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Study ID: 201025-001

Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Study, Evaluating Safety and Efficacy of LiRIS® 400 mg in Females With Interstitial Cystitis With Hunner's Lesions

Protocol Amendment 2 Date: 28-Apr-2016

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STUDY TITLE

A Multicenter, Randomized, Double-blind, Placebo-controlled Study, Evaluating Safety and Efficacy of LiRIS® 400 mg in Females With Interstitial Cystitis With Hunner's Lesions

Protocol Number:	201025-001 Amendment 2
Phase:	2
Name of Investigational Product:	LiRIS® (Lidocaine-releasing intravesical system)
Sponsor:	Allergan (North America) 2525 Dupont Drive Irvine, California USA 92612 +1-714-246-4500 +1-800-347-4500
Emergency Telephone Number(s):	Refer to the Study Contacts Page.

[redacted]

Refer to the final page of this protocol for electronic signature and date of approval.

The following information can be found on FDA Form 1572 and/or study contacts page: Name and contact information of Allergan study personnel and Emergency Telephone Numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB; US 21 CFR 312.23 section 6(iii)b.

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

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Protocol Summary

Study Compound(s): LiRIS® (Lidocaine-releasing intravesical system) AGN-201025

Phase: 2

Study Objective: To evaluate the safety and efficacy of a 28-day period of continuous release of lidocaine inserted into the bladder utilizing 2 consecutive LiRIS 400 mg compared with placebo for the treatment and corresponding symptoms of interstitial cystitis (IC) with Hunner's Lesions (HL) in female patients

Clinical Hypotheses: A 28-day period of continuous release of lidocaine inserted into the bladder utilizing 2 consecutive LiRIS 400 mg will have an acceptable safety profile and is more efficacious than placebo for the treatment and corresponding symptoms of IC with HL in female patients

Study Design

Structure: Multicenter, randomized, double-blind, placebo-controlled study

Duration:

For patients who participate in the study and receive only one treatment, the duration of study participation will be 28 weeks. For patients who qualify and receive Treatment 2 (active LiRIS only), the minimum duration of participation is 16 weeks and the maximum duration of study participation is 36 weeks

Study Treatment Groups:

1) LiRIS 400 mg, LiRIS 400 mg (Treatment 1 Period)/LiRIS 400 mg (Treatment 2 Period)
2) LiRIS Placebo, LiRIS Placebo (Treatment 1 Period)/LiRIS 400 mg (Treatment 2 Period)
3) LiRIS Placebo, LiRIS 400 mg (Treatment 1 Period)/LiRIS 400 mg (Treatment 2 Period)

Controls: LiRIS Placebo

Dosage/Dose Regimen:

Treatment 1 Period (Tx 1):

Treatment 1 includes the following: 2 consecutive LiRIS 400 mg, 2 consecutive LiRIS Placebo, or one LiRIS Placebo followed by one LiRIS 400 mg

Treatment 2 Period (Tx 2):

One LiRIS 400 mg

Randomization/Stratification: Randomization will be centralized and stratified by baseline pain score (≤ 5 or > 5) collected during the Screening period. Each patient within a stratum will be randomized to one of 3 groups (2 consecutive LiRIS 400 mg or 2 consecutive LiRIS Placebo or one LiRIS Placebo followed by one LiRIS 400 mg) in a 2:1:1 ratio that will define the patient's assignment in Treatment 1.

Visit Schedule:

Treatment 1:

Patients will be evaluated during the Screening period for eligibility.

Eligible patients will be:

[redacted]

Study Population Characteristics

Number of Patients: Approximately 76 patients will be enrolled into the study to ensure 72 evaluable patients overall for Treatment 1, including 36 patients in the LiRIS 400 mg/LiRIS 400 mg group, 18 patients in the LiRIS Placebo/LiRIS Placebo group, and 18 patients in the LiRIS Placebo/LiRIS 400 mg group.

Condition/Disease: Female patients with IC with HL

Key Inclusion Criteria:

- females ≥ 18 years of age
- a diagnosis of IC with HL defined as:
    - an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms (LUTS) of more than 6 months duration in the absence of infection or other identifiable causes (van de Merwe et al, 2008), documented history or patient reported

      and
    - documented history of an observation of HL via cystoscopic procedure in which a lesion is defined as a circumscript, reddened mucosal area that can be small vessels radiating towards a central scar, and/or a fibrin deposit of coagulum attached to this area. Lesions may also be linear, fissure-like, and may be bleeding.

[redacted]

[redacted]

See Section 4.3 for detailed inclusion criteria

Key Exclusion Criteria:

[redacted]

See Section 4.4 for detailed exclusion criteria.

Response Measures

Efficacy:

Primary:

- average daily bladder pain score patient experienced over the previous 24-hour period as measured by an NRS of 0 to 10, recorded on a 7-day pain assessment tool

  The primary timepoint is Week 4 following Treatment 1 2nd IP removal.

Secondary:

- number of HLs assessed by the Principal Investigator (PI) during cystoscopy
- composite score of HL calculated based on number, size, and severity of the lesions

[redacted]

Safety:

- adverse events and serious adverse events
- physical examination
- vital signs
- any abnormal cystoscopy findings at insertion and removal

- pregnancy testing for women of childbearing potential
- urine dipstick reagent test
- urine analysis (with urine culture and sensitivity, as applicable)
- urine cytology (at Screening only)
- post-void residual (PVR) urine volume measurement
- hematology and non-fasting serum chemistry
- concomitant medications
- concurrent procedures

Post-use Assessments and IP events

- voiding of the IP
- damage to the IP during insertion or removal procedures
- damage to the IP that is not related to insertion or removal procedures

General Statistical Methods and Types of Analyses:

Modified intent-to-treat (mITT) analysis population: The mITT population will include all patients who were randomized and received at least 1 IP insertion in Treatment 1. The efficacy data will be analyzed as randomized using the mITT population.

Safety analysis population: The safety population will include all patients enrolled in this study and received at least one IP. The safety data will be analyzed as treated using the safety population.

Pharmacokinetic evaluable population: The pharmacokinetic population will include all patients enrolled in this study and who have at least one plasma or urine pharmacokinetic concentration measurement post-IP insertion and for whom the IP is successfully removed.

Per-protocol (PP) analysis population: The PP population will include all patients who retain the 2 consecutive IPs inserted in Treatment 1 for the 28 days of the treatment period and complete the 4 Week Follow-up Visit post removal of the Treatment 1 2nd IP without any significant protocol deviations. Protocol deviations will be determined prior to database lock.

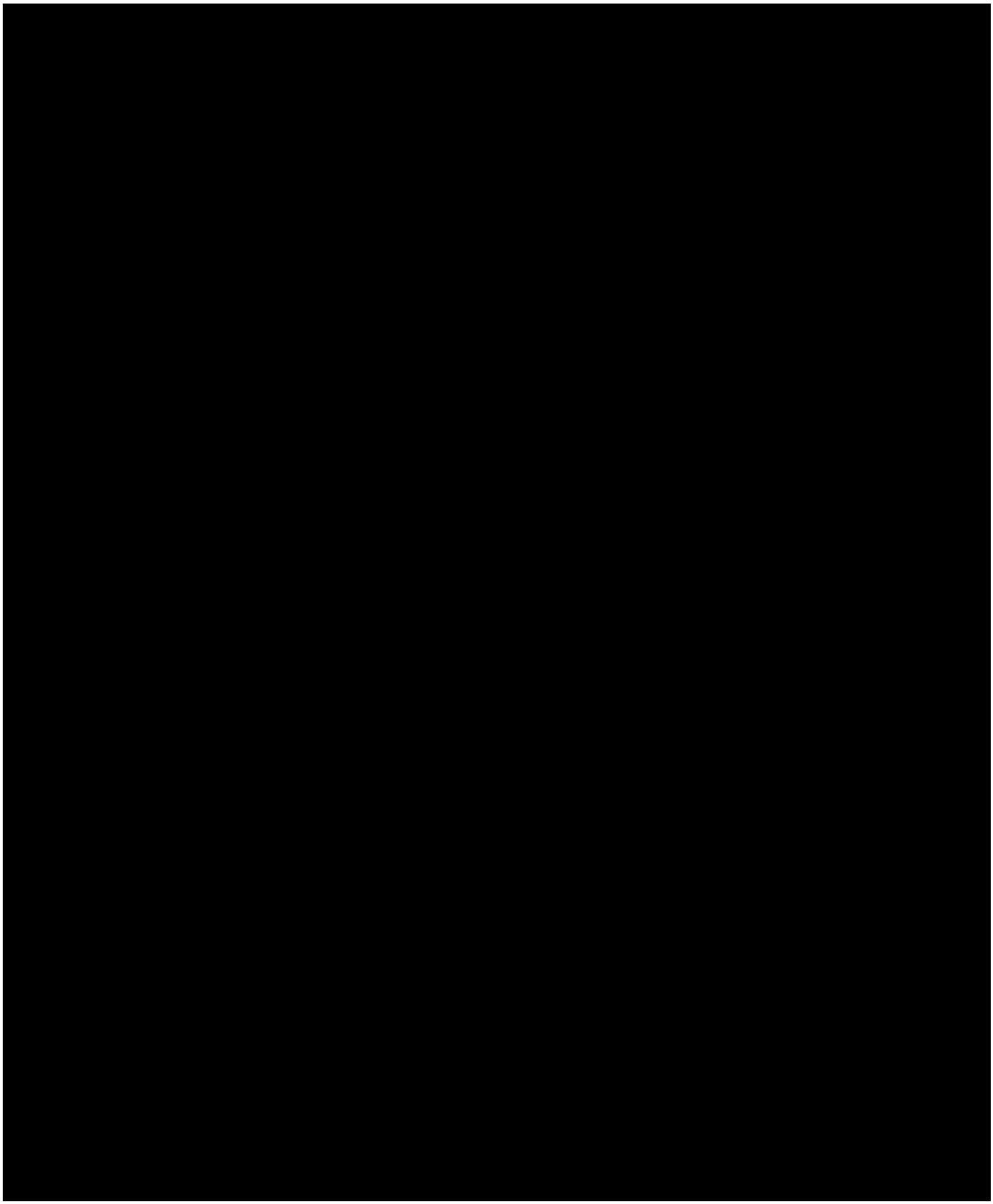
A primary analysis will be conducted at the time when the last patient has completed the primary timepoint (Week 4 following removal of the Treatment 1 2nd IP). The objective of the primary analysis is to support further development of this program in this indication. The final analysis will be conducted when all patients complete or exit the study.

All continuous variables will be summarized showing the number of observations, mean, median, standard deviation, minimum, and maximum values. Discrete variables will be summarized showing the frequency and percentage of the study population. Visual display of efficacy data (value and/or change from baseline) may be presented over time.

The primary efficacy variable will be analyzed using the analysis of covariance (ANCOVA) model using the baseline value as the covariate, and stratification factor (baseline bladder pain NRS: ≤ 5 or > 5) and treatment as factors. Similar ANCOVA analyses will be used for secondary efficacy analyses.

Sample Size Calculation: Approximately 76 patients will be enrolled into the study. Assuming that 5% of the randomized patients will not be evaluable for the primary anlysis, this will ensure 72 evaluable patients overall, including 36 patients in the LiRIS 400 mg/LiRIS 400 mg group, 18 patients in the LiRIS Placebo/LiRIS Placebo group, and 18 patients in the LiRIS Placebo/LiRIS 400 mg group.

A sample size of 36 patients in the LiRIS 400 mg/LiRIS 400 mg group versus 18 patients in the Placebo/Placebo group will have 76% power to detect a difference of 1.152 in mean daily average bladder Pain NRS, assuming that the common standard deviation is 1.67 using a 1-sided 2-group t-test with a 0.05 significance level. The calculation was performed using the commercial [redacted] The standard deviation assumption is based on the results of the TAR-100-105 open-label study, where the standard deviation is the Week 4 Follow-up raw average daily NRS.



