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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

Statistical Analysis Plan Date: 27-Mar-2018

1.0   **TITLE PAGE**

201025-001

A Multicenter, Randomized, Double-blind, Placebo-controlled Study, Evaluating Safety and Efficacy of LiRIS$^®$ 400 mg in Females With Interstitial Cystitis/Bladder Pain Syndrome

STATISTICAL ANALYSIS PLAN - Clinical Study Report

[Draft]: [06 Jun 2016]
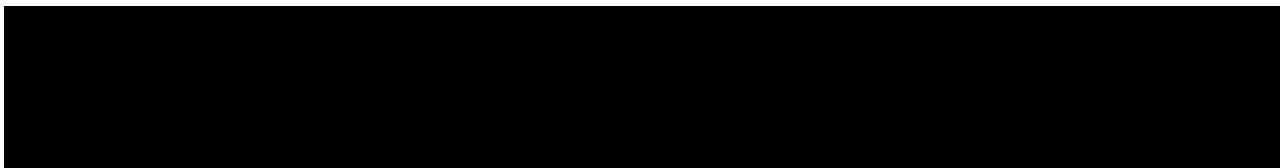
Confidentiality Statement

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3.0　　　　　LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
LOCF	Last observation carried forward
CI	Confidence interval
CRF	case report form
CV	Coefficient of variation
eCRF	electronic case report form
EQ-5D	EuroQol EQ-5D-5L
GM	Geometric mean
HRQoL	Health related quality of life
IC	informed consent
IC/BPS	interstitial cystitis/bladder pain syndrome
ICPI	Interstitial Cystitis Problem Index
ICSI	Interstitial Cystitis Symptom Index
IL-1β	Interleukin-1 beta
ITT	intent to treat
IP	investigational Product
LiRIS	lidocaine-releasing intravesical system
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MCP-1	Monocyte chemoattractant protein-1
mITT	Modified intent to treat
NRS	Numeric Rating Scale
PD	pharmacodynamics

PID	patient identification
PK	pharmacokinetics
PP	Per Protocol
PVR	post-void residual
QoL	Quality of life
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard deviation
TEAE	treatment-emergent adverse event
WBC	white blood cell

4.0   **INTRODUCTION**

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the final protocol of Study 201025-001 (version dated 20 January 2015) and the most recent amendment (Amendment 2 dated [28 April 2016]). Specifications of tables, figures, and data listings are contained in a separate document.

Study 201025-001 is a phase 2 multicenter, randomized, double-blind, placebo-controlled, study to evaluate the safety and efficacy of the LiRIS 400 mg in female patients with interstitial cystitis (IC) with Hunner's lesions (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).

The primary analysis will be conducted at the time when the last patient completes the primary timepoint that is Week 4 following removal of the Treatment 1 second investigational product (IP) removal. The final analysis will be conducted when all patients complete or exit the study. For each analysis timepoint all data available will be included in the analysis. The analyses outputs to be included will be the same for the primary and final analysis timepoints. The schedule of evaluations for Study 201025-001 is presented in Table **4–1**. The double-blind treatment period starts with the first IP insertion and ends with the last assessment prior to Treatment 2 IP insertion or Exit visit in the Treatment 1 period.

