIDs) as rescue medication, not sooner than 8 hours after receiving study medication and not within 6 hours prior to receiving study medication (Table 1).

9.1.1 Screening (Visit 1)

The purpose of the Screening Visit is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study is fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.1.

At the Screening Visit (V1), the following will be completed:

- medical history and demographics;
- medication history;
- the Pelvic Pain and Urgency/Frequency (PUF) questionnaire;
- 11-point NRS for bladder pain and urgency;
- a physical examination, including a pelvic examination (which may be performed without speculum) to confirm lower urinary tract tenderness and vital signs (i.e., systolic and diastolic blood pressure, heart rate, respiratory rate, and oral body temperature); Results from a pelvic examination performed within 7 days prior to the Screening Visit (V1) may replace a V1 pelvic examination.;
- blood and urine samples for safety laboratory assessments (including urine hematuria analysis);
- urine pregnancy test for women of childbearing potential;
- urine screen for drugs of abuse;
- adverse events;
- and concomitant medications.

With the exception of qualifying results for hematuria, drugs of abuse and pregnancy, no other clinical laboratory results are required prior to randomization.

9.1.2 Baseline and Single-Dose Administration (Visit 1a)

Randomization will occur after receipt of adequate qualifying urinalysis test results for drugs of abuse, hematuria and pregnancy and completion of qualifying assessments as documented in Section 9.3. Study drug administration may occur on the day of screening or on any following day up to 1 week after screening, depending on the qualifying day of dosing residual urine assessment and 11-point bladder pain and urgency analog scales, which are administered 15 minutes (± 5 minutes) after voiding just prior to administration of study drug.

The following assessments will occur at the site prior to study drug administration (Table 4):

- urine pregnancy test for women of childbearing potential (must be repeated at V1a if screening [V1] does not occur on the same day as baseline and drug administration [V1a]);
- urine screen for drugs of abuse (must be repeated at V1a if screening [V1] does not occur on the same day as baseline and drug administration [V1a]);
- [redacted]
- dispense urination log and symptom diary;
- 11-point NRS for bladder pain and urgency [redacted] prior to study drug administration [time 0]);
- vital signs measurements (i.e., systolic and diastolic blood pressure, heart rate, respiratory rate, and oral body temperature). Measurements will be obtained immediately prior to study drug administration (time 0);
- blood sample collection for prothrombin time (INR) and activated partial thromboplastin time (aPTT) prior to the dose at time 0;

- blood sample collection for plasma lidocaine prior to the dose at time 0;
- randomization;
- catheter tolerance assessment;

The following assessments will occur at the site after study drug administration (Table 4):

- study drug administration via urethral catheter installation (the study medication should left indwelling for 45 minutes [but not less than 30 minutes] before voiding);
- 11-point NRS for bladder pain and urgency 30 minutes (± 5 minutes), 1 hour (± 5 minutes), 2 hours (± 10 minutes) after study drug administration;
- blood sample collection for prothrombin time (INR) and activated partial thromboplastin time (aPTT) at 1 hour (± 10 minutes) after study drug administration;
- blood sample collection for plasma lidocaine at 1 hour (± 10 minutes) after study drug administration;
- the PORIS questionnaire at 1 hour (± 15 minutes) after study drug administration;
- vital signs measurements (i.e., systolic and diastolic blood pressure, heart rate, respiratory rate, and oral body temperature) will be obtained at 1 hour (± 15 minutes) after study drug administration;
- concomitant medications;
- and adverse events.

9.1.3 Home Assessment

After instructions, the subjects will be discharged from the clinic and reminded to

return the next day for the optional 24 hour Follow-up Visit. However, return of subject diaries including 24 hour assessments are mandatory. All assessments and their respective timing are provided in Table 4. The following assessments will occur >2 hours post study drug administration but before 24-hour Follow-up Visit (V2):

- 11-point NRS for bladder pain and urgency at 4 hours (± 30 minutes), 6 hours (± 30 minutes), 8 hours (± 30 minutes), 10 hours (± 30 minutes), and 12 hours (± 30 minutes) (only during times the subject is awake);
- the PORIS questionnaire at 12 hours after study drug administration or before the subject goes to bed for the evening;
- urination log;
- adverse event reporting;
- and concomitant medications.

9.1.4 24-Hour Follow-up Visit (Visit 2; Optional)

Approximately 24 hours after study drug administration, the subjects will return to the clinic for end-of-study assessments. The following assessments will occur:

- subject's diary collection is mandatory to evaluate the efficacy of URG101;
- 11-point NRS for bladder pain and urgency at 24 hours (± 2 hours) is mandatory to be completed and returned;
- the PORIS questionnaire at 24 hours (± 2 hours) after study drug administration is mandatory to be completed and returned;
- vital signs measurements at 24 hours (± 2 hours) after study drug administration (i.e., systolic and diastolic blood pressure, heart rate, respiratory rate, and oral body temperature) is optional;
- and recording of any adverse events or concomitant medications is mandatory to be collected and returned for safety evaluation.

In the opinion of the Investigator, if the subject appears responsible to perform the 24 hour assessments, correctly fill out the diary for all of the at home assessments, and the Investigator and the subject have made acceptable arrangements for the return of the diaries, answering of any follow up questions, and for the subject's treatment and care after 24 hours, then Visit 2 may be considered an optional protocol visit to the clinic.

9.1.5 End-of Study Follow-up

The site staff will call each subject within 48 to 72 hours of study drug administration to check on subject status and to ascertain AE and concomitant medication status.

9.1.6 Interim Study Analysis

After recruitment and treatment of the first ~90 (50%) of the planned 180 subjects, the IDMC will examine the conditional power and determine if a modification to the sample size up to 300 subjects is required to yield an overall power of 90%. An adjustment to the type 1 error rate will not be necessary if the conditional power is >39% at the interim assessment.

The IDMC will consist of 3 members: 1 physician expert in IC/BPS, 1 expert in clinical development, and a biostatistician. None of the IDMC members will be associated with study personnel; all communication between the IDMC and study personnel will be pre-defined and governed by the IDMC charter. The IDMC will have access to unblinded pain scores to perform their assessment of conditional power.

9.2 DISCUSSION OF STUDY DESIGN INCLUDING CHOICE OF CONTROL GROUPS

The URG101 drug product contains the active ingredients, heparin and lidocaine, buffered to a pH of 7.4 (± 0.2). The anesthetic effect of lidocaine is anticipated to provide primary symptom relief of anesthetizing and "down-regulating" the bladder sensory nerves[13,15,17,20]. Heparin is expected to potentiate this effect by coating the bladder epithelium and reducing the leak of additional potassium that would provoke

the nerves and initiate more symptoms. It is unlikely that heparin alone could provide much in the way of relief since the bladder sensory nerves would still remain "up-regulated" and volume sensitive even though the heparin would reduce the potassium leak. In a clinical trial that evaluated intravesical heparin, there was only minimal benefit, and most of the benefit of chronically administered heparin was after many months of use[18]. Therapeutic trials in this population are difficult to conduct due to recruitment issues. It has been shown that it can take more than 3 years to accrue 125 subjects with up to 10 active sites involved[9].

A practical solution is proposed to evaluate the contribution of the components which is a four-arm study: (1) combination product, URG101, heparin-lidocaine buffered to pH 7.4 (± 0.2); (2) placebo [redacted] pH 7.4 [± 0.2]); (3) lidocaine buffered to pH 7.4 ± 0.2; and (4) heparin buffered to pH 7.4 (± 0.2). Such a study would answer this critical question: Does heparin potentiate the lidocaine effect and justify the combination of the drugs?