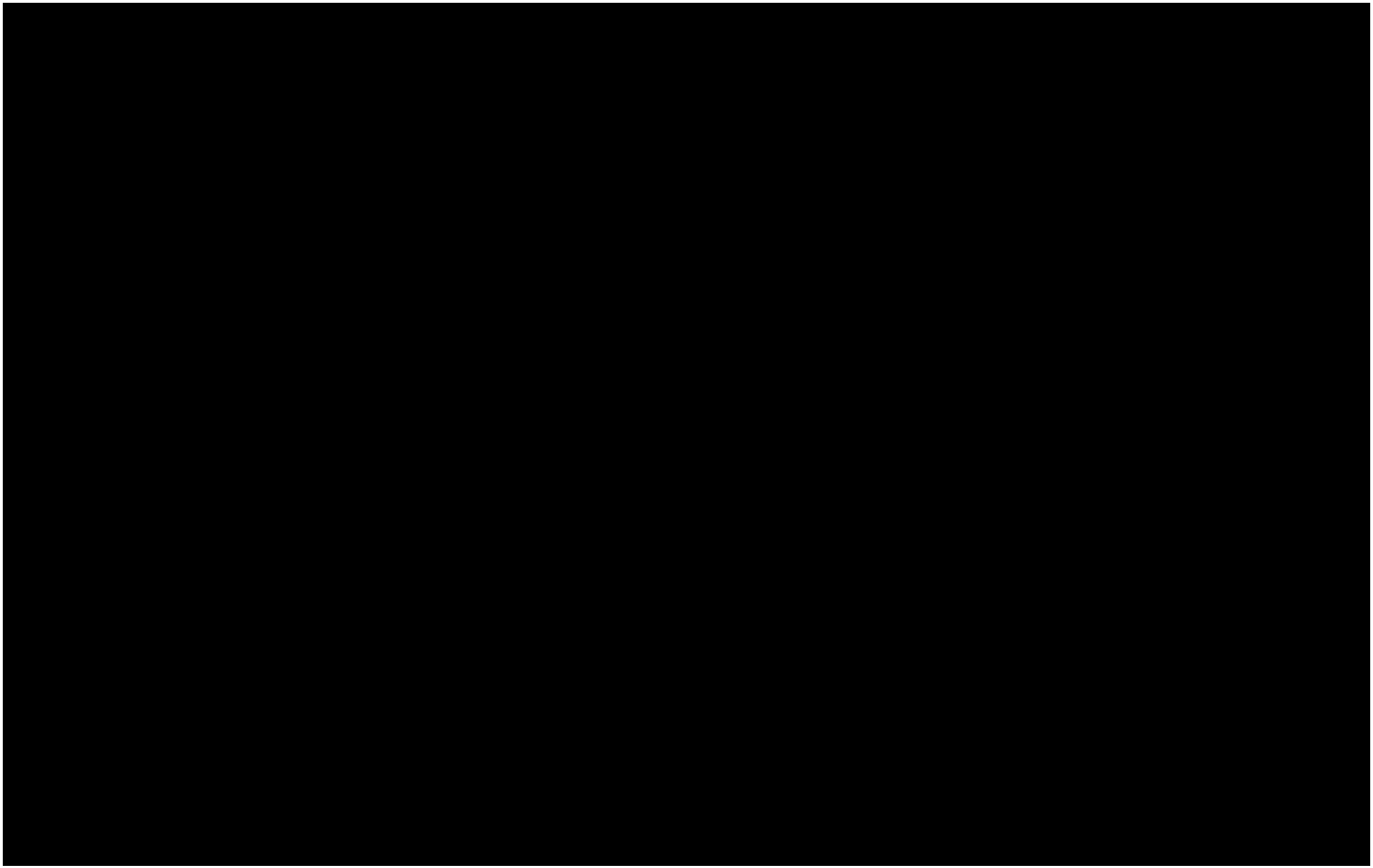


Table 2 Summary of IC Medication/Therapy Requirements in the Study

	Required stable duration prior to Screening (If continuing as stable therapy in the study)	Period off medication/treatment prior to Screening	Permissible Rescue[a] Therapy (Only if previously used the medication prior to study entry with no tolerability issues)
Oral Elmiron® (pentosan polysulfate)	≥ 6 months	≥ 4 weeks	Prohibited
Narcotic Analgesics	≥ 8 weeks (at a dose no greater than 120 mg morphine equivalent per day)	≥ 4 weeks	Permitted eg, tramadol, hydrocodone, oxycodone, fentanyl
All other oral medications used for the treatment of symptoms of IC such as: • Non-narcotic analgesics • Tricyclic antidepressants • Other antidepressants • Anticonvulsants and drugs for neuropathic pain • Antihistamines • Anticholinergics • Medications for LUTS	≥ 8 weeks	≥ 4weeks	Permitted - Any oral pain relieving medications used to treat IC, such as: • analgesics (eg, acetaminophen) • tricyclic and other antidepressants (eg, amitriptyline) • anticonvulsants and drugs for neuropathic pain (eg, gabapentin) Prohibited – • treatments for LUTS eg, anticholinergics • IV lidocaine
Bladder Instillation Therapy	N/A	Last instillation 4 weeks prior to Screening	Prohibited
Bladder Hydrodistention (or any procedure that may result in bladder distention)	N/A	Last treatment 6 weeks prior to Screening (or until no further beneficial effect is noted if greater than 6 weeks)	Prohibited
Botulinum toxin therapy (of any serotype) for any genitourinary condition	N/A	≥ 6 months	Prohibited
Physical Therapy	≥ 8 weeks	≥ 2 weeks	N/A
Fulguration	N/A	≥ 4 weeks	Prohibited

IC = interstitial cystitis; IV = intravenous; LUTS = lower urinary tract symptoms; N/A = not applicable

[a] Use of rescue medications should be minimized in the study and avoided if possible. They may be used on an as needed, short-term basis according to local site practice for patients who have an acute exacerbation of pain ("flare"). All use (dose and time of use) of rescue medication should be recorded in the pain diary.

1. Background and Clinical Rationale

Interstitial cystitis (IC)/bladder pain syndrome (BPS) is a chronic and debilitating urological complex of disorders characterized by symptoms of bladder pain, urinary frequency and urgency. The underlying disease process is poorly understood, however, there are 2 distinguishable and agreed upon phenotypes: the classic form of IC with Hunner's Lesions (HL) (type 3C) and non-lesion IC/BPS (Fall et al, 2014; Logadottir et al, 2014).

IC with HLs was originally described in 1887 as an inflammatory condition of the bladder, as the availability of cystoscopies in the early twentieth century allowed visualization of the pathognomonic bleeding lesions now referred to as HLs (Nordling et al, 2012). The European Society for the Study of IC (ESSIC) provides the following description of these lesions: "The Hunner's lesion typically presents in a singular or multiple form as a circumscript, reddened mucosal area with small vessels radiating towards a central scar, with a fibrin deposit of coagulum attached to this area. This site ruptures with increasing bladder distension, with petechial oozing of blood from the lesion and the mucosal margins in a waterfall manner. A rather typical edema develops post-distension with varying peripheral extension" (Nordling et al, 2012; Logadottir et al, 2012; Killinger et al, 2012).

The disease prevalence of IC/BPS varies widely due to lack of global epidemiological studies as various definitions are still being utilized in the diagnosis of IC/BPS. This is due to the fact that the identification of patients was primarily developed to track the course of the condition and not by identifying IC/BPS patients via patient-reported symptoms which is the current recommendation (Berry et al, 2010). Based on patient self-reported studies of the prevalence of IC/BPS in the United States (US), there are approximately 83,000 men and 1.2 million women with IC/BPS across the US (Hanno et al, 2014). In symptoms-based studies evaluating the prevalence of IC/BPS in the US, across multiple definitions, symptoms of IC/BPS were typically 2 to 3 times more common in women as in men, in which the prevalence was estimated to be approximately 3.3 to 7.9 million women, age 18 or older. Only 9.7% of these women reported having been given an IC/BPS diagnosis which suggests that IC/BPS may be underdiagnosed (Berry et al, 2011; Suskind et al, 2013). The confounding and overlapping conditions that are contributing to the underdiagnoses of IC/BPS seem to be chronic pelvic pain syndrome in women and chronic prostatitis in males (Berry et al, 2011; Suskind et al, 2013).

With regards to the prevalence of the phenotype of IC with HL, the ESSIC (van de Merwe et al, 2008) and the International Painful Bladder Foundation (IPBF) (Meijlink, 2014) describes

IC with HL in the range of 10% to50% of the BPS patient's population. IC with HL patients are underdiagnosed due to confounding factors such as:

- confusion caused by the name Hunner's ulcer while it is not an ulcer: the term Hunner's ulcer suggests that it can always been seen at cystoscopy without hydrodistention
- false impression that HL are rare
- even when cystoscopy with hydrodistention is performed, HL are likely to be detected mainly by experienced urologists. Biopsy may be necessary to prove that it is a HL and/or to exclude a carcinoma in situ

Current guidelines from the American Urological Association (AUA) and ESSIC state that the most effective treatments for IC with HL are fulguration by electrocoagulation, lasercoagulation (burning out and sealing the lesion), or resection (surgical removal of the lesion) (Hanno et al, 2014; Meijlink, 2014). These treatments seem to be most effective, improving dramatically symptoms caused by lesions. Unfortunately, the lesions tend to recur with this chronic condition and these treatments need to be administered accordingly between several months up to 5 years depending on the individual patients. These treatments are considered extremely invasive and painful procedures, they require general anesthesia and might introduce surgical complications. In addition, with repeated treatments, they may compromise the functionality of the bladder with accumulating fibrotic tissue from repeated fulgurations or repeated resections. Current oral treatments targeting symptomatic relief utilized both in IC/BPS and IC with HL are generally unsatisfactory, showing limited efficacy compared with placebo and introduces a systemic side-effects profile (Chancellor and Yoshimura, 2004).

1.1 Study Rationale

A major challenge in the treatment of IC with HL is to deliver effective therapeutic agents to ameliorate bladder symptoms and to intervene in the course of the disease, while minimizing adverse effects in a less invasive and compromising manner.

Lidocaine is a common local anesthetic used in many pain indications across different therapeutic areas. In IC/BPS lidocaine is used for pain treatment as a single agent or in combination with other agents (such as sodium bicarbonate or heparin) via bladder instillation aimed as a multi-modal treatments. It is also used as a rescue treatment for the relief of severe pain in a flare (Meijlink, 2014).

In addition to lidocaine's well established effects on nociception, studies suggest local anesthetics, including lidocaine, may also secondarily suppress inflammation and associated hyperalgesia (Cassuto et al, 2006). In chronic inflammatory conditions such as asthma, lidocaine and lidocaine derivative (non-anesthetic lidocaine analog JMF2-1) exhibit anti-inflammatory properties. Some animal models suggest that lidocaine inhibits respiratory smooth muscle contraction as well as T-cell proliferation and survival through enhancement of intracellular cAMP levels (Olsen et al, 2012; Olsen et al, 2011; Nakahara et al, 2001). Other animal models suggest that lidocaine potentiates the relaxant effect of agents that activate adenylyl cyclase in bovine tracheal smooth muscle due to blockade of muscarinic M2 receptor-mediated signal transduction. It is likely that lidocaine exerts a synergistic effect on the responses to agents that activate adenylyl cyclase in bronchoconstriction associated with the enhanced parasympathetic nerve activity (Yunoki et al, 2003).

Studies of lidocaine intravesical instillation in the bladder of IC/BPS patients and healthy subjects have consistently reported that intravesical administration of lidocaine at exposures up to 800 mg, for durations ranging from 15 minutes to 2 hours, is safe and well tolerated (Birch and Miller, 1994; Henry et al, 2001; Parsons, 2005; Nickel et al, 2008; Higson et al, 1979; Yokoyama et al, 1997; Yokoyama et al, 2000). Preliminary pharmacokinetic data from these studies also indicate a relatively small fraction of the dose administered intravesically is absorbed systemically. In one study, for example, peak lidocaine serum levels observed following daily intravesical instillations of 5mg/kg (~ 350 mg) of lidocaine for 2 days in IC patients averaged 1.3 µg/mL (range: 0.2 to 2.0) (Henry et al, 2001). This exposure is below that commonly achieved following intravenous (IV) lidocaine administration for the management of cardiac ventricular arrhythmias and is well below systemic levels associated with lidocaine toxicity (> 5.0 µg/mL; Lidoderm® Prescribing Information, 2013).

1.2 Investigational Product

The investigational product (IP), LiRIS®, is a passive nonresorbable Lidocaine-releasing intravesical system (LiRIS) whose primary mode of action is the controlled release of lidocaine into the bladder over a 14-day period. [redacted]

1.3 Nonclinical Studies

A series of Good Laboratory Practice (GLP)-compliant repeat-dose toxicity studies have been conducted in female mixed-breed hounds to assess the safety of TARIS Placebo platform (empty device constituent) and LiRIS (100 mg, 200 mg, 400 mg, and 650 mg). Across all studies the system was shown to be well tolerated with no evidence of local or systemic effects, no systemic toxicity and no impact on urodynamics.

1.4 Clinical Studies

A series of phase 1 and phase 2 studies have been conducted in humans including healthy female adults, IC/BPS and IC with HL female patients to assess the safety and efficacy of TARIS Placebo and LiRIS (200 mg, 400 mg, and 650 mg).

The TARIS Placebo system was tested in a phase 1, single-blind, randomized, placebo-controlled (via sham procedure), parallel group study (Study TAR-100-101), to evaluate the positional stability and patient tolerance of the system within the bladder over 14 days, evaluating design implications of the insertion and removal procedures. A total of 10 healthy female volunteers were enrolled in the study; 7 patients underwent insertion and retrieval of the TARIS Placebo system and 3 patients had the sham procedure (cystoscopy only). The results of this study showed that the TARIS Placebo system was generally well tolerated in healthy female volunteers as adverse events such as haematuria, dysuria, urethral pain, and abdominal pain were similar to those seen with the sham procedure.

The LiRIS 400 mg was tested in a phase 2a multicenter, randomized, double-blinded, placebo-controlled study (Study TAR-100-201) to evaluate safety, tolerability, and efficacy in female patients with IC/BPS in North America. The study compared LiRIS 400 mg to LiRIS Placebo over a 14-day treatment period and 4-week follow-up period. Data collected from the 104 enrolled patients showed trends of improvement with LiRIS 400 mg in sub-populations of IC/BPS patients with high bladder pain at baseline (7 or greater on 0 to 10 cm visual analogue scale [VAS]) and in patients 40 years of age or older at time of enrollment. Overall, adverse events seen in 10% or more of enrolled patients were bladder pain, dysuria, haematuria, and urinary tract infections (UTIs). The majority of adverse events were mild or moderate in intensity. There was no meaningful difference in the incidence of these events between the LiRIS 400 mg and LiRIS Placebo groups.

A phase 1b pilot safety, tolerability and preliminary efficacy, multicenter, open-label, ascending dose study (Study TAR-100-103) of LiRIS was conducted in a mixed female patient population with IC/BPS and IC with HL. The study enrolled 16 patients in 2 cohorts

with 7 patients diagnosed with IC with HL and the remaining the 9 patients with IC/BPS. Cohort 1 (200 mg) enrolled 9 patients, and 8 patients completed. Cohort 2 (650 mg) enrolled 9 patients and all 9 patients completed. All enrolled patients had LiRIS inserted and indwelling in the bladder for up to a 14-day period and were followed for safety assessments for 14 days after removal of LiRIS. Cohort 2 (650 mg) patients also had additional long-term safety and efficacy assessments at 60 and 90 days postinsertion. The results of this study show that LiRIS 200 mg and LiRIS 650 mg are well tolerated with the most common adverse events (> 20 % overall) being dysuria, haematuria, and bladder pain. The majority of adverse events observed were mild or moderate in intensity. One serious adverse event of "suicidal ideations" was reported and deemed to be unrelated to LiRIS or the cystoscopy procedure. LiRIS 650 mg resulted in higher plasma concentrations and greater amount of lidocaine and 2,6-xylidine recovered in urine compared with LiRIS 200 mg. However, these plasma concentrations of lidocaine after LiRIS insertion were much lower than those associated with toxicity (> 5.0 μg/mL). 2,6-xylidine concentrations were on average < 10% of the observed plasma concentrations of lidocaine. Overall, both LiRIS 200 mg and LiRIS 650 mg appear to be safe, tolerable, and efficacious in the treatment of bladder pain and irritative voiding symptoms. A subanalysis of the IC with HL patients, showed improvement in inflammatory findings with 6 out of the 7 patients enrolled with pre-existing HLs, revealing a resolution of lesions at the time of LiRIS removal. This interesting finding might be attributed to the anti-inflammatory properties of lidocaine described earlier.