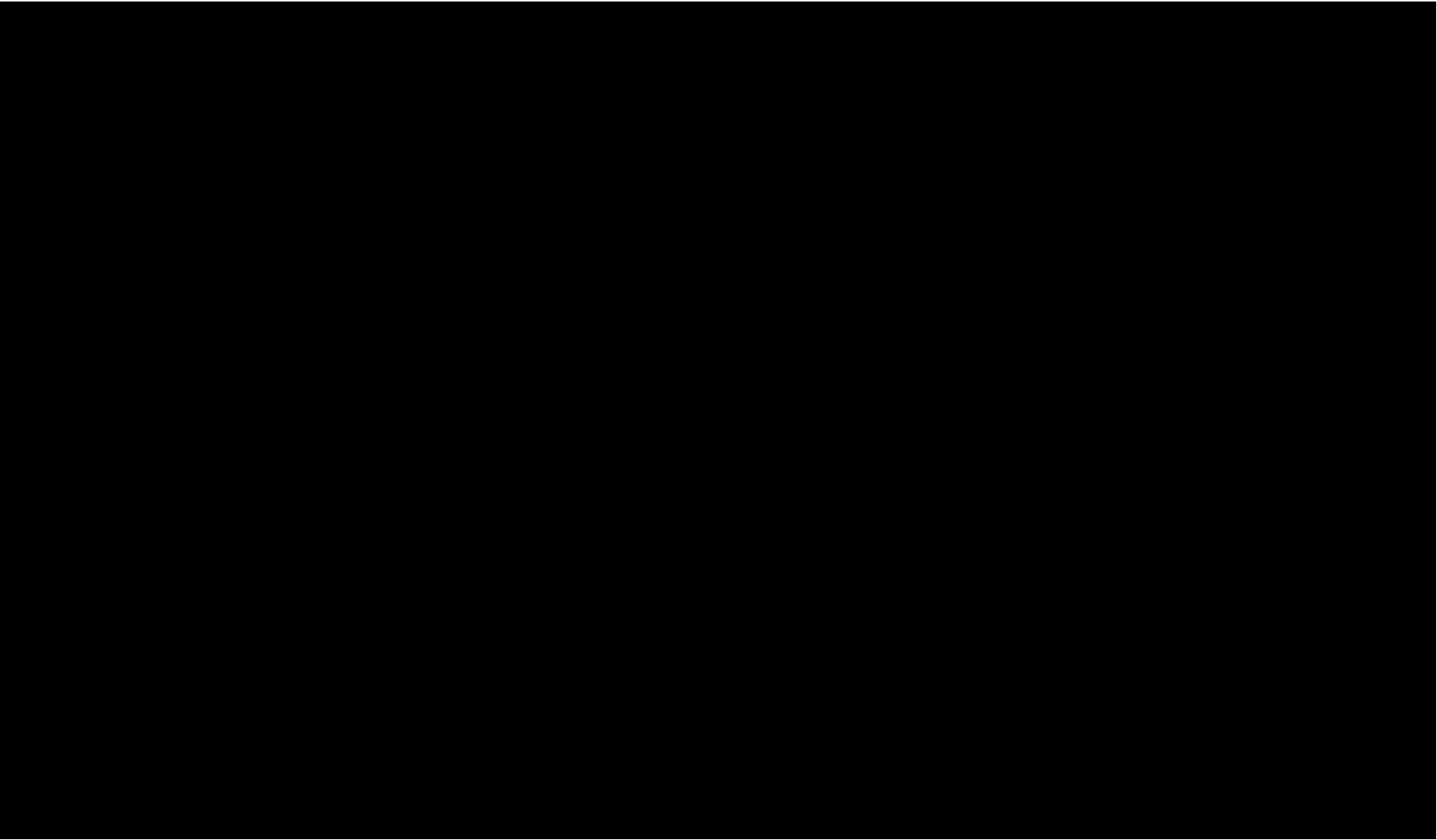Table 4–1.   Schedule of Evaluation for Study 201025-001