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are equal across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

9.3 SELECTION OF STUDY POPULATION

An estimated 180 subjects will be randomized at approximately 30 sites. A maximum of 300 subjects will be enrolled as determined by the IDMC. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects diagnosed with interstitial cystitis/bladder pain syndrome must meet all of the following criteria to participate in the study:

1. Have provided written informed consent to participate in this trial

2. Be male or female, ≥ 18 years of age

3. Have moderate-to-severe symptoms of bladder pain of bladder origin for at least 9 months prior to the study

4. May or may not have received a cystoscopy in association with their diagnosis of interstitial cystitis/bladder pain syndrome prior to or at time of screening

5. Have a score of ≥ 15 and < 30 on the PUF questionnaire, completed at screening

6. A minimum score of 5 is required on the 11-point bladder pain NRS

7. Have been using a stable dose of hormone therapy for ≥ 3 months, if female and currently taking hormone therapy (postmenopausal women who have not been stabilized on a regimen of hormone replacement therapy within 3 months of screening will not be included)

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. For females, have a positive pregnancy test at screening or be pregnant or lactating

   Note: Females considered to be of child-bearing potential must commit to using a consistent and medically acceptable method of birth control for the duration of the study: hormonal (i.e., oral, transdermal patch, implant, or injection) on a stable dose for at least 3 months prior to screening; double barrier (i.e., condom with spermicide or diaphragm with spermicide) consistently for at least 2 weeks prior to screening; and intrauterine device for at least 3 months prior to screening; or only have a partner who has been vasectomized for at least 6 months prior to screening or exclusively has same-sex partners. Females considered to be of non-childbearing potential include: at least 1 year postmenopausal; surgically sterile (tubal ligation, bilateral oophorectomy, salpingectomy, of hysterectomy); congenitally sterile; diagnosed as infertile and not undergoing treatment to reverse infertility. If male and sexually active, the patient is willing to commit to an acceptable method of birth control for the duration of the study or exclusively has same-sex partners.

2. Have a known hypersensitivity to heparin or lidocaine

3. Have used any local anesthetic by any route within 24 hours prior to study drug administration, or used a lidocaine patch within 14 days prior to study drug administration

4. Have used a tricyclic antidepressant, or a gamma-Aminobutyric acid (GABA) analogue (gabapentin or pregabalin), unless taking a stable dose of the medication for ≥ 3 weeks. The stable dose of gabapentin may not exceed 1,200 mg per day, and the stable dose of pregabalin may not exceed 150 mg per day.

5. Have used any pain medication within 6 hours prior to study drug administration

6. Have used narcotics or medical marijuana ≤ 3 weeks prior to study entry (generic names: fentanyl, hydrocodone, hydromorphone, levorphanol, medical marijuana, methadone, morphine, oxycodone, propoxyphene, tramadol). Subjects who have received codeine within this time period may be admitted if the use is not chronic, and not within 6 hours of enrollment, such that they are not at risk for GI or opiate withdrawal symptoms that in the opinion of the investigator would impact the subject's study participation due to their ability to follow the study protocol or bias study results.

7. Have used prohibited drugs as determined by self-report, positive urine drug screen, or in the opinion of the investigator be under the influence of drugs affecting mentation precluding their ability to follow the study protocol or bias study results

8. Have a known clinically significant abnormal laboratory test value defined by the investigator (If a known clinically significant abnormal laboratory value exists, the investigator can request a waiver from the medical monitor. The subject may not continue in the study without an approval waiver from the medical monitor)

9. Have a neurogenic bladder or other disorder that, in the opinion of the investigator, may cause neurogenic bladder (including Parkinson's disease, multiple sclerosis, epilepsy, myasthenia gravis, movement disorders, spinal cord damage)

10. Have pain or a pain disorder that, in the opinion of the investigator, would make it difficult to discriminate pelvic pain of bladder origin from the other pain

11. Have any of the following CNS conditions that in the opinion of the investigator would impact the subject's study participation due to their ability to follow the

study protocol or bias study results, severe diagnosed: major depressive disorder, bipolar disorder, schizophrenia, general anxiety disorder, attention deficit disorder, obsessive compulsive disorder, or other major central nervous system disorder

12. Have history of arrhythmias, conduction disturbances, or cardiac disease, or any coexisting medical condition that, in the opinion of the investigator, may be significant or interfere with study procedures or interpretation of study results

13. Had bladder instillation therapy within 7 days prior to study entry or had a prior bladder instillation with heparin and lidocaine and did not respond

14. Had dilatation (hydrodistention) of bladder within 3 months of study entry

15. Evidence or suspected presence of cancer detected during cystoscopy prior to or at time of initial screening.

16. Has received any investigational drug or device within 30 days prior to screening

17. Is currently enrolled in another investigational drug or device study

18. Is unwilling or unable to abide by the requirements of the study

19. Have an actively bleeding lesion or area in the bladder as detected by dipstick urinalysis and investigator assessment, immediately prior to randomization (Section 9.5.1.5. If the investigator determines that active bleeding is not occurring and that it is safe for the subject, the subject may continue in the study.)

20. Have had any of the following:

    - Bacterial cystitis within 30 days as demonstrated by a positive urine culture ($\geq 10^5$ bacteria per mL)
    - History of pelvic irradiation or radiation cystitis
    - History or presence of uterine, cervical, pelvic, rectal, ovarian or vaginal cancer
    - History of benign or malignant bladder tumors
    - Current chemotherapy
    - History or presence of tuberculous cystitis

- History or presence of chemical cystitis, including that due to cyclophosphamide
- History or presence of urinary schistosomiasis
- Bladder or ureteral calculi
- Clinically significant infectious vaginitis
- Currently uncontrolled genital herpes
- History or presence of urethral diverticulum
- Presence of bladder fistulae
- History of ketamine use

Immediately prior to receiving treatment of study drug, subjects will be re-evaluated as follows: Subjects will be asked to void; 15 minutes (± 5 minutes) after voiding, their urinary bladder volume will be measured to rule out diuresis by using an ultrasonic bladder scan or by inserting a catheter and collecting urine. The 11-point bladder pain NRS will also be administered at this time. Subjects will be excluded based on the following criteria:

- Score of < 5 on the 11-point bladder pain NRS (Note: No minimum is needed for urgency NRS.)
- [redacted]
- Significant urethral discomfort upon urethral catheterization

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may withdraw from the study at any time for any reason.

9.3.3.1 Entire Study or Treatment Arm(s)

If Urigen terminates or suspends the study for safety or unanticipated other reasons,

prompt notification will be given to IRBs, and regulatory authorities in accordance with regulatory requirements.

9.3.3.2 Individual Center

The investigator will notify Urigen promptly if the study is terminated by the investigator or the IRB at the site.

9.3.3.3 Individual Subject

If a subject discontinues from the study prematurely, the reason must be fully evaluated and recorded appropriately in source documents and the CRF. If the subject is being withdrawn because of an AE, that AE should be indicated as the reason for withdrawal.

Any episodes of suicidal ideation or homicidal ideation will result in withdrawal from the study, based on the investigator's discretion.