Based on the results from the TAR-100-103 study that showed resolution of lesions, a phase 1b open-label study of LiRIS 400 mg in female IC patients with HL (Study TAR-100-105) was initiated. In this study, patients were treated with 2 consecutive LiRIS 400 mg each, to support the evaluation of lesions resolution compared to baseline as a response to an accumulative dose of 800 mg of lidocaine released continuously over a period of 28 days. This is based on the assumption that the anti-inflammatory mechanism of action would require a higher dose over a longer treatment period to show further improvement in lesion resolution compared to results shown in the TAR-100-103 study, with no additional risk to the patients. The study has completed enrollment (N = 10) at 2 centers in the US. The last patient completed the final study visit, and the data are not yet available for final analysis. To date, no serious adverse events have been reported in the trial.

The LiRIS platform for bladder pain indication was acquired by Allergan from TARIS Biomedical Inc. in August 2014.

The purposes of this study is to develop a better understanding IC with HL and the potential of the LiRIS 400 mg as a therapeutic agent in both symptoms relief and intervening in the

natural course of the disease with resolution of lesions. Therefore, this study is designed to evaluate the treatment of 2 consecutive LiRIS 400 mg versus LiRIS Placebo and will explore the dosing with 2 consecutive LiRIS 400 mg compared with one in population of IC with HL.

2. Study Objective and Clinical Hypothesis

2.1 Study Objective

To evaluate the safety and efficacy of a 28-day period of continuous release of lidocaine inserted into the bladder utilizing 2 consecutive LiRIS 400 mg compared with placebo for the treatment and corresponding symptoms of IC with HL in female patients.

2.2 Clinical Hypotheses

A 28-day period of continuous release of lidocaine inserted into the bladder utilizing 2 consecutive LiRIS 400 mg will have an acceptable safety profile and is more efficacious than placebo for the treatment and corresponding symptoms of IC with HL in female patients.

3. Study Design

This study is a multicenter, randomized, double-blind, placebo-controlled, study to evaluate the safety and efficacy of the LiRIS 400 mg in female patients with IC with HL. This study includes up to 2 treatments. To receive Treatment 1, patients will be randomized in a 2:1:1 ratio to 1 of 3 treatment groups receiving over a 28-day treatment period either:

Group 1: 2 consecutive LiRIS 400 mg (N = 38)

Group 2: 2 consecutive LiRIS Placebo (N = 19)

Group 3: LiRIS Placebo followed by LiRIS 400 mg (N = 19)

Patients who qualify for Treatment 2, will receive LiRIS 400 mg over a 14-day treatment period followed by 4 weeks of observation until exit. Patients will be stratified based on screening baseline pain score (≤ 5 or > 5).

For patients who participate in the study and receive only Treatment 1, the duration will be 28 weeks, including a maximum of 4 weeks of screening, 4 weeks of randomized treatment, and 20 weeks of follow-up post IP removal. For patients who qualify and receive

Treatment 2 (active LiRIS only), the minimum duration of participation is 16 weeks (if qualification and Treatment 2 IP insertion occurs on Week 4 Follow-up Visit post removal of Treatment 1 IP) and the maximum duration of study participation is 36 weeks (if qualification and Treatment 2 IP insertion occurs on Week 20 Follow-up Visit post removal of Treatment 1 IP).

The study IP will be inserted into the bladder using a rigid cystoscope and removed using grasping forceps and a rigid or flexible cystoscope.

Patient-reported pain via the Numeric Rating Scale (NRS), and pain medication use will be recorded on a daily basis throughout the duration of the study on an electronic diary. Patient reported voiding frequency and urgency, including pre- and post-voiding pain will be recorded on a paper bladder diary. [redacted]

4. Study Population and Entry Criteria

4.1 Number of Patients

Approximately 76 patients will be enrolled at approximately 25 sites in the US and Canada to achieve 72 evaluable patients (N = 36, N = 18, and N = 18 in the 3 treatment groups, respectively) based on an anticipated dropout rate of 5%.

4.2 Study Population Characteristics

The study population will consist of adult female patients with a history of IC with HL along with the associated symptoms as previously reported in guidelines by van de Merwe et al (2008).

4.3 Inclusion Criteria

The following are requirements for entry into the study:

[redacted]

[redacted]

5. A diagnosis of IC with HL defined as:

- an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms (LUTS) of more than 6 months duration in the absence of infection or other identifiable causes (van de Merwe et al, 2008), documented history or patient reported

  and

  - documented history of an observation of HL via cystoscopic procedure in which a lesion is defined as a circumscript, reddened mucosal area that can be small vessels radiating towards a central scar, and/or a fibrin deposit of coagulum attached to this area. Lesions may also be linear, fissure-like, and may be bleeding.

[redacted]

[redacted]

4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

1. Patient who is pregnant, nursing, or planning a pregnancy during study participation
2. Patient of childbearing potential who is unable or unwilling to use a reliable form of contraception during the study (as defined in Section 4.5.1.1)

[redacted]

[redacted]

[redacted]

19. Previous exposure to LiRIS in a TARIS clinical study within 6 months prior to Screening.

[redacted]

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. Patient should be instructed to maintain a stable dose of chronic medications during the study whenever possible. Please see Table 2 for a list of permissible medications with the required stable duration prior to Screening (if continuing as stable therapy in the study), the period off medication/treatment prior to Screening, and permissible short-term rescue therapy (medication must have been used previously, prior to study entry with no tolerability issues). See Section 4.5.3 regarding rescue medication.

All medications, adjunct therapies, and concurrent procedures should be recorded on the appropriate electronic case report form (eCRF). If the permissibility of a specific medication/treatment is in question, please contact the assigned Medical Safety Physician of the study.

4.5.1.1 Definition of Females of (Non)Childbearing Potential and/or Acceptable Contraceptive Methods

For purposes of this study, females will be considered of childbearing potential unless they are naturally postmenopausal or permanently sterilized (ie, hysterectomy). Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathological or physiological cause. For women of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: hormonal contraceptives (ie, oral, patch, injection, implant), male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation, bilateral salpingectomy), vasectomized partner, or total sexual abstinence (when this is in line with the preferred or usual lifestyle of the patient).

The investigator and each patient will determine the appropriate method of contraception for the patient during the participation in the study.

If a female becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed and the patient will be exited from the study after appropriate safety follow-up. The investigator will (1) notify the patient's physician that the patient was being treated with an investigational drug LiRIS 400 mg or LiRIS Placebo, and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to the Medical Safety Physician assigned to this study.

4.5.2 Prohibited Medications/Treatments

Use of the following medications/treatments is prohibited throughout study participation:

- botulinum toxin treatment of any serotype for any genitourinary indication

- patients who are not on a stable dose of any oral medications/physical therapy (see Table 2) for the treatment of IC should not use them for the duration of the study unless they are being used as a rescue medication (Section 4.5.3)

  Note: Possible effects on study safety and endpoints should be taken into consideration when initiating treatment during the trial with any of the oral medications listed in Table 2 for an indication outside of IC.

- any intravesical pharmacotherapies (eg, dimethyl sulfoxide [DMSO], sodium hyaluronate [Cystistat®], chondroitin [Uracyst®], pentosan polysulfate sodium [Elmiron®], heparin, lidocaine, sodium bicarbonate, capsaicin or resiniferatoxin)

- use of electrical stimulation or neuromodulation devices (implanted and external) for the treatment of LUTS or pain. If a patient is enrolled into the study with a device still implanted, it must be inactive for 4 weeks prior to treatment on Randomization/Day 0 and must remain inactive for the duration of the study

- hydrodistention (or any other procedure that may result in bladder distention)

- general or spinal anesthesia may not be administered at the same time as the IP insertion/removal

- products other than IP that would result in systemic lidocaine exposure (eg, lidocaine patch [Lidoderm], IV lidocaine, intrathecal lidocaine)

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, the assigned Medical Safety Physician for this study should be notified before the prohibited medication/treatment is administered.

4.5.3 Rescue Medications

Use of confounding medications should be minimized in the study and avoided if possible, however rescue medications may be used on an as needed, short-term basis according to local site practice for patients who have an acute exacerbation of pain ("flare") (Table 2). The following medications may be used:

- any oral pain relieving medication (except herbal medications) that the patient has previously used for IC within the 3 months prior to Screening and has been tolerated

Use of any nonpain relieving medications (eg, anticholinergics) is prohibited as rescue medication.

All usage of rescue medication should be recorded (time of use and dose) on the pain diary by the patient and on the appropriate eCRF by the site staff. In addition sites should question patients at all visits regarding the use of rescue medications between visits and any such usage should be recorded in the appropriate eCRF.

4.5.4 Oral Prophylactic Antibiotics

Oral prophylactic antibiotics use before and after cystoscopy procedures are recommended and should be used per local site practice. Patients shall begin oral prophylactic antibiotics 3 days prior to, on the day of, and following the procedure, for 3 days .

Any oral antibiotics approved for the treatment of UTIs may be used at the discretion of the investigator and must be recorded on the concomitant medications eCRF.

4.5.5 Study Treatment Anesthesia

Study treatment administration and removal may be performed using local anesthesia (general or spinal anesthesia is prohibited) and/or sedation. The type of anesthesia used is at the investigator's discretion, depending on the patient's expected tolerability and available facilities.

One or more of the following options are permitted as per local site practice:

- local anesthesia or lubricating gel to the urethra to facilitate cystoscope insertion
- sedatives (oral or IV) may be administered

All anesthesia should be recorded on the appropriate eCRF.

4.5.6 Special Diet or Activities

No restriction on meals or diet is required for this study. Information about patient tobacco use will be collected in order to exclude those patients samples from the 2,6-xylidine analyses. Information about patients dietary lifestyle will be collected (vegan, vegetarian, non-vegetarian).

5. Study Treatments

5.1 Study Treatments and Formulations

The study treatment is LiRIS 400 mg (AGN-201025).

LiRIS is a passive nonresorbable lidocaine-releasing intravesical system whose primary mode of action is the controlled release of lidocaine into the bladder over a 2-week period. The device constituent of LiRIS (both active and placebo) is constructed of medical grade silicone (elastomer) and nitinol wire, which provides the bladder-retentive property of the system.

5.2 Control Treatment

LiRIS Placebo contains lactose minitablets in place of the lidocaine.

5.3 Methods for Masking/Blinding

All study treatments (active and placebo) and packaging will be identical in order to maintain masking of the study. The study treatment will be identified as an investigational compound. The study number and kit number will be identified on the unit label.

5.4 Treatment Allocation Ratio and Stratification

Patients will be randomized centrally and stratified on Randomization/Day 0 by baseline pain score (≤ 5 or > 5). Each patient within a stratification group will be randomized using an automated randomization system to 1 of 3 treatment groups (LiRIS 400 mg/LiRIS 400 mg; LiRIS Placebo/LiRIS Placebo; LiRIS Placebo/LiRIS 400 mg) in a 2:1:1 ratio.

5.5 Method for Assignment to Treatment Groups/Randomization

Following the Screening period, patients who meet the study inclusion/exclusion criteria and day of treatment criteria will be assigned a randomization number through the interactive voice response system (IVRS)/ interactive web response system (IWRS) which determines the treatment group assignment. Study medication will be labeled with medication kit numbers. The IVRS/IWRS system will provide the site with the specific medication kit number(s) for the patient that corresponds to the treatment group to which the patient was assigned. The site will also use IVRS/IWRS to assign a new kit number to each patient who meets Treatment 2 criteria.

5.6 Treatment Regimen and Dosing

5.6.1 Treatment 1

Eligible patients will be randomized on Randomization/Day 0 to receive Treatment 1, LiRIS 400 mg/LiRIS 400 mg; LiRIS Placebo/LiRIS Placebo or LiRIS Placebo/LiRIS 400 mg (Section 5.4). Patients will have the Treatment 1, 1st IP inserted on Randomization/Day 0 and removed on Day 14. On the same day, following the 1st IP removal, the 2nd IP (LiRIS 400 mg or LiRIS Placebo) will be inserted and subsequently removed on Day 28. Patients will be followed for 20 weeks post IP removal for additional safety and efficacy assessments. In the event that a patient does not receive Treatment 2, they will exit the study at Treatment 1 Week 20 Follow-up Visit.

5.6.2 Treatment 2

All patients will receive LiRIS 400 mg for their second treatment. Patients may request, qualify, and receive Treatment 2 IP from Week 4 Follow-up until Week 20 of Treatment 1. In the event that the Treatment 2 IP cannot be inserted on the day of qualification, Treatment 2 may be rescheduled within 14 days of qualification. The LiRIS will be inserted on Treatment 2/Day 0, and will be removed on Day 14. Patients will be followed for 4 weeks post-removal and will be exited from the study.

5.6.3 Premature IP Removal

The IP will be removed immediately and appropriate medical therapy should be instituted immediately, if any of the following occur:

- if patient requests removal of the IP for any reason

- if patient becomes pregnant
- haematuria that is considered by the investigator to be clinically significant
- urinary retention that is considered by the investigator to be clinically significant
- allergic reaction (shortness of breath, generalized edema, etc) to either LiRIS device constituent materials (silicone, nitinol), drug (lidocaine or lactose) and/or excipients (povidone, polyethylene glycol)
- signs of lidocaine toxicity (Xylocaine® Injection Package Insert, 2010) where toxicities associated with lidocaine include but are not limited to light-headedness, nervousness, perioral tingling, tingling or numbness of the tongue, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression, respiratory arrest and cardiovascular reactions which are usually depressant in nature and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest
- a condition or situation that, in the investigator's opinion, may put the patient at significant risk

5.7 Storage of Study Medications/Treatments

The study medication must be stored in a secure area and administered only to patients entered into the clinical study, at no cost to the patient, in accordance with the conditions specified in this protocol.

IP must be stored at room temperature [redacted] and protected from light, representing a usual and customary working environment. The IP must not be frozen. Sites must report any temperature excursions as described in the Study Manual or contact Allergan or its designee for further instructions.

5.8 Treatment Administration

The insertion, removal, and inspection of the IP are to be completed by the investigator(s) involved with the study. Detailed instructions for the insertion and removal of the IP are in the Study Manual .