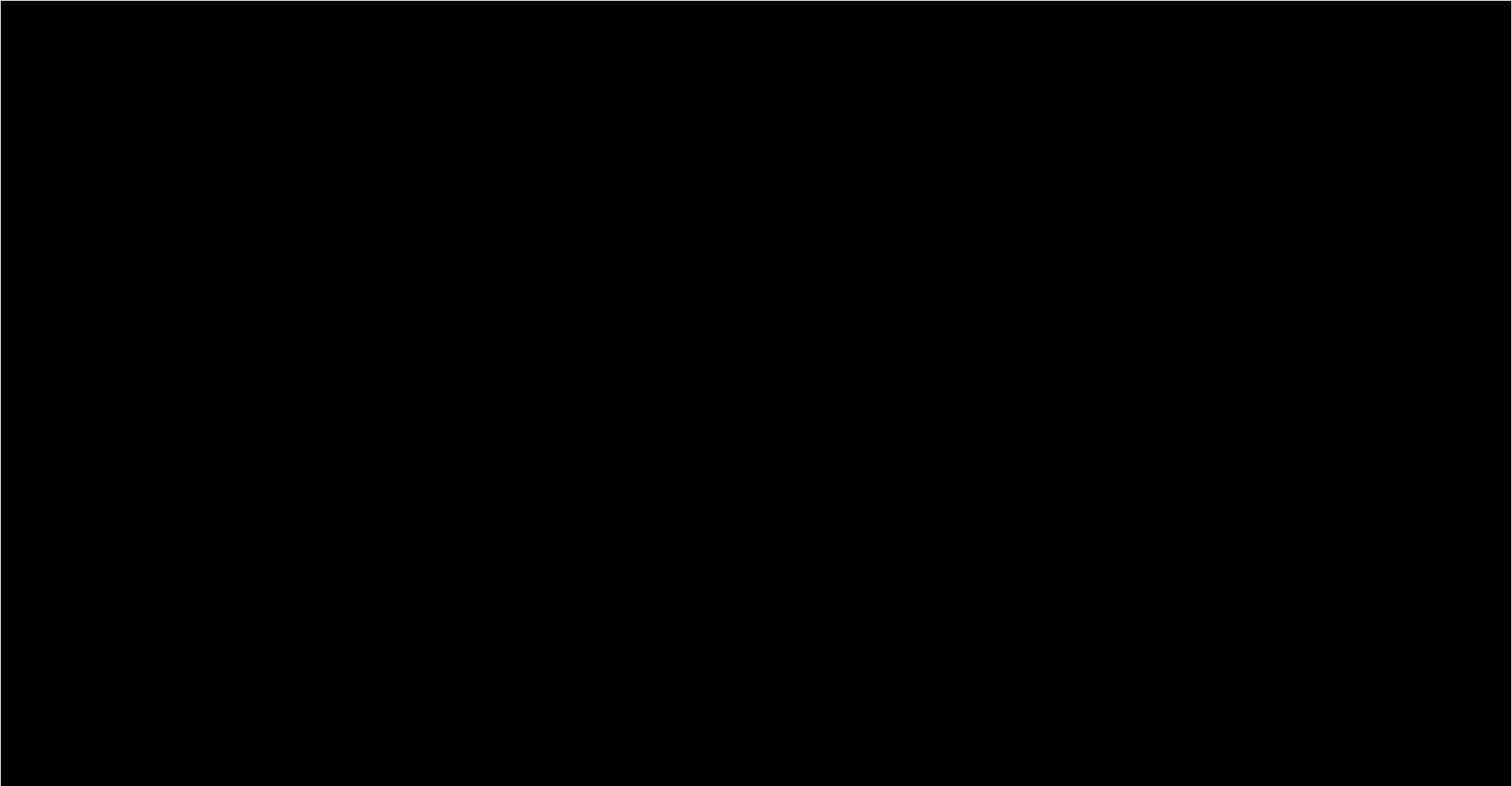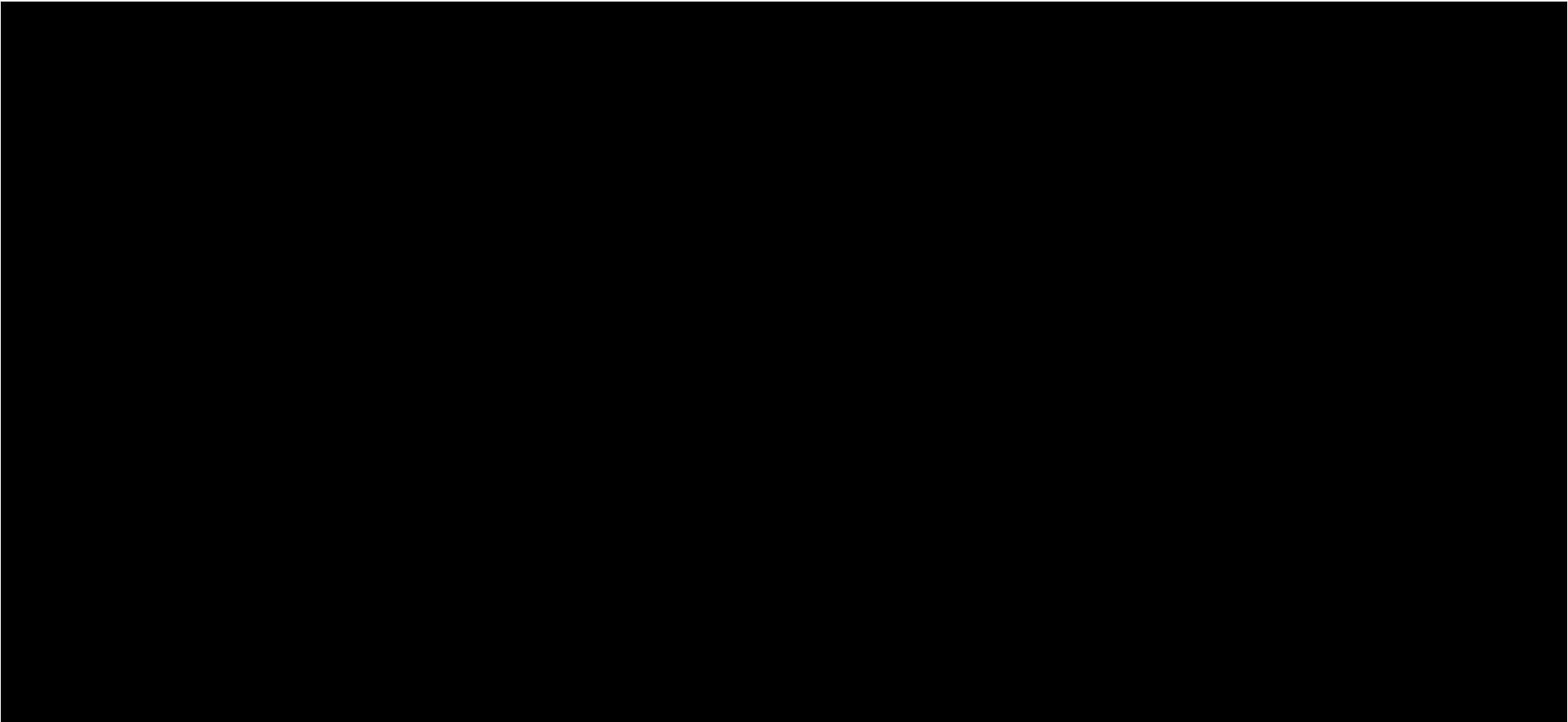Table 4–1.   Schedule of Evaluation for Study 201025-001