All subjects have the right to withdraw at any point during treatment without prejudice. The investigator can discontinue a subject's participation in the study at any time if medically necessary. In addition, subjects meeting the following criteria must be withdrawn from the study:

1. Occurrence of any AE, intercurrent illness or abnormality in a laboratory assessment which, in the opinion of the investigator, warrants the subject's permanent withdrawal from the study

2. Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator

3. Subject noncompliance, defined as refusal or inability to adhere to the study schedule or procedures per the investigator's discretion

4. At the request of the subject, investigator, Urigen or designee, or regulatory authority

5. Subject becomes pregnant

6. Subject is lost to follow-up

The investigator will notify Urigen promptly when a subject is withdrawn.

9.4 TREATMENTS

9.4.1 Treatments Administered

The study drugs will be blinded and assigned to each subject based on the randomization schedule. The contents of each kit will be admixed immediately prior to administration by the investigator who will administer the drug to the patient at no colder than room temperature. The following treatments will be administered as a single dose via urethral catheter:

- URG101 treatment comprises the following:
  - 18 mL containing heparin sodium [redacted] Lidocaine HCl buffered to pH 7.4 (± 0.2) with 1X [redacted] buffer, [redacted]
- Placebo treatment comprises the following:
  - 18 mL 1X [redacted] buffer (pH 7.4 [± 0.2])
- Heparin treatment comprises the following:
  - 12 mL Heparin Sodium [redacted] plus 6 mL 3X [redacted] buffer (final mixture buffered to pH 7.4 [± 0.2])
- Lidocaine treatment comprises the following:
  - 12 mL Lidocaine HCl [redacted] plus 6 mL 3X [redacted] buffer (final mixture buffered to pH 7.4 [± 0.2])

Prior to administering drug each subject will empty their bladder. Fifteen minutes later (± 5 minutes), the subject will complete the 11-point bladder pain NRS (requires a score of ≥ 5.0 to enter the trial and receive drug) and the 11-point urgency NRS (critical to administer 15 minutes (± 5 minutes) after voiding but no minimum score is required for study entry). These NRS scores will be the baseline scores for pain and

urgency. [redacted] The study medication is to be left indwelling for 45 minutes, with a minimum of 30 minutes, and after that may be voided by the subject. The test instruments will then be administered at the intervals listed in the schedule of assessments (Table 4).

9.4.2 Identity and Storage of Investigational Products

URG 101, Lidocaine HCl Injection, Heparin Sodium Injection, Placebo (1x [redacted]) and diluent buffers (3X [redacted]) will be prepared by a Good Manufacturing Practice compliant contract manufacturing organization and shipped to the designated responsible person at each site for oversight and preparation of the medications for patient treatments as described in the Study Procedures Manual. A study drug preparation log and inventory accountability record of drug supplies will be kept at the clinical site or the pharmacy associated with the site.

9.4.3 Labeling of Investigational Products

All study drug will be labeled in accordance with text that is in full compliance with FDA regulations.

9.4.4 Storage Conditions

Drug kits will be stored at room temperature on-site in the clinic in an area accessible only to site staff.

Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range of 15 to 25C. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained. The temperature should be monitored continuously by using either an in-house–validated data acquisition

system, a mechanical recording device (such as a calibrated chart recorder), or manual means, so that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.5 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated, randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

After the baseline period, subjects will be randomized to one of four treatment groups. Each treatment group will receive either URG101, placebo, lidocaine, or heparin as a single dose. The randomization ratio of the study is 2:1:2:1.

Randomization will be performed centrally by an interactive web response system (IWRS). The randomization schedule will be designed to randomly assign subjects to one of four treatment groups. The IWRS will generate the randomized identification numbers. At the time of randomization, the investigator or designee will use IWRS to register the subject information. The IWRS will assign each subject a unique 6-digit randomization number.

9.4.6 Prior and Concomitant Therapy

9.4.6.1 Prohibited Medications

Prohibited medications or therapies and restrictions for any drugs prior to receiving the double-blind study drug are provided in Table 1.

Table 1. Prohibited Concomitant Medications and Restrictions

Medication or therapy	Restrictions and timing with respect to study drug administration
Local anesthetic via any route	Within 24 hours
Lidocaine patch	Within 14 days
Tricyclic antidepressants	Prohibited unless the subject has been on a stable dose of the medication for ≥ 3 weeks
Gabapentin	Prohibited unless the subject has been on a stable dose ≤1200 mg daily for ≥ 3 weeks
Pregabalin	Prohibited unless the subject has been on a stable dose ≤150 mg daily for ≥ 3 weeks
Any pain medication other than short acting NSAIDs	Within 6 hours
Short acting NSAIDs	Within 6 hours but may be used as rescue medication 8 hours after study drug administration
Narcotics or medical marijuana	Within 3 weeks, except subjects on codeine may be admitted if use within this time period is not chronic and not within 6 hours of enrollment
Illegal drugs	Prohibited
Bladder instillation therapy	Within 7 days
Investigational device or drug	Within 30 days

9.4.7 Treatment Compliance

All study drug administration will be performed at the clinical site. Details of the study drug administration will be recorded on the CRF.

9.4.8 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator, or if regionally required, the head of the medical institution or the designated pharmacist, until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the institutional review board (IRB) or independent ethics committee (IEC) for the institution where the study is to be conducted

- A copy of the IRB- or IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB or IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Form FDA 1572, where applicable
- Financial Disclosure form(s) for the investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the investigator including a copy of the investigator's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical trials agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the import license (if required)

The investigator and the study staff, or if regionally required, the head of the medical institution or the designated pharmacist, will be responsible for the accountability of all study drugs and study supplies (dispensing, inventory, and record keeping) adherence to the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs or study supplies to be used other than as directed by this protocol. Study drugs and study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs and study supplies, dispensing of study drugs and study supplies to the subject, collection and reconciliation of unused study drugs and study supplies that are either returned by the subjects or shipped to the site but not dispensed to subjects, and return of reconciled study drugs and study supplies to the sponsor or (where applicable) destruction of reconciled study drugs and study supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs and study supplies, (b) study drugs and study supplies dispensing and return reconciliation log(s), (c) study drugs and study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs and study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (e.g., the FDA). Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 STUDY ASSESSMENTS

9.5.1 Screening and Baseline Assessments

Treatment may occur on the day of the Screening Visit (Visit 1) or any following day up to 1 week (Baseline and Drug Administration, Visit 1a). If drug administration occurs on same day as screening then all assessments in Visit 1 and Visit 1a listed in Schedule of Assessments (Table 4) will be combined.

9.5.1.1 Demographics

Subject demographic information will be collected at the Screening Visit. Demographic information includes date of birth (or age), sex, race, and ethnicity.

9.5.1.2 Medical History

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All relevant medical and surgical history must be recorded in the

CRF, including any record or history of cystoscopy and the diagnosis of IC/BPS.

9.5.1.3 Medication History

All relevant medication history must be recorded in the CRF.

9.5.1.4 Physical and Pelvic Examination

A comprehensive physical examination will be performed at the Screening Visit (V1). The physical examination will include evaluations of the following: general appearance; eyes, ears, nose, and throat; chest (including heart and lungs); abdomen (palpation and gastrointestinal sounds), extremities; and skin. Weight and height will also be measured and will be recorded in the CRF. A pelvic examination will also be conducted which may be performed without speculum. Results from a pelvic examination performed within 7 days prior to the Screening Visit (V1) may replace a V1 pelvic examination. Documentation of the physical and pelvic examination results will be included in the source documentation. Significant findings at the Screening Visit will be recorded in the CRF.