5.8.1 Day of Treatment Criteria

The following day of treatment criteria must be fulfilled prior to the administration of study treatment.

- confirm that patient did not have a symptomatic UTI during the baseline pain eligibility criteria assessment period
- negative urine dipstick reagent strip test (for leukocyte esterase and/or nitrites) and, in the investigator's opinion, patient is asymptomatic for a UTI on the day of study treatment
- negative urine pregnancy result (for patients that are of child bearing potential)
- investigator continues to deem treatment is appropriate and no condition or situation exists which, in the investigator's opinion, puts the patient at significant risk from receiving treatment

5.8.2 Qualification for Retreatment

Patients can request retreatment (Treatment 2) at any time from the Week 4 Follow-up clinic visit up through the Week 20 Follow-up clinic visit. A patient will be eligible to receive Treatment 2 (LiRIS 400 mg) only if all of the following criteria are met:

- completed Treatment 1 schedule of visits and procedures from the Week 4 Follow-up visit through qualification, in the opinion of the investigator
- negative urine dipstick reagent strip test (for leukocyte esterase and/or nitrites) and, in the investigator's opinion, patient is asymptomatic for a UTI on the day of study treatment
- negative urine pregnancy result (for patients that are child bearing potential) and are willing to continue using acceptable method of contraception
- Investigator continues to deem treatment is appropriate and no condition or situation exists which, in the investigator's opinion, puts the patient at significant risk from receiving treatment

6. Response Measures and Summary of Data Collection Methods

6.1 Efficacy Measures

6.1.1 Primary Efficacy Measure

- average daily bladder pain score patient experienced over the previous 24-hour period as measured by an NRS of 0 to 10, recorded on a 7-day pain assessment tool.
  The primary timepoint is Week 4 following Treatment 1 2nd IP removal.

6.1.2 Secondary Efficacy Measures

- number of HLs assessed by the PI during cystoscopy
- composite score of HL calculated based on number, size, and severity of the lesions

6.1.3 Other Efficacy Measures

[redacted]

6.1.4 Health Outcomes Measures

[redacted]

- [redacted]

6.2 Pharmacokinetics Measures

[redacted]

6.3 Safety Measures

- adverse events and serious adverse events
- physical examination
- vital signs
- any abnormal cystoscopy findings at insertion and removal
- pregnancy testing for women of childbearing potential
- urine dipstick reagent test
- urine analysis (with urine culture and sensitivity, as applicable)
- urine cytology (at Screening only)
- post-void residual (PVR) urine volume measurement
- hematology and non-fasting serum chemistry
- concomitant medications
- concurrent procedures

6.4 Post-use Assessments and Investigational Product Events

- voiding of the IP
- damage to the IP during insertion or removal procedures
- damage to the IP that is not related to insertion or removal procedures

6.5 Examination Procedures, Tests, Equipment, and Techniques

Screening procedures can commence once the informed consent and data authorization/protection form have been obtained. Screening will be considered to have started (eg, Day -28) at the time of the first Screening activity or procedure. On completion of Screening, when all the required inclusion/exclusion have been met, the patient will be randomized and be considered enrolled into the study.

Evaluations should be performed by the same evaluator throughout the study whenever possible. If it is not possible to use the same evaluator to follow the patient, then it is preferable to have the evaluations overlap (examine the patient together and discuss findings for at least one visit).

6.5.1 Medical History/Demographics

A complete medical history will be obtained and is to include diagnosis or symptom, date of onset, current status, associated surgical procedures, detailed genitourinary history, prior medications/treatments, and reasons for discontinuation. In addition key demographics (ie, information about patients dietary lifestyle [vegan, vegetarian, non-vegetarian], smoker versus non-smoker) will be documented for each patient.

6.5.2 Physical Examination

The physician or appropriately qualified designee will perform a complete physical examination (PE) and examine the patient for any physical abnormalities of the following body systems: head, ears, eyes, nose, and throat (HEENT) and neck, cardiovascular, respiratory, abdomen, musculoskeletal, and skin systems will be performed at the appropriate scheduled visits (see Table 1).

An abbreviated PE includes cardiovascular, respiratory, and abdomen examination. Please refer to Table 1 for the scheduled visit in which the abbreviated PE should be performed compared with a complete PE.

6.5.3 Pelvic Examination

A pelvic examination by a physician investigator should be performed to ensure that the urethra and bladder are palpated last. The initial examination should comprise visual inspection of the external genitalia for signs of infection, tumors, or urethral caruncle, a superficial tactile examination of the external genitalia to elicit superficial non-bladder related tenderness and a careful, gentle palpation of the vulval fourchette and levator ani muscles to assess pelvic floor pain etiology and to rule out high muscle-tone pelvic floor dysfunction as the primary source of the patient's pain. Finally the posterior urethra, bladder neck, and bladder should be palpated to elicit bladder-related pain. This examination must be included as a part of the Screening period PE.

6.5.4 Vital Signs, Weight and Height Measurements

Vital signs will be measured prior to any invasive procedures as outlined below:

- pulse rate (beats per minute): patients should be resting in a seated position
- blood pressure (mm Hg): patients should be resting in a seated position. Systolic/diastolic blood pressure is then measured with a sphygmomanometer.
- temperature (^{o}F or ^{o}C): patients should be seated and the body temperature taken according to local site practice
- body weight (Screening and exit) and height (Screening visit only) will be measured according to local site practice

6.5.5 Clinical Laboratory Assessments

All clinical laboratory samples will be analyzed at a central facility. For schedule of blood and urine samples collection, please refer to Table 1.

Analytes will be tested as specified below:

Hematology: red blood cells (RBC); RBC Indices: mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC morphology; white blood cells (WBC); WBC differential (% and absolute): neutrophils, lymphocytes, monocytes, eosinophils, basophils, hematocrit; hemoglobin; and platelets

Blood Chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT [SGPT]), aspartate aminotransferase (AST [SGOT]), total and direct bilirubin, blood urea nitrogen (BUN), calcium, chloride, creatinine, gamma glutamyltransferase (GGT), globulin, non-fasting glucose, potassium, total protein, and sodium

Urine Analysis and Urine Culture and Sensitivity: Urinalysis will be performed at all clinic study visits; a urine culture and sensitivity test will also be performed when urinalysis results are suggestive of a potential UTI (positive leukocyte esterase, nitrites, blood and/or microscopic sediments such as WBCs, RBCs, and/or bacteria).

Urine analytes to be tested are listed below:

Urinalysis: Color, appearance, specific gravity; pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin, urobilinogen, crystals; microscopic examination if positive for protein, leukocyte, occult blood, nitrite, or crystals

Urine Culture and Sensitivity: Culture, quantitation, isolation, identification, and susceptibility

Urine cytology is performed at the Screening visit only. Abnormal urine cytology suspicious for a urothelial malignancy should be investigated by the investigator according to local site practice, and only if such malignancy is ruled out should the patient be enrolled. Results of the investigation will be recorded in the source documents.

Serum and Urine Pregnancy Test: Beta-human chorionic gonadotropin (β-HCG) performed. Pregnancy testing will be conducted for women of childbearing potential using serum β-HCG test with the exception of any day of IP insertion where urine will be used.

Urine Dipstick Reagent Strip Tests (Urine Dipstick): The urine dipstick is used to identify a potential UTI and to provide immediate information to the investigator.

6.5.6 Pharmacokinetic Analysis Assessments

All enrolled patients will have blood and urine collected for pharmacokinetic analysis of lidocaine and 2,6-xylidine (non-smokers only) during both Treatment 1 and Treatment 2 (if applicable).

Plasma samples will be collected and stored at -20°C or colder until shipped to the central laboratory facility. Detailed instructions for the collection, processing, storage and shipment of samples are provided in the Central Laboratory Manual.

6.5.7 Bladder Post-void Residual

Bladder PVR is to be assessed per the site's standard of care method (eg, bladder scan) but should be performed preferably immediately after voiding. The same method should be consistently used throughout the study. Please see Table 1 for the visits at which PVR should be assessed.

6.5.8 Cystoscopic Examination

All patients will undergo a cystoscopic examination on the days of Insertion of the IP to rule out the presence of any bladder or urethra anatomical feature that, in the opinion of the investigator, might prevent the safe placement, indwelling use, or removal of IP, such as bladder fistulae or stone. In addition, prior to the intial IP insertion on Day 0, the presence of HLs will be confirmed. If during the cystoscopic exam, the investigator discovers an abnormality that would prevent the safe placement, indwelling use, or removal of the IP, the patient will not receive treatment and will be withdrawn from the study.

A brief cystoscopic examination for safety purposes will also be conducted on all patients at the Treatment 1 and Treatment 2 Day of Removal Visits (see Table 1).

During each cystoscopy, the investigator will count the number of lesions visible while performing the bladder scan for bladder mapping.

Investigators may recommend that the patient take pain medication up to 6 hours prior to the cystoscopic procedure and continuing for 24 hours after the procedure to minimize patient anxiety and discomfort.

6.5.9 Bladder Mapping

During the cystoscopic exams, a standardized video capture protocol for bladder mapping will be followed in order to assess any changes in the number, size, and severity of lesions during the study as a result of treatment.

6.5.10 Insertion and Removal of IP

For instructions on insertion and removal of IP, please see the Study Manual.

6.5.11 Post-use Assessment

Immediately after removal of the IP, the investigator will take 2 photographs of the IP (wireform side up and wireform side down), and will perform a visual inspection of the IP to confirm that it was removed from the patient in its entirety and none of the IP components (nitinol wire, silicone) are missing. The investigator will document any observations of visible damage or changed appearance of IP (eg, wireform protrusion, torn silicone, change in color, etc) in the eCRF, and notify Allergan or designee within 48 hours so that a product investigation can be initiated if appropriate. If the IP is not removed from the patient in its entirety, the investigator should conduct appropriate testing to confirm that no IP components are left indwelling in the patient, such as a pelvic examination, abdominal x-ray, abdominal ultrasound, and/or cystoscopic exam.

Each IP removed from the bladder of a study patient will be retained and sent to Allergan for a post-use assessment. Detailed instructions for the storage and shipment of the IP post-removal are provided in the Study Manual.

6.5.12 Bladder Pain NRS

A pain assessment tool will be utilized in the study to capture the daily average pain and the daily worst pain scores on an electronic hand held device. Patients will be asked to rate their daily pain on a pain NRS consisting of an 11-point integer scale ranging from 0 for “no pain” to 10 for “worst pain imaginable”. The pain assessment tool will be provided to patients at the Screening visit and patients will be instructed on how to correctly complete the bladder pain assessment by the site staff. If the patient has a confirmed or suspected UTI, pain data should not be collected until the signs and symptoms of the UTI have resolved.

The pain assessment will continue every day up to and including the day prior to the Exit Visit. Patients should complete the pain assessment questions at approximately the same time each day on the pain assessment tool (preferably at the end of each day, prior to 12:00 midnight, with instruction that it reflects the last 24-hour period).

Baseline and Follow-up Visit Pain Assessment

The baseline pain assessment will be calculated based on at least 5 consecutive days of data collected in the 7 days immediately prior to the Randomization/Day 0 visit to determine eligibility and obtain baseline values. Pain assessment data collection should be completed for at least 14 days immediately prior to Randomization/Day 0 in order to acclimate the patient to the process of assessing their pain on a daily basis.The primary timepoint for the

daily average pain score is at 4 weeks following Treatment 1, 2nd IP removal. The patient's Pain NRS for this timepoint will be the average of the 7-day "average pain in your bladder over the last 24 hours".

If the patient's study visit is rescheduled, the site must ensure that adequate time has been provided for the patient to record at least 5 consecutive pain assessment days during the 7 days immediately prior to the rescheduled visit.

6.5.13 Bladder Diary

A paper bladder diary will be utilized in the study to capture micturition parameters. Prior to receiving the diary, patients will be instructed and trained on the use of the diary, the data to be collected and instructed on how to correctly complete the bladder diary by the site staff.

Patients should enter data into the bladder diary following each void (day and night) for 3 consecutive days immediately prior to the designated clinic visit (see Table 1).

The 3-day bladder diary will capture the number of day-time voids and the number of night-time voids (where night time is defined as the time the patient goes to bed until the time the patient gets out of bed the next morning) over a period of 3 days. Patient will also indicate all urinary urgency episodes defined as time they experienced a sudden and urgent need to urinate whether it was associated with a recorded void or not. The bladder diary will also capture patient-reported pre-void and post-void bladder pain.

6.5.14 Pain Catastrophizing Scale

The PCS is a 13-item self-administered scale which assesses the psychological impact of pain that will be evaluated at the Screening visit for study eligibility. Items are rated on a scale from 0 to 4 and the PCS has 3 different categories: Rumination, Magnification, and Helplessness. It is hypothesized that pain catastrophizing is related to various levels of pain, physical disability, and psychological disability in clinical and nonclinical populations.

[redacted]

[redacted]

6.5.18 Concomitant Medications and Concurrent Procedures

Patients will be instructed to capture all pain medication (stable dose and rescue medications) taken for IC pain during the study on the electronic diary which will capture what medication was taken and when (date and time). Site staff will review the pain medication electronic

diary and capture missing or incomplete pain medication information as required. Site staff will also query patients regarding use of any other medications while participating in the study.

Concomitant medication information, including name of medication, dose, route, date will be collected at each study clinic and phone visit starting at the time of Screening and ending at the patient Exit Visit (either at completion of follow-up to Treatment 1 or Treatment 2, as applicable).

All concomitant medications and concurrent procedures must be recorded in the eCRF with all specific details associated with each use of the medication/procedure.

6.5.19 Adverse Events

Details regarding the definitions, documentation, and reporting of adverse events/serious adverse events are in Section 9.