Table 4–1.   Schedule of Evaluation for Study 201025-001

5.0   **OBJECTIVES**

The study objective is 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. The clinical hypotheses is that a 28-day period of continuous release of lidocaine inserted into the bladder utilizing two consecutive LiRIS 400 mg will have an acceptable safety profile and will be more efficacious than placebo for the treatment and corresponding symptoms of IC with HL in female patients.

The study will consist of up to two treatment periods. At the start of the first treatment period (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 open label LiRIS 400 mg over a 14-day treatment period followed by 4 weeks of observation until exit.

The central randomization will be stratified by baseline pain Numeric Rating Scale (NRS) (≤ 5 or > 5) collected during the Screening period. For patients who participate in the study and receive only Treatment 1, the maximum 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 (open label LiRIS 400 mg), 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).

Details of the study design and objectives are given in the study protocol.

6.0 PATIENT POPULATIONS

6.1 INTENT-TO-TREAT POPULATION

Not applicable.

6.2 MODIFIED INTENT-TO-TREAT POPULATION

The Modified Intent-to-Treat (mITT) Population will include all patients that are randomized and received at least one IP insertion in the Treatment 1 period. The efficacy data will be analyzed as randomized using the mITT population.

6.3 SAFETY 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.

6.4 PER-PROTOCOL POPULATION

The Per-Protocol (PP) population will include all patients who retain the 2 IP inserted in Treatment 1 for the 28 days of the treatment period (complete the two cycles of IP insertion) 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.

6.5 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 at the scheduled Treatment 1 Day 14 visit.

6.6 DATA COLLECTED BUT NOT ANALYZED

The Investigator's signature will not be analyzed.

7.0 PATIENT DISPOSITION

The number and percentage of patients in 2 of the study populations (mITT and PP) will be summarized by treatment group and study center; the number of patients screened will be summarized overall by study center.

Screen-failure patients (i.e., patients screened but not randomized) and the associated reasons for failure to randomize will be presented in a patient listing. The number and percentage of patients who complete the study and who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups for the mITT and PP Population. The reasons for premature discontinuation from the study as recorded on the termination pages of the electronic case report form will be summarized (number and percentage) by treatment group for the mITT and PP Population. Furthermore, this summary table will be generated for cohort of mITT patients that receive Treatment 2. Associated patient listing containing information on reasons for premature study discontinuation will be generated.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

8.1 DEMOGRAPHIC

Demographic parameters (age; age group; race; ethnicity; sex, smoking status and dietary lifestyle),baseline characteristics (weight; height; and body mass index, calculated as weight $[kg]/(height [m])^2$), will be summarized descriptively by treatment group for the mITT and PP populations and for the cohort of mITT patients that received Treatment 2. Continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

8.2 DISEASE CHARACTERISTICS

The following baseline disease information will be summarized as described for the demographic information, by treatment group for the mITT and PP populations and for the cohort of mITT patients that received Treatment 2:

- information on stratification factors baseline average pain score ≤ 5 vs. > 5),

- daily average 24-hour pain Numeric Rating Scale (NRS),

- daily average worst pain NRS,

- Pain Catastrophizing Scale (PCS) total score,

- daily average number of micturition episodes,

- daily average number of urgency episodes,

- daily average pre- and post-void bladder pain NRS, and

- result of pelvic examination at baseline.

8.3 PAST MEDICAL HISTORY

Abnormalities in patients' medical and surgical histories will be coded using the *Medical Dictionary for Regulatory Activities,* version 18.1 or newer. The number and percentage of patients with abnormalities in medical and surgical histories in each system organ class and preferred term will be summarized by treatment group for the mITT Population. No statistical comparisons will be performed.

9.0   **PRIOR OR CONCOMITANT MEDICATION**

Prior medication is defined as any medication taken before the date of the first IP insertion. *Concomitant medication* is defined as any medication taken on or after the date of first IP insertion. The WHO drug dictionary, version 2015 quarter 4 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

9.1   **BLADDER PAIN MEDICATION**

Daily bladder pain and rescue bladder pain medication is recorded in the bladder pain diary for the screening period and treatment period. Both prior and concomitant daily bladder pain medication will be coded by drug name and therapeutic class. The use of these prior and concomitant medications will be summarized by the number and percentage of patients in each treatment group for the mITT Population. If a patient took a specific medication multiple times or took multiple medications within a specific therapeutic class, that patient would be counted only once for the coded drug name or therapeutic class. Formulations (including salts, esters, etc.) containing the same active ingredient will be pooled under the coded drug name of the base compound.