9.5.1.5 Urine Screening Tests

A 30-mL urine sample will be collected and analyzed for pregnancy in women of childbearing potential, drug screen, and for standard urine analysis testing.

The urine sample will be analyzed for hematuria by dipstick urinalysis. If the urine dipstick is positive for blood, the investigator will evaluate the subject further before proceeding, (such as assessing the subject's history to determine if the subject is menstruating, or performing a full urinalysis and if appropriate, a urine culture, to determine if the subject has a kidney or urinary tract infection, or cystoscopy prior to enrollment). If the investigator determines that active bleeding is not occurring and that it is safe for the subject, the subject may continue in the study.

9.5.1.6 Catheter Tolerance

All subjects will be catheterized with the hydrophilic ColoplastSpeediCath 8 Fr and 12 Fr, respectively (for females and males). Each subject will be assessed for the ability to tolerate the catheter after randomization into the study, based on the

investigator's judgment.

9.5.1.7 [redacted]

[redacted]

9.5.1.8 Pelvic Pain and Urgency/Frequency (PUF) Questionnaire

Subjects will be asked to fill out the Pelvic Pain and Urgency/Frequency (PUF) Questionnaire, and it will be scored by the investigator. Subjects must have a score of ≥ 15 and < 30 on the PUF questionnaire to qualify for the study.

9.5.1.9 Bladder Pain and Urgency 11-Point Numerical Rating Scales (NRS)

As part of screening, subjects will be asked to fill out two sets of the 11-point bladder pain NRS and the 11-point urgency NRS, one at screening and one 15 minutes (± 5 minutes) after voiding just prior to study drug administration. There is no minimum score requirement for the urgency NRS scales for patients to enter the study. For the Pain NRS, both the screening and [redacted] pain NRS requires a score of ≥ 5.0 to enter the trial and receive study drug.

9.5.1.10 Safety Assessments

Safety will be assessed by clinical laboratory tests (hematology, clinical chemistry, and urinalysis), vital signs measurements, and AE reporting.

9.5.1.10.1 Clinical Laboratory Testing

The local laboratory will be used for all laboratory testing required during the study

except for baseline and 1-hour plasma lidocaine, which will be analyzed by the central laboratory. Reports from the laboratory should be filed with the source documents for each subject. Samples will be obtained at the visits designated in Table 4. Additional samples may be collected for further evaluation of safety as warranted by the investigator's discretion. The clinical laboratory tests performed during the study are provided in Table 2. However, with the exception of qualifying results for hematuria, drugs of abuse and pregnancy, no other clinical laboratory results are required prior to randomization.

Table 2. Clinical Laboratory Tests

<table>
<tr><td>Hematology:
Complete blood count (CBC):
As defined by local laboratory</td><td rowspan="2">Serum Chemistry:
Alanine transaminase (ALT)
Alkaline phosphatase (ALP)
Aspartate transaminase (AST)
Blood urea nitrogen (BUN)
Calcium
Creatinine
γ-glutamyltransferase (GGT)
Glucose
Lactate dehydrogenase (LDH)
Potassium
Protein, total
Sodium</td></tr>
<tr><td>Dipstick Urinalysis:
Color
pH
Specific gravity
Blood/hemoglobin
Leukocyte esterase
Ketones
Protein</td></tr>
<tr><td colspan="2">Additional Tests:
Urine β-hCG for women of childbearing potential
Urine drug screen
INR and activated partial thromboplastin time
Clean catch urine for bacterial culture if the urinalysis indicates:
Plasma for lidocaine concentration</td></tr>
</table>

β-hCG = beta human chorionic gonadotropin;

9.5.1.10.2 Vital Signs

Vital sign measurements (i.e., systolic and diastolic blood pressure [mmHg], and pulse [beats per minute]) will be obtained at the visits designated on the schedule of assessments (Table 4). Blood pressure and pulse will be measured after the subject has been sitting for 3 to 5 minutes. All blood pressure measurements should be performed on the same arm, preferably by the same person.

9.5.1.10.3 Adverse Events and Other Events of Interest

An AE is any untoward medical occurrence in a subject who is administered an investigational product. An AE does not necessarily have a causal relationship with the study drug.

The criteria for identifying AEs include the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product
- Any new disease or exacerbation of an existing disease
- Any deterioration in non–protocol-required measurements of a laboratory value or other clinical test (e.g., electrocardiogram [ECG] or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (e.g., headache) not present pretreatment (baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not, and after repeat confirmatory testing has been conducted

A laboratory result should be considered by the investigator to be an AE if it includes the following:

- Results in an intervention, based on medical evaluation (e.g., potassium supplement for hypokalemia)

- Results in any out of range laboratory value that in the investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the ICF through the last visit. AEs reported prior to randomization will be termed medical history. SAEs will not be considered medical history and will be collected for 72 hours after the last dose.

Abnormal laboratory values should not be listed as separate AEs if the values are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an AE should be reported as an AE on the CRF.

It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events:

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.10.3, Serious Adverse Events and Other Events of Interest for the definition of an SAE).

The causal relationship of the study drug to an AE will be assessed as related or unrelated, as follows:

Assessing Causality of Adverse Events:

Table 3. Assessment of Causality of AEs

Term	Definition
Definitely related	The AE *is clearly related* to the investigational agent(s) or research intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention and follows a known pattern of response, and no alternative cause is present.
Probably related	The AE is *likely related* to the investigational agent(s) or intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention and follows a known or suspected pattern of response, but an alternative cause may be present.
Possibly related	The AE *may be related* to the investigational agent(s) or intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention and follows a suspected pattern of response, but an alternative cause is present.
Unrelated (or Not Related)	The AE is *clearly not* related to the investigational agent(s) or intervention: the AE has no temporal relationship to the administration of the investigational agent(s) or research intervention, and follows no known or suspected pattern of response, and an alternative cause is present.

AE = adverse event.

9.5.1.10.4 Serious Adverse Events

An SAE is any untoward medical occurrence that, at any dose, meets one of the following criteria:

- Results in death
- Is life-threatening (i.e., the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of an SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

Other events of interest include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error; and any treatment-emergent significant laboratory abnormality. These events of interest are to be captured using the SAE procedures but are to be considered SAEs only if they meet one of the above criteria. All AEs associated with events of interest are to be reported on the CRF whether or not they meet the criteria for SAEs.

The following hospitalizations are not considered to be SAEs because there is no AE (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

9.5.2 Efficacy Assessments

9.5.2.1 11-Point Bladder Pain and Urgency Scales

The 11-point bladder pain and urgency NRSs are provided in Appendix 3. The 11-point pain and urgency scales are two scales that are used to assess bladder pain, the primary endpoint of this study, and urinary urgency. The subject will be asked to circle the number, from 0 to 10, that best describes the symptom the subject is feeling "right now." The 11-point bladder pain and urgency scales will be explained to the

subject by the investigator or designee prior to the subject completing the questionnaire. Guideline scripts for the 11-point pain and urgency scales are provided in Appendix 4.

9.5.2.2 Patient Overall Rating of Improvement of Symptoms Questionnaire

The PORIS questionnaire is provided in Appendix 5. It comprises three questions that ask the subject to report the overall change in pain and urgency *now* as compared with *before* study drug administration. The choices are the same for each symptom: worse, no better (0% improvement), slightly improved (25% improvement), moderately improved (50% improvement), greatly improved (75% improvement), and symptoms gone (100% improvement). The PORIS questionnaire will be explained to each subject by the investigator or designee prior to the subject completing the questionnaire. A guideline script for the PORIS questionnaire is provided in Appendix 6.