6.5.20 IP Events

An IP event includes any observation of the IP not performing as intended. Examples of IP Events are:

- voiding of the IP
- damage to the IP during insertion or removal procedures
- damage to the IP that is not related to insertion or removal procedures

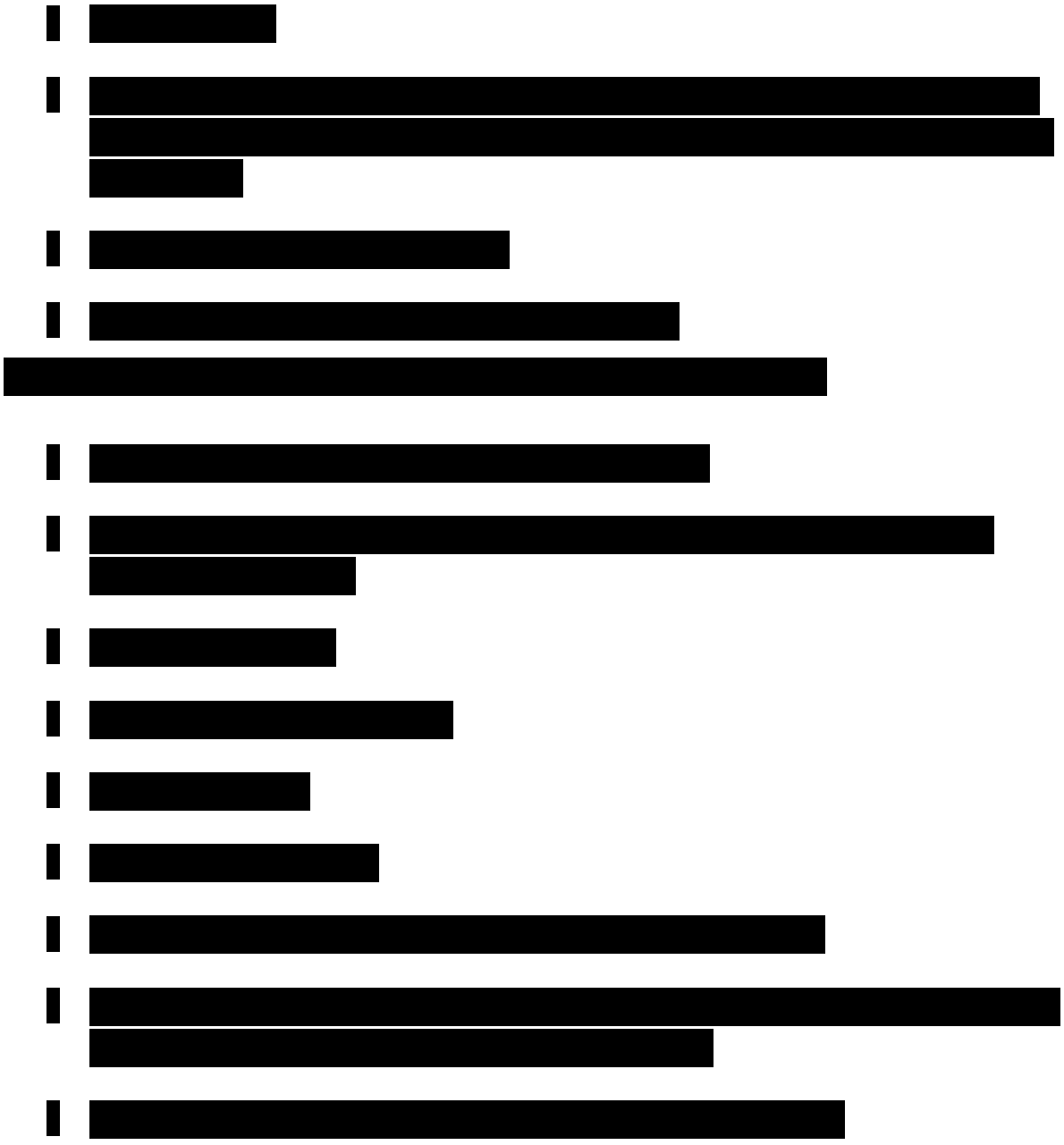
An IP Event could occur any time between when the IP is removed from the packaging through the insertion/removal procedures and the return of the IP.

Each IP Event will be assessed by the investigator to determine if it is associated with an adverse event, and any adverse events identified will be managed according to details in Section 9.

All IP Events, in the opinion of the investigator, should be reported to Allergan or designated representative.

6.6 Other Study Supplies

The following will be provided by Allergan:



6.7 Summary of Methods of Data Collection

Pain assessment and pain medication use will be recorded by the patient on an electronic diary. Voiding frequency and urgency, and pre- and post-void pain scores will be reported by patients in a paper bladder diary. All clinical study data will be entered into an electronic data

capture (EDC) system via eCRFs. Source documents will be used and stored at the sites, and may include a patient's medical records, hospital charts, clinical charts, patient chart, copy of the EDC file, as well as the results of diagnostic tests (if performed).

7. Statistical Procedures

All statistical analyses will be detailed in the study statistical analysis plan (SAP), which will be finalized prior to database lock. This document will provide a more technical and detailed description of the proposed data analysis methods and procedures. Two analyses are planned for this study, including the primary analysis and the final analysis. The primary analysis will be conducted at the time when the last patient completes the primary timepoint that is Week 4 following Treatment 1 2nd IP removal. The final analysis will be conducted when all patients complete or exit the study.

7.1 Analysis Populations

The modified intent-to-treat (mITT) analysis population: The mITT population will include all patients who were randomized and received at least 1 IP insertion in Treatment 1. The efficacy data will be analyzed as randomized using the mITT population.

Safety analysis population: The safety population will include all patients enrolled in this study and received at least one IP. The safety data will be analyzed as treated using the safety population.

Pharmacokinetic evaluable population: The pharmacokinetic population will include all patients enrolled in this study and who have at least one plasma or urine pharmacokinetic concentration measurement post-IP insertion and for whom the IP is successfully removed.

Per-protocol (PP) analysis population: The PP population will include all patients who retain the 2 IP inserted in Treatment 1 for the 28 days of the treatment period and complete the 4 Week Follow-up Visit post removal of the 2nd IP of Treatment 1 without any significant protocol deviations. Protocol deviations will be determined prior to database lock.

7.2 Collection and Derivation of Primary, Secondary, and Other Efficacy Assessments

Average daily bladder pain NRS: The pain NRS will be used to assess bladder pain over the previous 24-hour period. The pain NRS consists of an 11-point integer scale ranging from 0 for "no pain" to 10 for "worst pain imaginable." Patients are instructed to complete the pain

NRS in an electronic handheld diary by choosing the number that answers the following question regarding their bladder pain:

Please describe the average pain in your bladder over the last 24 hours.

The patient's baseline pain NRS will be the average of the 7-day "average pain in your bladder over the last 24 hours" NRS scores from the 7 reported days prior to randomization/1st IP insertion.

Study baseline for a patient is defined as the last measurement available prior to the first treatment.

Missing Data

Every effort will be made to obtain required data at each scheduled evaluation from all patients who have been enrolled. Missing data will only be imputed for the analysis of the primary efficacy variable.

7.2.1 Primary Efficacy Variables

The primary efficacy variable is the change in average daily bladder pain NRS at Week 4 Follow-up Visit post removal of 2nd IP of Treatment 1 as compared to study baseline.

The average daily pain NRS of the preceding 7 days (at least 5 consecutive days) will be calculated and used to calculate baseline and change from baseline at each scheduled visit. If no data are available for at least a period of 5 consecutive days, that average will be considered missing for that patient. The primary timepoint is 4-week follow up after removal of the 2nd IP of Treatment 1. If there is no valid Week 4 Follow-up NRS assessment and there is a valid Week 2 or 3 Follow-up NRS assessment, the Week 4 Follow-up value will be imputed using the latest of the 2 values that is available (ie, Week 2 or 3 Follow-up).

7.2.2 Secondary Efficacy Variables

There are 2 secondary efficacy variables:

- change from baseline in number of HLs assessed by the PI during cystoscopy

  During each cystoscopy, the investigator will count the number of lesions visible while preforming the bladder scan for bladder mapping.

- change from baseline in composite score of HL calculated based on number, size, and possibly severity of the lesions

  A standardized video capture protocol for bladder mapping will be followed in order to assess any changes in the number, the size and the severity, of lesions during the study as a result of treatment.

[redacted]

[redacted]

7.3 Hypothesis and Methods of Analysis

For the primary efficacy analysis, the null hypothesis is that the mean change from baseline in average daily bladder pain NRS at Week 4 Follow-up post IP removal visit is the same

between the LiRIS 400 mg/LiRIS 400 mg group and the LiRIS Placebo/LiRIS Placebo group (2 consecutive placebo's).

The alternative hypothesis is that the mean change from baseline in average daily bladder pain NRS at Week 4 Follow-up post IP removal is different between the LiRIS 400 mg/LiRIS 400 mg group and the LiRIS Placebo/LiRIS Placebo group.

Methods of Analysis

All continuous variables will be summarized showing the number, mean, median, standard deviation, minimum, and maximum values. Discrete variables will be summarized showing the frequency and percentage of the study population. As this is a phase 2 trial, there will be no p-value adjustment for multiplicity. Plots of efficacy variables (value and/or change from baseline) will be presented over time.

7.3.1 Demographics, Baseline Characteristics and Disposition Analyses

Demographic and baseline characteristic data, including age, race, ethnicity, and abnormal PE results will be summarized and presented by treatment group for Treatment 1 and Treatment 2 separately.

Patient disposition for both Treatment 1 and Treatment 2 will be displayed by treatment group. For those discontinuing the study prematurely, the reason for study termination will be recorded and time on study will be calculated.

7.3.2 Efficacy Analyses

All efficacy analyses will be performed on the mITT population. Analyses of the primary efficacy variable will also be performed on the PP population.

Plots of values and change from baseline or percentage in each variable category, as appropriate, will be presented by treatment over time.

All analyses are based on 2-sided tests with significance level of 0.10 unless otherwise specified.

7.3.2.1 Primary Efficacy Analyses

The primary endpoint was the change in bladder pain at Week 4 Follow-up Visit post last IP removal of Treatment 1 as compared to study baseline.

The average daily pain NRS of the preceding 7 days (at least 5 consecutive days) will be calculated and used to calculate change from baseline at each scheduled visit. Calculation of averages will employ available data without imputation. If no data are available for a given 7-day period (at least 5 consecutive days) that average will be considered missing for that patient.

The change from baseline in average daily bladder pain score at Week 4 Follow-up Visit post IP removal of Treatment 1 will be analyzed using the analysis of covariance (ANCOVA) model, using the baseline value as the covariate, and stratification factor (baseline bladder pain NRS: ≤ 5 or > 5) and treatment as factors. If there is no valid Week 4 Follow-up NRS assessment and there is a valid Week 2 or 3 Follow-up NRS assessment, the Week 4 Follow-up value will be imputed using the latest of the 2 values that is available (ie, Week 2 or 3 Follow-up).

The same ANCOVA analysis will also be performed at all other postbaseline timepoints.

7.3.2.2 Secondary Efficacy Analyses

The analysis of the continuous secondary efficacy variables at Week 4 Follow-up Visit post IP removal of Treatment 1 may be analyzed similarly as for the primary efficacy variable of average daily bladder pain NRS, as described in Section 7.3.2.1 Primary Efficacy Analyses. However, no imputation method will be applied.

[redacted]

[redacted]

7.3.3 Safety Analyses

Safety data will be analyzed using safety population.

Safety assessments will be reported by treatment group and will include:

- adverse events
- clinical laboratory results
- urinalysis
- urine culture and sensitivity
- vital signs
- PVR volumes

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ classification (SOC) using MedDRA.

The following analyses will be performed:

1. Summaries by treatment group and overall for Treatment 1
2. Overall summaries for all patients who received Treatment 2
3. Summaries for patients who participated in both Treatment 1 and Treatment 2 by treatment group and overall

Safety Analyses

1. Occurrence of adverse events using MedDRA preferred term, primary SOC, and severity. If a patient experiences multiple events that map to a single preferred term, the greatest severity and strongest investigator assessment of relation to the IP will be assigned to the primary SOC and preferred term for the appropriate summaries.
2. All adverse events for individual patients showing both verbatim, preferred term, and primary SOC
3. Serious adverse events and adverse events related to the IP, the device constituent alone (silicone device/nitinol wire/elastomer components), and the drug (lidocaine) constituent alone; overall summary by preferred term, primary SOC, and severity
4. Serious adverse events and adverse events related to the procedure (cystoscopy, IP insertion procedure or the IP removal procedure); overall summary and summary by preferred term, primary SOC, and severity
5. Descriptive summaries of clinical laboratory results (see Section 6.5.5 for detailed listings of the specific laboratory analytes)
6. Clinical laboratory abnormality shifts from baseline
7. Descriptive summaries of vital signs including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature
8. Descriptive summaries of PVR volume measurements

9. Prior and concomitant medication (coded using World Health Organization [WHO]-Drug Dictionary)

7.4 Pharmacokinetic Analysis

Blood and urine concentration data generated for lidocaine and 2,6-xylidine will be used for pharmacokinetic assessment in plasma and urine. A contributing report will be provided for inclusion in the final report.

7.5 Missing Data

Every effort will be made to obtain required data at each scheduled evaluation from all patients who have been enrolled. Missing data will only be imputed for the analysis of the primary efficacy variable. Any deviations to the SAP made after database lock will be documented in the final Clinical Study Report.

7.6 Subgroup Analyses

There is no pre-planned subgroup analysis. Any subgroup analysis will be done in an ad hoc manner after data base lock.

7.7 Sample Size Calculation

Based on the assumption that 5% of the randomized patients will not be evaluable for the primary analysis, approximately 76 patients will be enrolled into the study to ensure 72 evaluable patients overall. At a randomization ratio of 2:1:1, 72 evaluable patients will ensure that there will be about 36 patients in the LiRIS 400 mg/LiRIS 400 mg group, 18 patients in the LiRIS Placebo/LiRIS 400 mg group, and 18 patients in the LiRIS Placebo/LiRIS Placebo group.

A sample size of 36 patients in the LiRIS 400 mg/LiRIS 400 mg group versus 18 patients in the LiRIS Placebo/LiRIS Placebo group will have 76% power to detect a difference of 1.152 in mean daily average bladder Pain NRS, assuming that the common standard deviation is 1.67 using a 1-sided 2-group t-test with a 0.05 significance level. [redacted] The standard deviation assumption is based on the results of the TAR-100-105 open-label study, where the standard deviation is the Week 4 Follow-up raw average daily NRS.