Prior and concomitant rescue bladder pain medication will be similarly summarized.

The number of days a given patient took concomitant rescue bladder pain medication will be summarized by treatment group and overall for the mITT population.

9.2   **MEDICATION OTHER THAN BLADDER PAIN MEDICATION**

Medication other than bladder pain medication will be collected in the concomitant medication eCRF. For both prior and concomitant medication collected in the eCRF, the frequency and percentage of medications will be summarized for the base preferred (drug) name (WHODDE) with the same active ingredients by the Primary System Organ Class and Preferred Term of the MedDRA dictionary.

The clinical team will also identify pain medication recorded in the concomitant medication eCRF prior to data base lock. For these medications a prior and concomitant medication table will be similarly generated.

10.0   EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

In this study patients receive two insertions of IP in Treatment 1 and one insertion of IP in Treatment 2. Treatment 2 is provided if the patient makes a request and qualifies for re-treatment. A request for re-treatment can only be made 4-weeks after the second IP had been removed. Hence, what are relevant in this study would be the duration of each treatment period (Treatment 1 and 2), whether or not the insertion and removal of the IP was completed as per the instruction provided in the protocol and whether or not a patient completed the 14 days cycle for each inserted IP.

10.1   EXTENT OF EXPOSURE (DURATION OF EFFECT)

Treatment duration for each Treatment period (1 or 2) will be displayed by treatment groups as well as the cumulative study duration over the entire study period. For Treatment 1 period, the treatment duration could be thought of as duration of effect. The following formula will be used to derive treatment duration:

Cumulative treatment duration:

      Cumulative duration = exit date – Date of Treatment 1 first IP insertion + 1

Treatment 1 duration:

      exit date – Date of Treatment 1 first IP insertion + 1,

for patients that exit without receiving Treatment 2 or,

      Date of Treatment 2 IP insertion - Date of Treatment 1 first IP insertion

Treatment 2 duration:

      exit date – Date of Treatment 2 IP insertion + 1,

If the date of exit date is missing, the date of the last visit will be used.

10.2   MEASUREMENT OF TREATMENT COMPLIANCE AND TOLERABILITY

In this study, compliance to the insertion and removal procedures outlined in the protocol is assessed by the investigator. This information is collected in the IP insertion and removal eCRFs. The information in these eCRFs will be summarized by treatment group for each treatment period. Furthermore, associated listing will be produced.

For patients that spontaneously abort the IP or ask the IP to be removed prior to the Day 14 post-IP insertion, a summary table of such events will be presented by treatment group and overall.

11.0   **EFFICACY ANALYSES**

The efficacy analyses will be primarily based on the mITT Population with selected tables being repeated using the PP population. Unless stated otherwise, baseline for efficacy is defined as the last non-missing efficacy assessment prior to first Treatment 1 IP insertion. All statistical tests will be 1-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 90% confidence intervals, unless stated otherwise.

11.1   **PRIMARY EFFICACY PARAMETER(S)**

The primary efficacy measure is the 7-day mean of the average daily bladder pain NRS (See Section 17.2.1 for definition of average daily bladder pain score).

The primary efficacy variable is the change from baseline to Week 4 Follow-Up post removal of the last IP in Treatment 1 period, using the 7-day mean of the average daily bladder pain NRS score. Patients are scheduled to have two IP insertion in Treatment 1 period and then a Week 4 Follow-Up visit. However, if a patients receives only one IP insertion in the study and has Week 4 Follow-Up assessment, it will be considered in the analysis.