9.5.2.3 24-Hour Pain and Urgency Scale Diary and Urination Log

Each subject will be provided with a set of pain and urgency questionnaires that use the 11-point NRSs that will be recorded by the subject at home after receiving the study medication, until going to bed. Pain measurements will be recorded on-site up to 2 hours after study drug administration [at Time 0, 30 minutes (± 5 minutes) and 1 hour (± 5 minutes), 2 hours(± 10 minutes)], and at home at 4 hours (± 30 minutes), 6 hours (± 30 minutes), 8 hours (± 30 minutes), 10 hours (± 30 minutes), and 12 hours (± 30 minutes) while the subject is awake. The last set of pain and urgency questionnaires will be completed at 24 hours, and may be completed at the clinic if the subject returns to the clinician's office (Visit 2) at 24 hours (± 2 hours) after study drug administration or, at the Investigator's discretion, will be completed at home and retuned to the clinic per the Investgator's directions. The site staff will ensure that the proper subject initials and numbers, and study drug administration time are recorded in each subject's diary prior to dispensing them. The diary also contains a urination log. The diary will be explained to each subject by the investigator or designee prior to the subject recording any data in the diary. Site staff will be tasked with placing phone calls to remind each subject to complete the diary at the assigned times, and if the subject has been given permission by the Investigator to not return for Visit 2 to confim the return of the completed subject diary and answer any follow up questions.

9.5.3 Pharmacokinetic Assessments

9.5.3.1 Lidocaine Concentration

A blood sample will be collected to determine the concentration of lidocaine in the peripheral blood. An initial blood sample will be collected at baseline prior to study drug administration, and a second blood sample will be collected 1 hour (± 10 minutes) after administration of the study drug (i.e., 1 hour after instillation) to determine plasma lidocaine concentrations.

9.5.4 Schedule of Assessments

The schedule of assessments for the study is provided in Table 4.

Table 4. Schedule of Assessments

Procedure	Visit 1 Clinic Screening	Visit 1a Clinic Baseline and Drug Administration	Home Assessment	Optional Visit 2 Clinic	Follow-up telephone check[k]
		Time after study drug administration			
		0 - 2 hrs	> 2 hrs	24 hrs	48 - 72 hrs
[redacted]					

[redacted]

9.5.5 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of IC/BPS.

The safety assessments to be performed in this study (including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs) are standard evaluations to ensure subject safety.

9.5.6 Reporting of Serious Adverse Events, Pregnancy, and Other Events of Interest

9.5.6.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study drug, must be reported on a completed SAE form by email or fax as soon as possible to [redacted] but should be reported no later than 24 hours from the time the investigator becomes aware of the SAE.

Any death or any life-threatening event should be reported immediately by telephone to [redacted] The immediate report should be followed up within 1 business day by emailing or faxing the completed SAE form.

SAEs, regardless of causality assessment, must be collected through the last visit and up to 72 hours after drug administration. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment should be reported to the sponsor regardless of the length of time that has passed since study completion.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject, and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received about SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions of additional information including copies of hospital case reports, autopsy reports, and other documents, if requested by the sponsor.

The investigator must notify the IRB of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor or the contract research organization to be filed in the sponsor's Trial Master File.

9.5.6.2 Reporting of Pregnancy

Any pregnancy in which the estimated date of conception is either before the last visit or within 30 days of study drug administration must be reported to Urigen.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported, regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during the perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.6.1, Reporting of Serious Adverse Events).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the investigator study file. The Pregnancy Report Form must be used for reporting pregnancies. All pregnancies must be followed to outcome, whenever possible. The outcome of the pregnancy must be reported as soon as possible but no

later than 1 business day from the date the investigator becomes aware of the outcome.

9.5.6.3 Reporting of Other Events of Interest

REPORTING OF ADVERSE EVENTS ASSOCIATED WITH STUDY DRUG OVERDOSE, MISUSE, ABUSE, OR MEDICATION ERROR

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose (If applicable, define the study-specific criteria for overdose that should be applied when determining whether an overdose occurred.)
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject

All AEs associated with an overdose should be captured in the Adverse Event CRF. Adverse events associated with overdose, misuse, abuse, or medication error should be reported using the procedures detailed in Section 9.5.6.1, Reporting of Serious Adverse Events even if the AEs do not meet serious criteria. Drug abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner; however, the AE should be noted as nonserious on the SAE form and in the Adverse Event CRF.

9.5.6.4 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may request that the medical monitor break the blind for an individual subject as described in the Study Procedures Manual. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented.

9.5.6.5 Regulatory Reporting of Adverse Events

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.7 Completion and Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason without prejudice. All subjects who discontinue the study are to complete the study's Visit 2 procedures and the follow-up phone call indicated in the schedule of assessments (Table 4) whenever possible.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms. This information will be recorded in the CRF.

Subjects who discontinue early from the study will be discontinued for one of these primary reasons: AE(s), lost to follow-up, catheter intolerance, inadequate therapeutic effect, withdrawal of consent, pregnancy, study terminated, or other (to be specified). In addition to the primary reason, the subject may indicate one or more secondary reasons for discontinuation.

9.6 DATA QUALITY ASSURANCE

9.6.1 Monitoring

The study will be monitored by designees of Urigen N.A., Inc. at all stages of study conduct, from inception to completion, in accordance with current GCP. This monitoring will be in the form of site visits and other communication and will include review of original source documents and CRFs. The monitor will notify the investigator prior to conducting any investigational site visit. The frequency of these visits will depend upon the progress of the study, and will include monitoring to assess facilities and equipment, recruiting, record-keeping, protocol adherence, data collection, AE reporting, and other factors.

9.6.2 Investigator's Responsibility

The investigator will retain all study documents required to be maintained (1) for at least 2 years after the date a marketing application is approved for the drug for the indication for which it is being investigated, or (2) if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified.

9.7 STATISTICAL METHODS

All statistical analyses, except the interim analysis, will be performed after each study is completed, the database is locked and released, and randomization codes have been released. Statistical analyses will be performed using SAS or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. All hypothesis tests will be 2-sided and will use an alpha level of 0.05. Additional details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Primary Endpoint

The primary endpoint for the investigative phase of the study is the sum of bladder pain intensity differences from baseline to 12 hours (SPID-12) after administration of URG101 compared with the SPID-12 after administration of lidocaine alone, heparin alone, and placebo as determined by using the 11-point NRS for bladder pain.