7.8 Interim Analyses

After approximately 50% of patients enrolled complete the Treatment 1 Week 4 Follow-up visit, an estimate of the standard deviation for the primary variable may be derived based on the blinded data review. If such an assessment results in a drastically different standard deviation than what is assumed for the derivation of the sample size in the protocol, the study sample size may be decreased or increased, depending on the result of the sample size derivation.

Futhermore, an interim analsyis may be performed after at least 25 patients have been enrolled. If such an interim analysis is to be performed, details of the interim analysis and procedures to maintain blinding of treatment groups and confidentiality of results will be presented in the SAP.

8. Study Visit Schedule and Procedures

Please see Table 1 for the schedule of visits and procedures, Figure 1 for the visit flow chart, and Section 6.5 for detailed information on study procedures, tests, equipment, and techniques.

8.1 Patient Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective patients as defined by the criteria in Sections 4.3 and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

8.1.2 Informed Consent and Patient Privacy

The study will be discussed with the patient and a patient wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The patient must also give authorization (US only) and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

Each patient that provides informed consent and/or assent will be assigned a patient number by IVRS/IWRS that will be used on patient documentation throughout the study.

8.2 Procedures for Final Study Entry

Final study eligibility will be determined at the Randomization/Day 0 visit to confirm that patient baseline pain assessment and bladder diary record support protocol requirement for IC with HL. In addition, the investigator should confirm that the "day of treatment criteria" have been fulfilled (Section 5.8.1). Patients should continue to meet other inclusion and exclusion criteria as specified in Sections 4.3 and 4.4 of the protocol.

A patient is considered to have entered the study when they are randomized to treatment.

See Section 5.5 for the method for assignment to treatment groups/randomization.

8.3 Visits and Associated Procedures

For a summary of the procedures to be performed, see Table 1 (Schedule of Visits and Procedures). A description of individual procedures is provided in Section 6.5. The total number of clinic visits and study duration for each patient will depend on whether patients request and qualify for retreatment. Evaluations should be performed by the same evaluator throughout the study whenever possible. During the study, every effort should be made to perform the study procedures as indicated in Table 1.

8.4 Instructions for the Patients

Patients will be instructed on the following:

- pain assessment tool and bladder diary completion (Sections 6.5.12 and 6.5.13)
- complete and bring diaries (electronic and paper) to the study site at each scheduled clinic study visit
- contact the study site (or have a family member or friend contact the study site) to report any hospitalizations
- maintain the dose of any concurrent medication. If there are changes to medications, dosage, or frequency, the changes should be reported to the investigator at the next study visit.
- report all usage of rescue medications to the investigator at the next study visit (see Section 4.5.3)

- call the study site if they are experiencing any difficulties following study procedures
- call the study site as soon as possible in order to reschedule, if the patient cannot make their next scheduled study visit

8.5 Unscheduled Visits

Unscheduled visits can be performed if safety concerns arise and at the discretion of the investigator. Additional examinations may be performed as necessary to ensure the safety and wellbeing of patients during the study. eCRFs will be completed for each unscheduled visit.

8.6 Compliance With Protocol

Participating patients should be able to adhere to the diary completion and testing parameters as described in this protocol.

Data will be recorded on the appropriate eCRF supported by appropriate source documentation. At each visit, patients should be asked if any concomitant medications had been used, if they had undergone any concurrent procedures (nonstudy procedures), and their compliance with the protocol since the previous visit.

8.7 Early Discontinuation of Patients

Patients may voluntarily withdraw from the study at any time. If the withdrawal occurs during the treatment period in which the IP is in the patient's bladder, the patient should contact the study site to schedule a visit for IP removal. If a patient exits the study prior to completion, all Exit Visit assessments should be performed at the time of exit.

Notification of early patient discontinuation from the study and the reason for discontinuation will be made to Allergan and will be clearly documented on the appropriate eCRF.

8.8 Withdrawal Criteria

Patients have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or the institution. The investigator and Allergan also have the right to withdraw a patient from the study at any time for any reason.

Patients should be discontinued from the study if any of the following criteria are met:

- patient develops (or has an exacerbation of) any medical condition that, in the opinion of the investigator, would put the patient at an unacceptable medical risk or compromises the patient's ability to participate in the study
- patient becomes pregnant (see Section 4.5.1.1 for Definition of Females of Childbearing Potential and Acceptable Contraceptive Methods)
- patient is unwilling or unable to continue to comply with study procedures

Where possible, the decision to withdraw a patient from study treatment or the study should be discussed with Allergan.

8.9 Study Termination

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification.

9. Adverse Events

Adverse events occurring during the study will be recorded on an adverse event eCRF. If adverse events occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the Screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study IP.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and/or lack of efficacy, should NOT be reported as

adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

Adverse events will be assessed, documented, and recorded in the eCRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each patient a general, non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate eCRF.

9.1.2 Definition of Adverse Event of Urinary Tract Infection

An adverse event of UTI is defined as a UTI based on the investigator's decision to initiate antibiotic treatment (due to results from urine analysis + urine culture or patient's symptoms with appropriate findings in the urine analysis and culture in the investigator's opinion).

Note: If urinalysis/culture results are reported which, in the opinion of the investigator, are considered clinically relevant but do not fulfill the above definition of a UTI as no antibiotic treatment is initiated by the investigator, the findings should be recorded as adverse events (eg, bacteriuria, leukocyturia).

9.1.3 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (See Section 9.3 for procedures for reporting a serious adverse event.)

Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as a serious adverse event.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization is not reportable as a serious adverse event.

Any pre-planned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the patient's entry into the

study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as a serious adverse event and reported to Allergan.

9.1.4 Severity

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.
Not applicable	In some cases, an adverse event may be an "all or nothing" finding which cannot be graded.

9.1.5 Relationship to Study Investigational Product or Study Procedure

A determination will be made of the relationship (if any) between an adverse event and the study IP or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the IP or study procedure.

9.2 Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate eCRF.

All adverse events that are IP-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health authorities. Any adverse event that is marked "ongoing" at the Exit Visit must be followed-up as appropriate.

9.3 Procedures for Reporting a Serious Adverse Event

Any serious adverse event occurring during the study period (beginning with informed consent) and for at least 28 days after the last dose of study IP must be immediately reported but no later than 24 hours after learning of a serious adverse event. Serious adverse events

must be reported to Allergan (or agent of Allergan) as listed on the Allergan Study Contacts Sheet and recorded on the serious adverse event Form. All patients with a serious adverse event must be followed up and the outcomes reported. The investigator must supply Allergan and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of a serious adverse event, the investigator must:

1. Notify Allergan immediately by fax or email using the serious adverse event form (contact details can be found on page 1 of the serious adverse event form); phone numbers and relevant Allergan personnel contacts are also on the front page of protocol.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.

3. Provide Allergan with a complete, written description of the adverse event(s) on the serious adverse event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational IP.

4. Promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities.

9.4 Procedures for Unblinding of Study Medication

When necessary for the safety and proper treatment of the patient, the investigator can unblind the patient's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. When possible, the sponsor (Allergan Medical Safety Physician) should be notified prior to unblinding study medication. The investigator should inform the sponsor (Allergan Medical Safety Physician) of the unblinding if there is no notification prior to the unmasking.

The treatment assignment for the patient can be determined by designated site personnel calling into the IVRS or IWRS system via password protected access. The reason for breaking the code must be recorded in the patient's source documents.

10. Administrative Items

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, eg, the International Conference on Harmonisation (ICH) Guideline on GCP.

10.1 Protection of Human Patients

10.1.1 Compliance With Informed Consent Regulations (US 21 Code of Federal Regulations [CFR] Part 50) and Relevant Country Regulations

Written informed consent is to be obtained from each patient prior to any study-related activities or procedures in the study, and/or from the patient's legally authorized representative. If the patient is under the legal age of consent, the consent form must be signed by the legally authorized representative in accordance with the relevant country and local regulatory requirements.

10.1.2 Compliance With IRB or IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to Allergan.

10.1.3 Compliance With Good Clinical Practice

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

10.1.4 Compliance With Electronic Records; Electronic Signatures Regulations (US 21 CFR Part 11)

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

10.2 Changes to the Protocol

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.3 Patient Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the patient's name will not be disclosed in these documents. The patient's name may be disclosed to the sponsor of the study, Allergan, or the governing health authorities or the Food and Drug Administration (FDA) if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

10.3.1 Patient Privacy

Written authorization (US sites only) and other documentation in accordance with the relevant country and local privacy requirements (where applicable) is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information ("HIPAA").

In accordance with HIPAA requirements, additional purposes of this study may include publishing of anonymous patient data from the study.

10.4 Documentation

10.4.1 Source Documents

Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, electronic diaries, as well as the results of diagnostic tests such as x-rays, and laboratory tests. The investigator's copy of the eCRFs serves as part of the investigator's record of a patient's study-related data.

The following information should be entered into the patient's medical record:

- patient's name
- patient's contact information
- a statement that informed consent was obtained (including the date). A statement that written authorization (US sites only), or other country and local patient privacy required documentation for this study has been obtained (including the date).
- the date that the patient was randomized into the study, patient number, and patient medication kit number, and date and details of study IP administration
- the study title and/or the protocol number of the study and the name of Allergan
- dates of all patient visits and date of any request for retreatment
- all concurrent medications (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
- all usage of rescue medications
- occurrence and status of any adverse events (including any procedure-related adverse events)
- date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation
- results of laboratory tests performed by the central laboratory
- concurrent procedures performed during the study
- vital signs and PE findings
- questionnaire/diary data entered directly onto the appropriate form will be considered source data

10.4.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each patient's eCRF and related documents. An investigator who has signed the protocol signature page should personally sign for the eCRF (as indicated in the eCRF) to ensure that the

observations and findings are recorded on the eCRF correctly and completely. The eCRFs are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan and will be maintained in a central data repository.

10.4.3 Study Summary

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB/IEC.

10.4.4 Retention of Documentation

All study-related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of eCRFs should be maintained on file.

For countries falling within the scope of the ICH guidelines, Allergan-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by Allergan.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

10.5 Labeling, Packaging, and Return or Disposal of Study Medications/Treatments

10.5.1 Labeling/Packaging

Each LiRIS (both active and placebo) is provided sterile and in an individually labeled Tyvek sealed pouch. The pouch is placed into a secondary, standard paper based carton stock, which is labeled with a standard adhesive backed paper label containing appropriate clinical

study information and sealed with tamper proof seals. Active and placebo treatments will be provided in identical appearing pouches.

10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed to the patients, the number of units returned to the investigator by the patient, and the number of units returned to Allergan during and at the completion of the study. A detailed inventory must be completed for the study medication. The study medication must be dispensed only by an appropriately qualified person to patients in the study. The medication is to be used in accordance with the protocol by patients who are under the direct supervision of an investigator. A unit is defined as one LiRIS.

10.5.3 Return or Disposal of Study Medications/Treatments and/or Supplies

All clinical study medications/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction.

Each LiRIS removed from the bladder of a study patient will be retained and sent to Allergan for a post-use assessment. Detailed instructions for the storage and shipment of LiRIS post-removal are provided in the Study Manual.

10.6 Monitoring by the Sponsor

A representative of Allergan will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

10.7 Handling of Biological Specimens

Blood and urine samples will be analyzed for lidocaine and 2,6-xylidine concentrations (pharmacokinetics) at a bioanalytical laboratory that meets GLP requirements.

Samples of blood and urine specified in Section 6.5 will be analyzed at a central laboratory with certification from a recognized accreditation agency (eg, College of American Pathology [CAP] or Clinical Laboratory Improvement Amendments [CLIA] certification). The Central Laboratory Manual provides details regarding laboratory collection and shipment procedures for blood and urine samples in this study.

Allergan shall have full ownership rights to any biological samples derived from the study.

10.8 Publications

Allergan as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

10.9 Coordinating Investigator

A signatory Coordinating Investigator will be designated prior to the writing of the Clinical Study Report.

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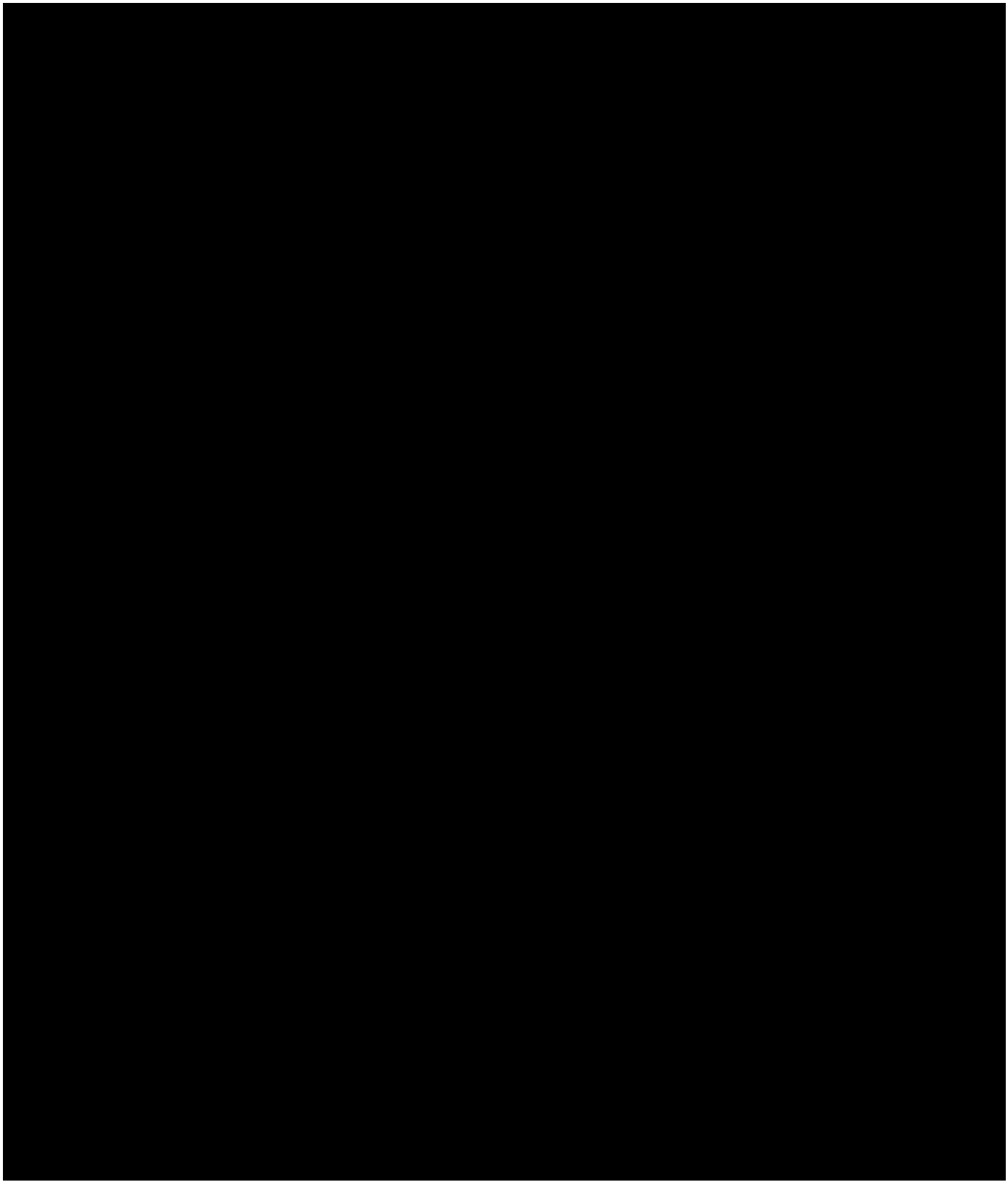
12. Attachments