The baseline 7-day mean daily average NRS score will be derived using the diary information from Day -7 to Day -1. In contrast, for patients that receive two IP insertion, the Week 4 Follow-Up mean 7-day average daily pain score will be derived from data collected from Day 50 to Day 56 from date of 1nd IP insertion or Day 36 to Day 42 for patients that receive just one insertion during Treatment 1 period. The mean baseline NRS will be derived if there are at least *any* 5 consecutive valid assessments within the 7-day assessment window (i.e., for baseline it would be day -7 to day -1). If the data that is available is for less than 5 consecutive days, as described above, then the value will be considered missing for that patient. Similarly, the Week 4 Follow-Up NRS will be derived if there are at least *any* 5 consecutive valid assessments within the 7-day assessment window (Day 50 to Day 56 for patients that received two insertion or Day 36 to Day 42 for patients that received just one IP in Treatment 1).

For the primary analysis, for patients that get two IP inserted during Treatment 1 period, the Week 4 Follow-up is counted from the 2nd IP removal time. In contrast, for patients that just received one IP before exiting the study, the Week 4 Follow-Up is counted from the IP removal date. Hence, for Treatment 1 period, Week 1 Follow-Up- Week 4 Follow-Up assessment are from last IP removal, whether or not a patient received one or two IPs.

 For the primary analysis, for patients that have IP inserted, if there is no valid Week 4 Follow-Up NRS assessment and there is a valid Week 2 or 3 Follow-Up, weekly mean of the average daily bladder pain NRS, the Week 4 Follow-Up value will be imputed by the latest of the two values that is available (i.e., Week 2 or 3 Follow-Up).

For the primary efficacy analysis, the null and the alternate hypothesis are as follows:

Null hypothesis: The mean change from baseline in average daily bladder pain NRS at Week 4 Follow-Up post IP removal is the same or worse for the treatment group that utilizes 2 consecutive LiRIS 400 mg compared to the treatment group that utilizes 2 consecutive LiRIS Placebo.

Alternative hypothesis: The mean change from baseline in average daily bladder pain NRS at Week 4 Follow-Up post IP removal is greater for the treatment group that utilizes 2 consecutive LiRIS 400 mg compared to the treatment group that utilizes 2 consecutive LiRIS Placebo.

The change from baseline in average daily bladder pain NRS score will be summarized using descriptive statistics by treatment group. Between group comparison of the change from baseline in average daily bladder pain NRS at Week 4 Follow-Up post IP removal of Treatment 1 will be analyzed using the analysis of covariance (ANCOVA) model, using the baseline values as the covariate, and stratification factor (baseline average daily bladder pain NRS: ≤ 5 or > 5) and treatment as factors. The fitted model will be used to derive the adjusted mean treatment differences for the primary variable (least-squares [LS] mean difference) and associated 90% CI, for the comparison of the treatment group that utilizes 2 consecutive LiRIS 400 mg versus the treatment group that utilizes 2 consecutive LiRIS Placebo. If the 1-sided p-value is < 5% and there is greater reduction in the treatment group that utilizes 2 consecutive LiRIS 400 mg then the null hypothesis is rejected in favor of the treatment group that utilizes 2 consecutive LiRIS 400 mg. The fitted model will also be used to estimate the adjusted treatment difference and associated 90% CI between treatment group that utilizes consecutive treatment of LiRIS placebo and LiRIS 400 mg versus the treatment group that utilizes 2 consecutive LiRIS Placebo.

11.1.1 Other Analysis of Primary Efficacy Variable

The ANCOVA Analyses of the primary efficacy variable will also be performed using the PP population and with no imputations for missing Week 4 Follow-Up weekly mean of the average daily bladder pain NRS.

Average daily 24-hour pain NRS and the corresponding change from baseline values will also be summarized for each week post randomization for the Treatment 1 Period (see Table 17.2.1–1). For each weekly (mean) change from baseline values, the ANCOVA analysis outlined for the primary timepoint will be applied without any imputation for missing values.

A sensitivity analysis using a mixed-effects model for repeated measures (MMRM) (Mallinckrodt et al, 2001a and 2001b) based on all post-baseline weekly mean data up to Treatment 1 Week 4 Follow-Up, will be performed to compare treatment effect at each post-baseline week (see Table 17.2.1–1). The MMRM analysis will include treatment group, assessment week, and treatment group–by-assessment week interaction as factors and baseline value as covariate. An unstructured covariance matrix will be used to model the correlation over time in change from baseline values for the primary efficacy variable.