9.7.1.2 Secondary Endpoints

The secondary endpoints of the study are:

1. The sum of bladder pain intensity differences from baseline to 24 hours (SPID-24) after administration of URG101 compared with lidocaine alone, heparin alone, and placebo as determined by using the 11-point bladder pain NRS

2. The sum of urgency intensity differences from baseline to 12 and 24 hours (SUID-12 and SUID-24) after administration of URG101 compared with lidocaine alone, heparin alone, and placebo using the 11-point urgency NRS

3. Absolute and percentage change in bladder pain from baseline to 1, 12, and 24 hours after administration of URG101 compared with lidocaine alone, heparin alone, and placebo as determined by using the 11-point NRS for bladder pain

4. Absolute and percentage change in urgency intensity from baseline to 1, 12, and 24 hours after administration of URG101 compared with lidocaine alone, heparin alone, and placebo using the 11-point urgency NRS

5. Patient Global Assessment: Comparison of the percentage of subjects achieving ≥ 50% improvement in the PORIS questionnaire, Question 3, from baseline to 1 hour, 12 hours and 24 hours after administration of URG101, lidocaine alone, heparin alone, and placebo

6. Time to first administration of rescue medication for pain after treatment with URG101 compared to alkalinized Lidocaine Hydrochloride Injection (20 mg/mL) alone, alkalinized Heparin Sodium Injection (5,000 USPU/mL) alone, and placebo [redacted])

7. To evaluate the safety and tolerability of intravesical administration of URG101

9.7.1.3 Safety Endpoints

The safety endpoints of the study are:

1. Change from baseline in INR at 1 hour after study drug administration.
2. Change from baseline in aPTT at 1 hour after study drug administration.
3. Adverse events

9.7.1.4 Pharmacokinetic Endpoints

Samples for plasma lidocaine concentrations will be collected at baseline and at 1 hour after study drug administration. The pharmacokinetic endpoints of the study are:

1. Comparison of plasma lidocaine concentrations at 1 hour post treatment with absolute and percentage change in pain using the 11-point bladder pain NRS, at 1, 12 and 24 hours after administration of URG101, lidocaine alone, heparin alone, and placebo.

2. Comparison of plasma lidocaine concentrations at 1 hour post treatment with absolute and percentage change in urgency using the 11-point urgency NRS, at 1, 12 and 24 hours after administration of URG101, lidocaine alone, heparin alone, and placebo.

3. Comparison of plasma lidocaine concentrations at 1 hour post treatment with the sum of bladder pain intensity differences from baseline to 12 and 24 hours (SPID-12 and SPID-24) after administration of URG101 compared with lidocaine alone, heparin alone, and placebo as determined by using the 11-point bladder pain NRS.

4. Comparison of plasma lidocaine concentrations at 1 hour post treatment with the sum of urgency intensity differences from baseline to 12 and 24 hours (SUID-12 and SUID-24) after administration of URG101 compared with lidocaine alone, heparin alone, and placebo as determined by using the 11-point urgency NRS.

9.7.1.5 Definitions of Analysis Sets

The safety analysis set will include all subjects who receive at least one dose of study drug and have at least one post dose safety assessment.

The intent-to-treat set will include all randomized subjects who receive study drug.

The per protocol set will include all subjects who sufficiently comply with the protocol. Details of the evaluability criteria will be determined before database lock and treatment unblinding.

The pharmacokinetic (PK) set will include all subjects who receive at least one dose of study drug and have sufficient data to calculate PK parameters.

9.7.1.6 Subject Disposition

Descriptive statistics will be utilized. By-subject listings and summary tables will be provided.

9.7.1.7 Demographic and Baseline Characteristics

Descriptive statistics will be utilized. By-subject listings and summary tables will be provided.

9.7.1.8 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary. The number (percentage) of subjects who took prior and concomitant medications will be summarized on the safety analysis set by treatment group, Anatomical Therapeutic Chemical class, and World Health Organization Drug Dictionary preferred term. Prior medications will be defined as medications that stopped before the dose of study drug. Concomitant medications will be defined as medications that (1) started before the dose of study drug and were continuing at the time of the dose of study drug, or (2) started on or after the date and time of the dose of study drug up to 72 hours after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.9 Safety Analyses

All safety analyses will be performed on the safety analysis set. Safety data, presented by treatment group, will be summarized on an "as-treated" basis using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables will include physical examinations, treatment-emergent adverse events (TEAEs), clinical

laboratory parameters, vital signs. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

9.7.1.10 Extent of Exposure

By-subject listings and summary tables will be provided.

9.7.1.11 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA lower level term closest to the verbatim term. The linked MedDRA preferred term and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at baseline and:

- Reemerges during treatment, having been present before treatment (baseline) but stopped before treatment,

or

- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Adverse events will be summarized and listed for the safety analysis set. Only those AEs that are treatment-emergent will be included in summary tables. Summary tables will be by treatment group and overall. The incidence (%) will be determined by calculating the number of subjects with at least 1 event and the percentage of subjects with TEAEs by SOC and by preferred term. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and preferred term. A subject will be counted only once within a SOC and preferred term, even if the subject experiences more than one TEAE within a specific SOC and preferred term. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (possibly related, probably related, and not related).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and preferred term. Treatment-related TEAEs include those AEs considered by the investigator to be possibly or probably related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

A subject data listing of all AEs leading to death will be provided. Additionally, a subject data listing of all AEs leading to discontinuation from study drug will be provided.

The number (percentage) of subjects with SAEs will be summarized by MedDRA SOC and preferred term for each treatment group. A subject data listing of all SAEs will be provided.

9.7.1.12 Laboratory Values

Summary statistics for changes from baseline and the incidence of treatment emergent abnormal values in coagulation measurements at 1 hour post drug administration will be provided.

9.7.1.13 Physical Examination, Pelvic Examination, and Vital Signs

By-subject listings will be provided for physical examination and pelvic examination. Summary statistics for change from baseline and incidence of potentially clinically significant results in vital signs will be provided.

9.7.1.14 Efficacy Analyses

All SPID endpoints will be calculated using Simpson's trapezoidal rule. SPID will be calculated as follows, where *n* is the total number of time points within the time period with non-missing imputed PID values:

If multiple scores are recorded at the same date and time, the most conservative PI scores (highest) will be used.

Primary Efficacy Analyses

The primary efficacy analyses will be performed on the intent-to-treat set. As a sensitivity analysis, the primary efficacy analysis will also be performed on the PP set. Primary efficacy analyses will also be conducted on the per protocol set, which will include all subjects in the ITT set who sufficiently comply with the protocol.

The primary efficacy endpoint will be compared between the URG101 group and the lidocaine, heparin, and placebo groups using an analysis of covariance model including factors for site and randomized treatment assignment; baseline pain will be added to the model as a covariate. Pairwise comparisons of least squares means between URG 101 and the two active treatment arms, as well as the placebo arm, will be performed. The probability values will be derived using the contrast statement from the model. If the p-value associated with these comparisons is < 0.05 in favor of URG101, the primary aim of the trial will be confirmed.

Sites with small numbers of patients enrolled may be pooled for analysis. The method used to determine pooling will be specified in the statistical analysis plan and any pooling will be finalized and documented prior to database lock and unblinding.

Secondary Efficacy Analyses

Analyses of the secondary endpoints relating to changes in the pain and urgency NRS will be performed using analysis of covariance models similar to those used for the primary efficacy endpoint. The ITT set will be used. Nonparametric methodology in exploratory analyses may be used to supplement the parametric analyses.

Treatment differences based on the PORIS questionnaire, Question 3, will be analyzed by pairwise Cochran-Mantel-Haenszel Tests based on ≥ 50% improvement of symptoms.

Time to first pain medication use will be analyzed using Kaplan-Meier methodolgy. Log-rank tests will be used to compare the treament groups.

9.7.1.15 Safety Analyses

All safety analyses will be performed on the safety analysis set.

The change in INR and aPTT from baseline at 1 hour after study drug administration will be compared using descriptive statistics for the various treatment groups.

9.7.1.16 Pharmacokinetic Analyses

Samples collected at baseline will be analyzed to determine if plasma lidocaine concentrations are detected prior to study drug administration. A comparison of peak pain and urgency as measured by 11–point NRSs to plasma lidocaine levels at 1 hour after study drug administration will be made for the PK set.