12.1 Questionnaires

12.1.1 Overview

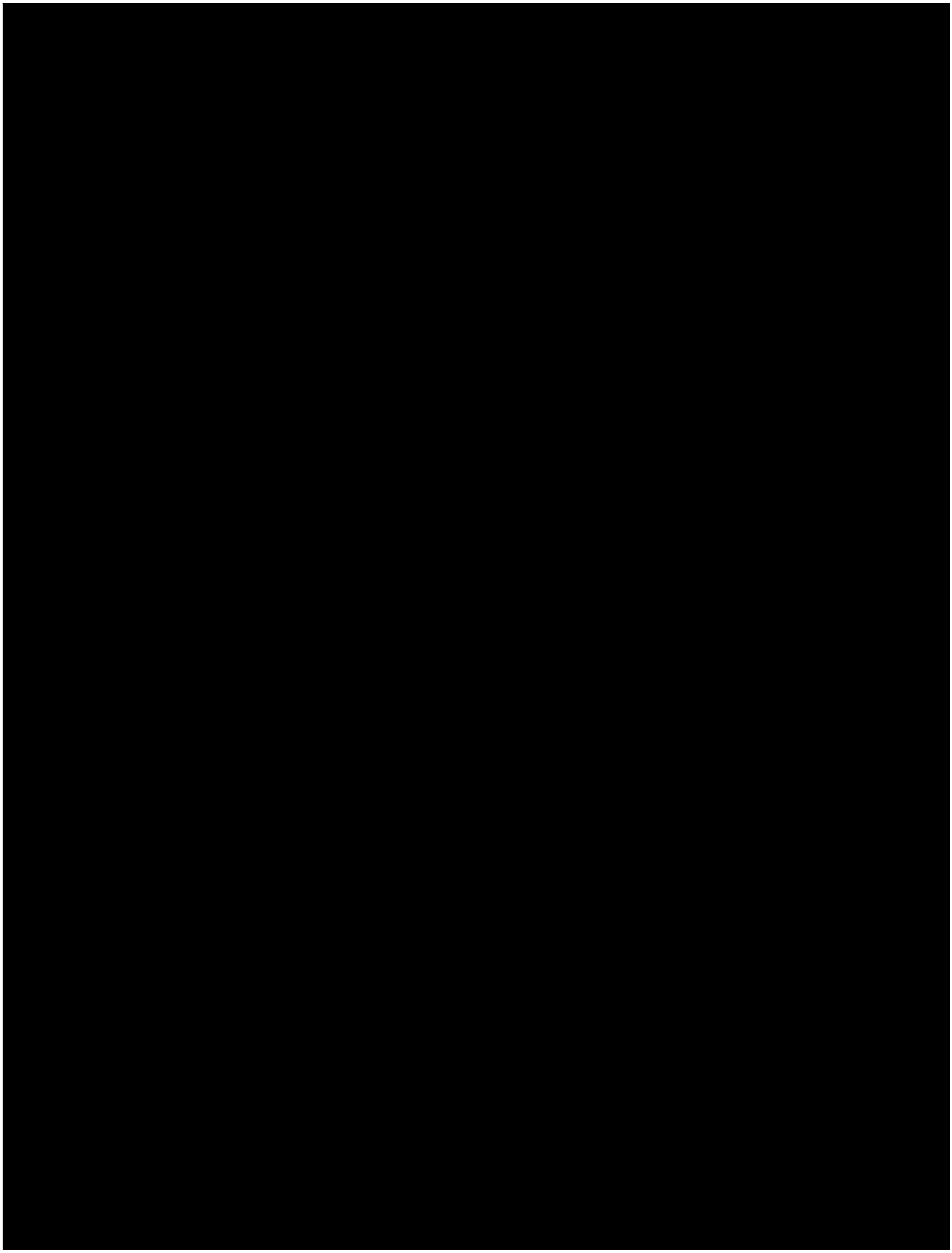
Patient questionnaires will be:

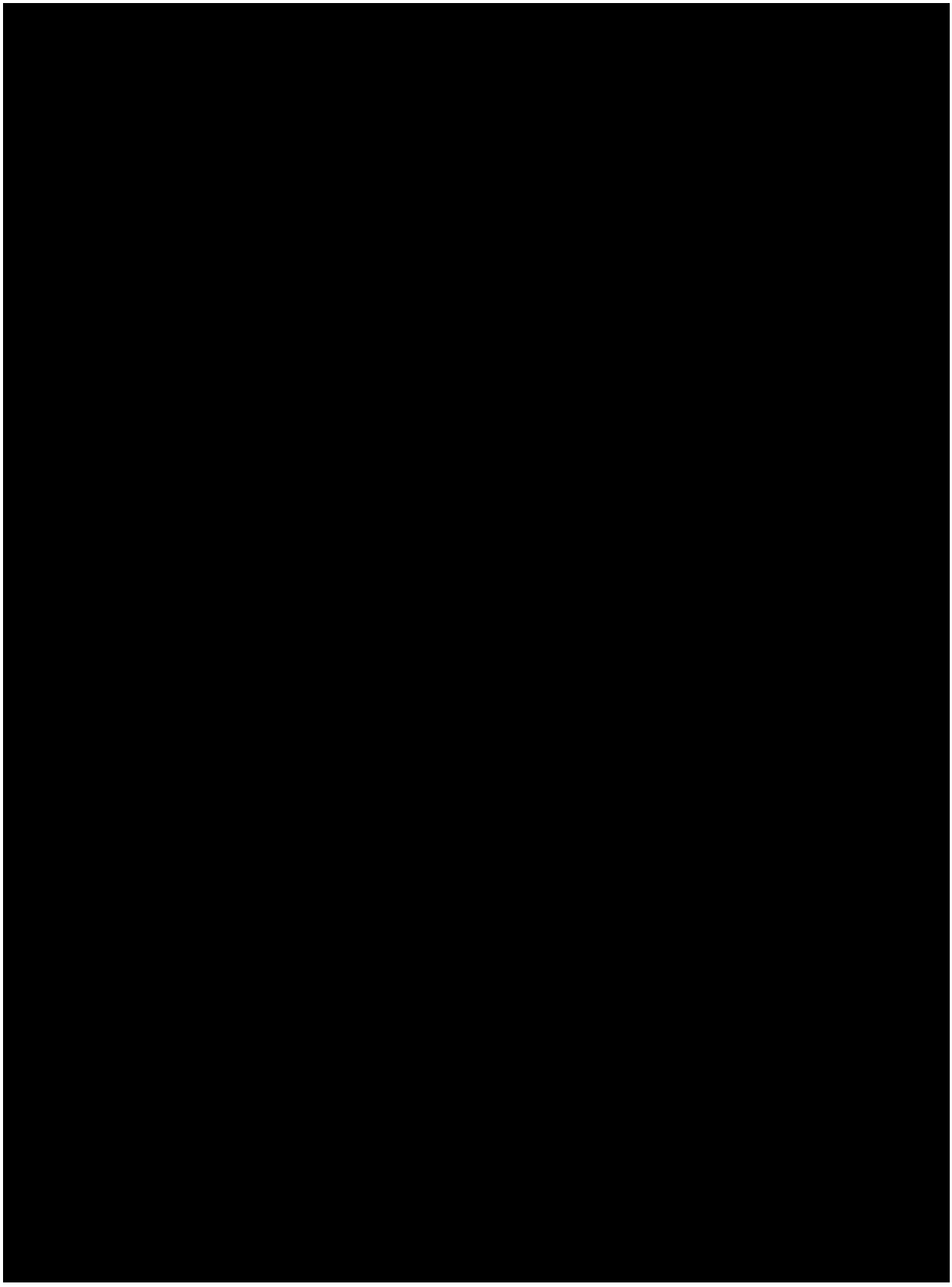
- administered to all patients in the study prior to having any study procedure performed
- completed only by the patient, using a blue or black ballpoint pen on a firm writing surface
- administered in a quiet place with ample time for the patient to complete the questionnaire
- filled out completely by patients (every question must be answered)
- completed only at protocol-specified study visits (no attempt should be made at any subsequent visit to administer missed questionnaires)
- a source document; please do not make or use any photocopies of the forms
- checked for completeness, and not content, in the patient's presence - study site personnel should not change responses on the questionnaires
- administered only in countries where the scale has been appropriately culturally adapted in local languages as per the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient Reported Outcomes Measures (Wild et al, 2005). The versions of the questionnaires provided in the protocol are samples and will be replaced with the appropriate versions for the country where the questionnaire will be administered.