9.7.2 Handling of Missing Data

9.7.2.1 11-Point Bladder Pain and Urgency Scales

For the 11-point numerical data, if subjects are administered any rescue pain medication, the pain score recorded immediately prior to receiving the rescue pain medication will be carried forward for 4 hours. Data for subjects who withdraw will be imputed using the baseline observation carried forward method. The imputed dataset will be used to derive the SPID score.

9.7.2.2 24-Hour Symptom and Urination Diaries

During the 24 hours after treatment, subjects are required to fill in their symptom diaries only while they are awake. Missing data occurring will be imputed using LOCF methodology.

If the number of missing data points in the 12-hour period after treatment administration is 6 or greater, then the subject is considered a major protocol violator and his or her data are excluded from the per protocol analysis. If the number of missing data points in the first 6-hour period following treatment administration is 3 or greater, then the subject is considered a major protocol violator and the subject's data are excluded from the per protocol analysis.

9.7.3 Determination of Sample Size

Sample size estimates were based on a pilot trial of heparin-lidocaine versus lidocaine alone and a prior two-arm study of URG101 versus placebo. The primary efficacy endpoint is SPID-12. The sample size calculation is based on a one-way analysis of variance, comparing SPID-12 from four treatment groups. A target sample size of approximately 180 subjects allocated among the four treatment groups.. This sample size will be sufficient to achieve 90% power to detect a difference between the URG101 and components groups assuming a treatment effect size of 0.60. Once 50% of the subjects (90) have been enrolled, an unblinded interim assessment will be performed. The number of subjects for the study may be increased, based on the recommendation of the IDMC. Overall, a maximum of 300 subjects will be enrolled in Study URG101-105.

9.7.4 Interim Analysis

Re-estimation of the Sample Size

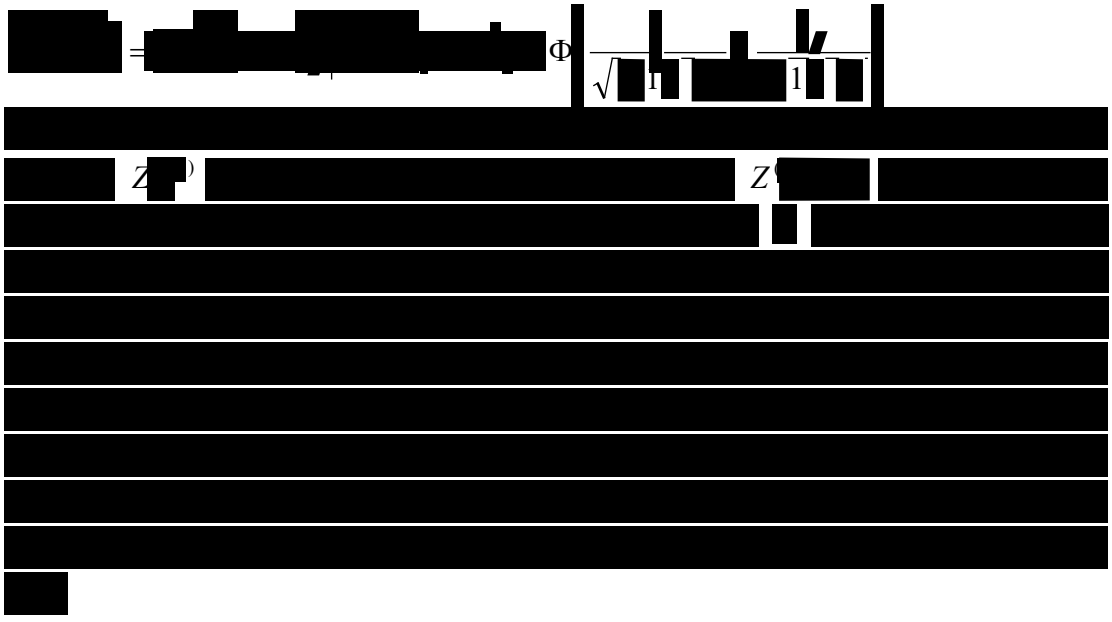
[redacted]

The two possible types of interactions are defined as being either **quantitative** or **qualitative**. A quantitative interaction exists where the relationship of the treatment groups are consistent across the sites, moving in the same direction, but at different magnitudes. A qualitative interaction is much more serious and exists where one treatment group shows a positive effect of the study medication at certain sites, and the other sites show a negative effect of the same study treatment. In most clinical studies, if an interaction is present between site and treatment, there will be a quantitative interaction where the effect size at some sites is greater than at other

sites, but all sites have a positive effect size for the active treatment. Qualitative interactions require additional investigation because of the mixed signals on the effect of a study treatment by study site.

In order to minimize the impact of a small sample effect, for the purposes of the interim analysis, the smaller study sites will be merged to form a pseudo-site. In this way a possible aberration in outcomes that might arise from small samples due to over or under representation of patients with characteristics that may either increase or decrease study results will have a diminished impact on the sample size recalculation.

[redacted]



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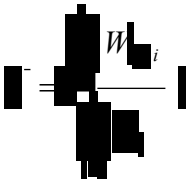

[redacted]:

[redacted]

[redacted]

The IDMC will make one of following non-binding recommendations to the sponsor:

- Continue enrolling patients to the pre-specified target sample size
- Continue enrolling patients to a sample size that exceeds the pre-specified target sample size but ≤ the maximum sample size
- Stop enrolling patients based on futility

The instructions from the IDMC for the sample size adjustment will be described in detail in the IDMC Charter. An alpha level adjustment will not be necessary for the

procedure described below if the conditional power for the primary endpoint is > 39%.

9.7.5 Other Statistical and Analytical Issues

Not applicable.

9.7.6 Procedure for Revising the Statistical Analysis Plan

If the SAP requires revision after finalization, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10.0 ADMINISTRATIVE PROCEDURES AND INSTRUCTIONS

10.1 CHANGES TO THE PROTOCOL

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the investigator, IRB, and Urigen before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs. These requirements should in no way prevent any immediate action from being taken by the investigator, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, Urigen and the IRB for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB, but the health or regulatory authority and IRB should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB detailing such changes.

10.2 ADHERENCE TO THE PROTOCOL

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

10.3 MONITORING PROCEDURES

The sponsor's contract research organization or clinical research associate (CRA) will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator, or if regionally required, the head of the medical institution will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's

representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB or IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (e.g., sonograms, computed tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, polysomnographs, pulmonary function tests), regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality-of-life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (e.g., urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs
- CRF components (e.g., questionnaires) that are completed directly by subjects and serve as their own source

10.4 RECORDING OF DATA

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF.

10.5 IDENTIFICATION OF SOURCE DATA

All data to be recorded on the CRF must reflect the corresponding source documents.

10.6 RETENTION OF RECORDS

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (e.g., Form FDA 1572, ICFs, and IRB correspondence). The site should plan to retain study documents for the length of time agreed upon in the study contract.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact Urigen, allowing Urigen the option of permanently retaining the study records.

10.7 AUDITING PROCEDURES AND INSPECTION

In addition to the routine monitoring procedures, the Urigen Clinical Quality Assurance department conducts audits of clinical research activities in accordance with Urigen’s procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform Urigen immediately.

10.8 REPORTING AND PUBLICATION OF RESULTS

A clinical study report will be finalized within 1 year of the end of data collection.

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by Urigen in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Study Agreement between Urigen and the institution or investigator. The review is aimed at protecting Urigen's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study, will be set out in the agreement between the investigator and Urigen, as appropriate.

10.9 DISCLOSURE AND CONFIDENTIALITY

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of Urigen. No data collected as part of this study will be used in any written work, including publications, without the written consent of Urigen. These obligations of confidentiality and nonuse will in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Study Agreement executed between Urigen and the institution or investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and nonuse set forth in either the Confidentiality Agreement or Clinical Study Agreement executed between the institution or investigator and Urigen.

10.10 DISCONTINUATION OF STUDY

Urigen reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, Urigen will promptly inform the investigators or institutions and the investigator will inform the

regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB will also be informed promptly and provided the reason(s) for the termination or suspension by the investigator or institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study if his or her judgment so dictates. If the investigator terminates or suspends a study without prior agreement of Urigen, the investigator should inform the institution where applicable, and the investigator or institution should promptly inform Urigen and the IRB and provide Urigen and the IRB with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.0 REFERENCE LIST

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12.0 APPENDICES

Appendix 1 Pelvic Pain and Urgency/Frequency Questionnaire

Appendix 2 Guideline Script for Pelvic Pain and Urgency/Frequency Questionnaire

Appendix 3 11-Point Pain and Urgency Scales

Appendix 4 Guideline Script for 11-Point Pain and Urgency Scales

Appendix 5 Patient Overall Rating of Improvement of Symptoms Questionnaire

Appendix 6 Guideline Script for Patient Overall Rating of Improvement of Symptoms Questionnaire

Appendix 7 Protocol Signature Pages

Appendix 1: Pelvic Pain and Urgency/Frequency Questionnaire

PELVIC PAIN and URGENCY/FREQUENCY SCALE

Please circle the answer that best describes how you feel for each question.

		0	1	2	3	4	Symptom Score	Bother Score
1	How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+		
2	**a.** How many times do you go to the bathroom at night?	0	1	2	3	4+		
	b. If you get up at night to go to the bathroom, does it bother you?	Never Bothers	Occasionally	Usually	Always			
3	**a.** Do you now or have you ever had pain or symptoms during or after sexual intercourse?	Never	Occasionally	Usually	Always			
	b. Has pain or urgency ever made you avoid sexual intercourse?	Never	Occasionally	Usually	Always			
4	Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum, testes, or scrotum)?	Never	Occasionally	Usually	Always			
5	**a.** If you have pain, is it usually		Mild	Moderate	Severe			
	b. Does your pain bother you?	Never	Occasionally	Usually	Always			
6	Do you still have urgency after going to the bathroom?	Never	Occasionally	Usually	Always			
7	**a.** If you have urgency, is it usually		Mild	Moderate	Severe			
	b. Does your urgency bother you?	Never	Occasionally	Usually	Always			
8	Are you sexually active? Yes____ No____							

SYMPTOM SCORE = (Add scores from top of column: 1, 2a, 3a, 4, 5a, 6, 7a)		
BOTHER SCORE = (Add scores from top of column: 2b, 3b, 5b, 7b)		
TOTAL SCORE (Symptom Score + Bother Score) =		

Appendix 2: Guideline Script for Pelvic Pain and Urgency/Frequency Questionnaire

Guideline script:

[redacted]

……

Once the subject has answered all questions the coordinator will enter the scores (0, 1, 2, 3, or 4 as indicated at the top of the page) to the right, and then calculate the total SYMPTOM SCORE, total BOTHER SCORE, and TOTAL SCORE (Symptom score + Bother Score).

Appendix 3: 11-Point Bladder Pain and Urgency Scales

1. Please circle the number that best describes the PAIN ASSOCIATED WITH YOUR BLADDER you are **EXPERIENCING NOW**.

BLADDER PAIN

none										worst ever
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

2. Please circle the number that best describes the URGENCY or NEED TO URINATE that you are **EXPERIENCING NOW**.

URINARY URGENCY

none										worst ever
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Appendix 4: Guideline Script for 11-Point Bladder Pain and Urgency Scales

[redacted]

Appendix 5: PORIS Questionnaire

PATIENT OVERALL RATING OF IMPROVEMENT OF SYMPTOMS

Please check the category that **BEST** describes your condition **NOW** in **COMPARISON** to your condition **BEFORE** you started study medication.

1. Please check the category that best describes the **OVERALL CHANGE** in **PAIN** associated with your pelvic/bladder pain now compared to before receiving study medication. (Check one box)

   [ ] Worse
   [ ] No better (0% improvement)
   [ ] Slightly improved (25% improvement)
   [ ] Moderately improved (50% improvement)
   [ ] Greatly improved (75% improvement)
   [ ] Symptoms gone (100% improvement)

2. Please check the category below that best describes the **OVERALL CHANGE** in **URGENCY** to urinate associated with your bladder now compared to before receiving the study medication. (Check one box)

   [ ] Worse
   [ ] No better (0% improvement)
   [ ] Slightly improved (25% improvement)
   [ ] Moderately improved (50% improvement)
   [ ] Greatly improved (75% improvement)
   [ ] Symptoms gone (100% improvement)

3. Considering your response to items 1 and 2, please check the category below that best describes the **OVERALL CHANGE** in your problem **COMPARED TO BEFORE YOU RECEIVED** the study medication. (Check one box)

   [ ] Worse
   [ ] No better (0% improvement)
   [ ] Slightly improved (25% improvement)
   [ ] Moderately improved (50% improvement)
   [ ] Greatly improved (75% improvement)
   [ ] Symptoms gone (100% improvement)

Appendix 6: Guideline Script for PORIS Questionnaire

[redacted]

Appendix 7: Protocol Signature Pages

Protocol Signature Page

Study Protocol Title: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Multi-Center Single Dose Study to Evaluate the Safety and Effectiveness of URG101 Compared with the Individual Components Lidocaine and Heparin in Subjects with Interstitial Cystitis/Bladder Pain Syndrome (Protocol URG101-105, the ENGAGE-24 Study)

Investigational Product: URG101 (Alkalinized lidocaine-heparin)

SIGNATURES

[redacted]: **Project Manager**

[redacted] Date

[redacted]: **Medical Monitor**

[redacted] Date

[redacted]: **Statistician**

[redacted] Date

Urigen N.A., Inc.

[redacted] Date

PI Signature Page

Study Protocol Title:	A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Multi-Center Single Dose Study to Evaluate the Safety and Effectiveness of URG101 Compared with the Individual Components Lidocaine and Heparin in Subjects with Interstitial Cystitis/Bladder Pain Syndrome (Protocol URG101-105, the ENGAGE-24 Study)
Investigational Product:	URG101 (Alkalinized lidocaine-heparin)

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and all applicable local Good Clinical Practice guidelines, including the Declaration of Helsinki.

I have read the attached protocol and agree that it contains all the necessary details for performing the study.

I will provide copies of the protocol and of the additional information on the test article, which was furnished to me by the sponsor, to all members of the study team. I will discuss the material with them to ensure they are fully informed regarding the test article and the conduct of the study.

Once the protocol has been approved by the institutional review board (IRB) or ethics committee, I will not modify this protocol without obtaining the prior approval of the sponsor and of the IRB or ethics committee. If I would like the protocol or informed consent form modified, I will first submit the proposed modifications to the sponsor for review and, if approved, to the IRB or ethics committee before any modifications are implemented.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date