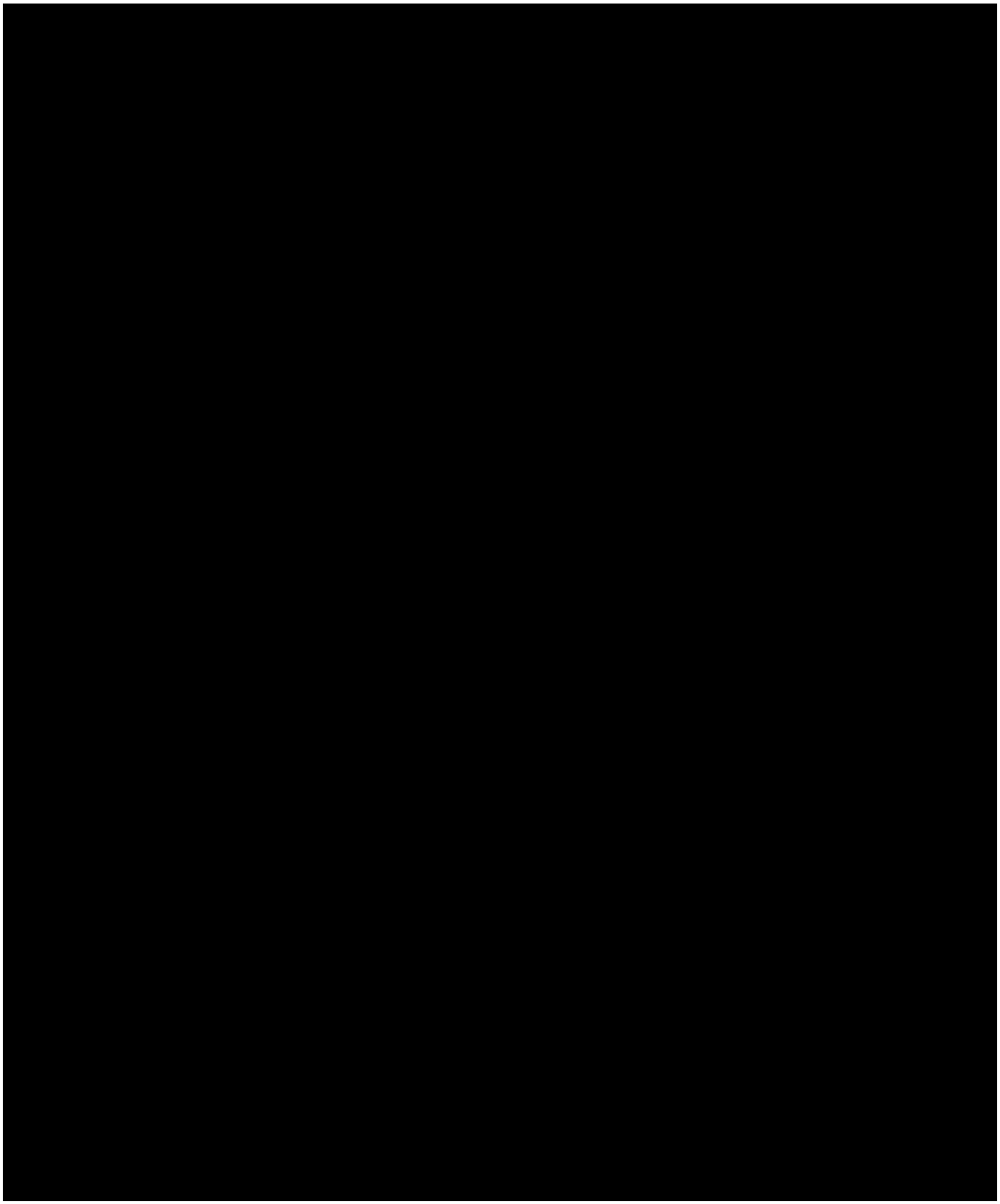


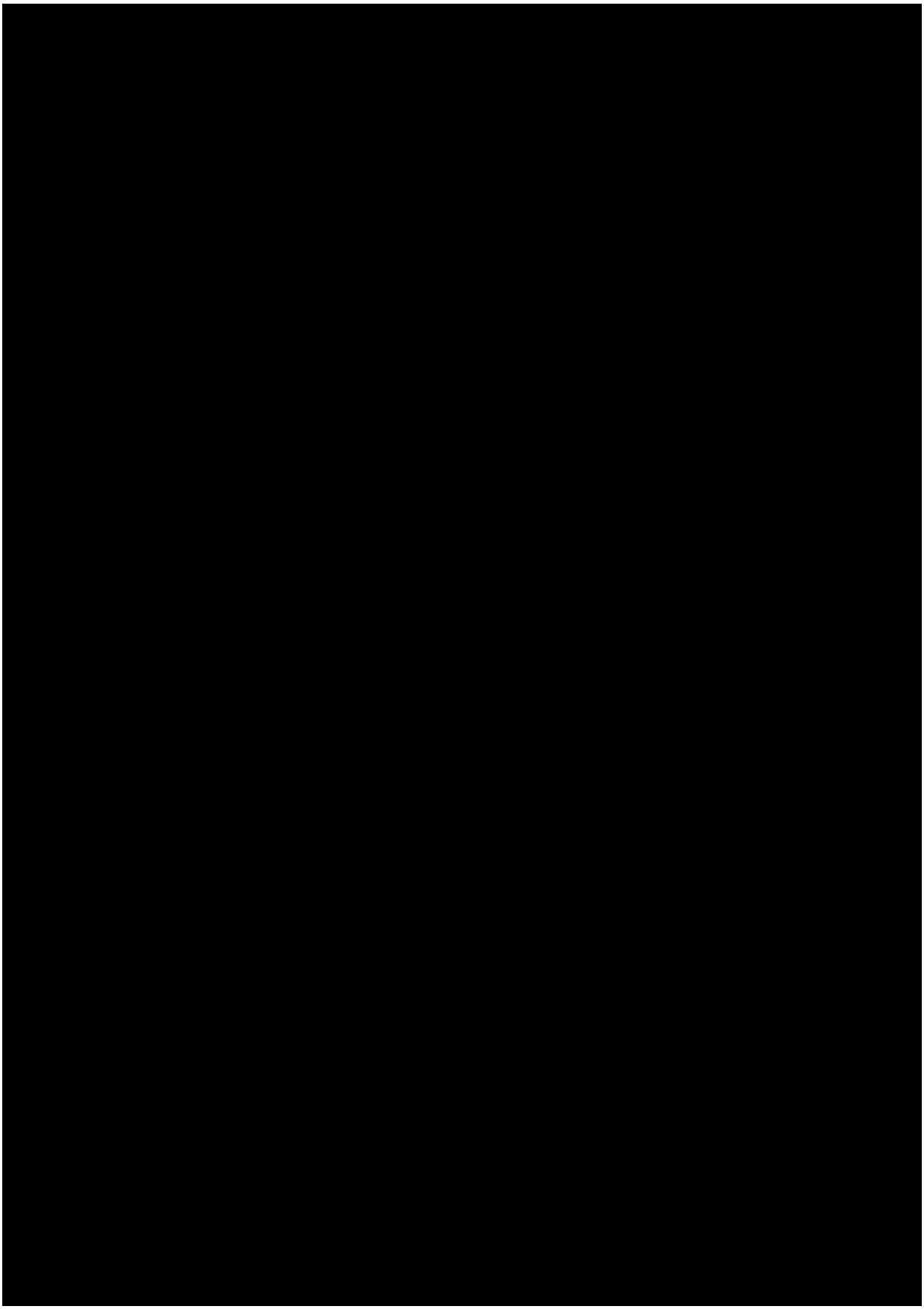
Health Questionnaire

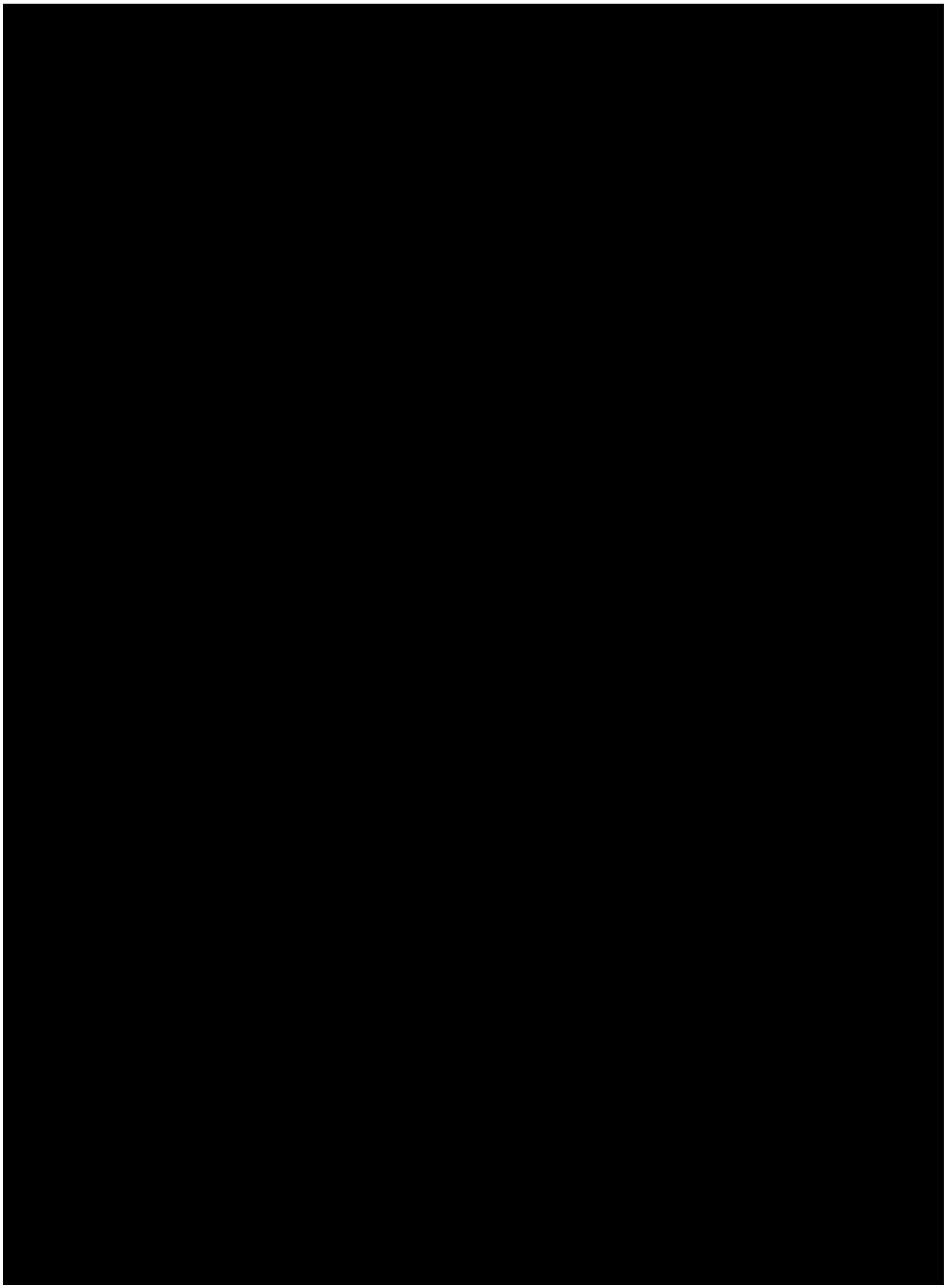
English version for the USA











12.2 Handling of Biological Specimens

Details relating to the handling of biological samples are provided in the Central Laboratory Manual.

12.3 Glossary of Abbreviations

Term/Abbreviation	Definition
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
AST	aspartate aminotransferase (SGOT)
AUA	American Urological Association
β-HCG	beta-human chorionic gonadotropin
BPS	bladder pain syndrome
CFR	Code of Federal Regulations
eCRF	electronic case report form
EDC	electronic data capture
[redacted]	[redacted]
ESSIC	European Society for the Study of IC
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
GLP	Good Laboratory Practice
HEENT	head, ears, eyes, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HL	Hunner's Lesion
HRQoL	health-related quality of life
IC	interstitial cystitis
ICH	International Conference on Harmonisation
[redacted]	[redacted]
[redacted]	[redacted]
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
ITT	intent-to-treat
IL-1β	interleukin-1 beta
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LiRIS	lidocaine-releasing intravesical system
MCH	mean corpuscular hemoglobin

Term/Abbreviation	Definition
MCHC	mean corpuscular hemoglobin concentration
MCP-1/CCL2	monocyte chemotactic protein 1
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NRS	Numerical Rating Scale
PCS	Pain Catastrophizing Scale
PK	pharmacokinetic
PI	Principal Investigator
PP	per protocol
PVR	post-void residual
RBC	red blood cells
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
Tx 1	Treatment 1 Period
Tx 2	Treatment 2 Period
US(A)	United States (of America)
USP	United States Pharmacopeial Convention
UTI	urinary tract infection
WBC	white blood cells

12.4 Protocol Amendment 1 Summary

Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Study, Evaluating Safety and Efficacy of LiRIS® 400 mg in Females With Interstitial Cystitis With Hunner's Lesions

Protocol 201025-001 Amendment 1

Date of Amendment: February 2015

Amendment Summary

This summary includes changes made to Protocol 201025-001 (20 January 2015). This protocol was amended to delete the instructions for insertion and removal of Investigational Product (IP) from the protocol. The directions for IP use will be included in the Study Manual.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Section 5.8/Treatment Administration and Section 6.6.11/Insertion and Removal of IP	Revised the reference for instructions on insertion and removal of IP to Study Manual instead of protocol Attachment 12.1	The instructions for IP use are being included in the Study Manual instead of as an attachment to the protocol
Section 7.3.3/Safety Analyses	# 5: Deleted the detailed list of specific laboratory analytes for which descriptive summaries will be provided	The list of laboratory analytes are included in Section 6.6.5/Clinical Laboratory Assessments. A reference has been provided to Section 6.6.5.
Section 7.3.3/Safety Analyses, Section 10.4.1/Source Documents	Deleted electrocardiogram (ECG)	ECG will not be assessed during this study
Section 12.1/ Investigational Product Directions for Use	Deleted Attachment 12.1 Investigational Product Directions for Use including Attachment 12.1.1 Directions for Insertion of LiRIS® 400 mg and LiRIS® Placebo and Attachment 12.1.2 Directions for Removal of LiRIS® 400 mg and LiRIS® Placebo	The instructions for IP use are being included in the Study Manual instead of as an attachment to the protocol. Succeeding attachment numbers were adjusted accordingly.

12.5 Protocol Amendment 2 Summary

Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Study, Evaluating Safety and Efficacy of LiRIS® 400 mg in Females With Interstitial Cystitis With Hunner's Lesions

Protocol 201025-001 Amendment 2

Date of Amendment: April 2016

Amendment Summary

This summary includes changes made to Protocol 201025-001 Amendment 1 (February 2015). This protocol was amended to expand entry criteria to increase the rate of enrollment.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Summary, Table 1, Sections 6.3, 6.6.7, 7.5, 10.7	[redacted]	[redacted]
Summary, Sections 3, 4.1, 7.7	Sample size of estimated evaluable population was increased	Revision based on results of Study TAR-100-105
Summary, Sections 4.2, 4.3	AUA guidelines were replaced with ESSIC (van de Merwe et al, 2008) in diagnostic criteria	Clarification of diagnostic criteria: ESSIC requires 6 months of symptoms before confirmed diagnosis, consistent with protocol (AUA requires 6 weeks)
Table 2, Section 4.4	Period off medication/treatment before screening was reduced for Elmiron and Botulinum toxin for genitourinary treatment	There is no indication of any increased risk resulting from this change based on previous LiRIS studies
Section 4.1	Increased number of study sites	Increase enrollment
Section 4.4	Cardiac & pelvic pain exclusion criteria were generalized to specify investigator judgment	There is no indication of any increased risk resulting from this change based on previous LiRIS studies

Section	Revision	Rationale
Section 4.4	[redacted]	There is no indication of any increased risk resulting from this change based on previous LiRIS studies
Section 4.4	[redacted]	There is no indication of any increased risk resulting from this change
Section 4.4	[redacted]	There is no indication of any increased risk resulting from this change based on previous LiRIS studies
Section 4.5.2	Removed prohibition on medications for treating LUTS	Based on results from previous LiRIS studies, LUTS medications did not affect outcomes
Section 5.8.2	Removed requirement that request for retreatment occur at a study visit	In practice, patients often want to request retreatment by phone in between visits
Section 6.5.12	Collection of baseline pain assessment specified to be calculated based on at least 5 consecutive days	To allow 5 consecutive days out of 7 instead of 7 consecutive days to allow patients more flexibility
Section 7.1	Clarified the mITT definition	Clarification
Section 7.2 and throughout	Removed the Day 1 reference and replaced it with Day 0	Clarification for investigators to make consistent with the procedures intended and that the sites have been trained on
Sections 7.2 and 7.3.2.1	Included imputation for primary analysis	Patients that have values close to the primary timepoint can now be included in the primary analysis
Section 7.2.1	Clarified the baseline NRS calculation and imputation method to be applied	Clarification
Section 7.2.2	Clarified that severity of lesions may not be analyzed	This may be highly variable and difficult to quantify
Section 7.2.3	Removed the analysis of threshold of reduction in the number of lesions	There is no consensus in the field as to what defines a meaningful threshold
Section 7.3	Clarified the treatment arms	Clarification
Section 7.3.2	Removed sensitivity analysis based on last observation carried forward method	For pain medication this is not standard

Section	Revision	Rationale
Section 7.3.2	Changed the significance level from 0.05 to 0.1	To reflect exploratory nature of the study
Section 7.3.2.2	Clarified that no imputation method will be used for secondary efficacy variables analysis	Clarification
Sections 7.3.2.3 and 7.3.2.4	Clarified the treatment arms to be compared	Clarification
Section 7.3.3	Removed the adverse event analysis based on onset time and the analysis of clinically significant laboratory abnormalities	These safety variables were not considered to be relevant to this study
Section 7.5	Clarified that imputation method will only be applied to the primary analysis	Clarification
Section 7.6	Removed the pre-planned subgroup analysis for efficacy	Such analysis was deemed non-essential and can be done in ad hoc manner post database lock
Section 7.7	Corrected the sample size derivation	Clarification
Section 7.8	Added that blinded sample size estimation may be conducted. Clarified when a potential interim analysis may occur.	Clarification

ALLERGAN

Protocol 201025-001 Amendment 2

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
[redacted]	[redacted]	[redacted]