Plots of weekly mean of the average daily bladder pain values and the associated change from baseline values will be presented by treatment group over time.

11.2   SECONDARY EFFICACY PARAMETER(S)

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. The video image will be captured at baseline and at scheduled post-baseline visits. These will be used to categorize the change from baseline bladder images to categories such as complete responders, partial responders, stable disease and worsened disease. The number and percentage of patients in each category will be analyzed by treatment group. Furthermore, for each category of responders, at each post-baseline visit, the number of patients with 1, 2 and ≥ 3 point reduction in daily average pain NRS will be summarized by treatment group.

During each cystoscopy, the investigator will count the number of lesions visible while preforming the bladder scan for bladder mapping. The number of lesions and the change from baseline in the number of lesions will be summarized for each relevant visit by treatment group.

12.0   SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs) and clinical laboratory and vital signs parameters, physical and pelvic assessments. For each clinical laboratory and vital sign parameters, the last non-missing safety assessment before the first Treatment 1 IP insertion will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

All safety analyses will be performed using the safety population. For such analyses, subjects will be analyzed according to actual treatment received at the study treatment visit (i.e., "as treated" rather than "as randomized").

The following safety analyses will be performed unless otherwise mentioned:

- Summaries by treatment group and overall for the Treatment 1 period

- Summaries for patients who participated in both the Treatment 1 period and Treatment 2 period by treatment group and overall patient population. In this analysis, the treatment groups will be the safety treatment groups.

12.1   ADVERSE EVENTS

Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities,* version 18.1 or newer.

An AE will be considered a treatment-emergent adverse event (TEAE) if it was present after the first dose of study treatment or was present before the date of the first dose of study treatment and increased in severity after the first dose of study treatment or became serious after the first dose of study treatment. If more than 1 AE was reported before the first dose of study treatment and coded to the same preferred term, the AE with the greatest severity will be used for comparison with the AEs occurring during the study period.

Analysis of the incidence of TEAEs will be performed for the Treatment 1 Period using the Safety population. For the cohort of safety patients that received Treatment 2 IP, the incidence of TEAEs will be summarized over the Treatment 2 Period and over the entire study period (Treatment 1 and 2 period). The following rules will be used to count TEAEs at each treatment period.

- For the analyses of TEAEs by treatment period, an event will be counted once in the particular period if the onset of this event begins during that corresponding period.

- If an event occurs during the Treatment 1 period and continues to the Treatment 2 period without increasing in severity, this event will be counted as an event during the Treatment 1 period but will not be counted again as an event in the Treatment 2 period.

- If an event occurs during the Treatment 1 period or earlier and continues to the Treatment 2 period and the severity increases to a grade that is greater than the maximum severity of the Treatment 1 period or the pre-treatment period or becomes serious in Treatment 2 period then the event will be counted as an event in the Treatment 2 period.

For each treatment phase and for the overall treatment period the number and percentage of patients reporting TEAEs in each treatment group will be tabulated by descending percentage in any group, by system organ class and preferred term, and further categorized by severity and causal relationship to the study treatment. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship. All AE summary tables will be by treatment group and the overall safety population.

The total number of TEAEs by severity and causal relationship to the study treatment will be summarized by treatment group.

The number and percentage of patients who have Treatment emergent SAEs will be summarized by preferred term and treatment group. In addition, the incidence of treatment emergent SAEs that led to death will be summarized separately by preferred term for each treatment group.

The number and percentage of patients in the Safety Population who have AEs leading to premature discontinuation of the study treatment will be summarized by preferred term and treatment.

Pretreatment AEs are the AEs that occur after signing of the informed consent (IC) and prior to first dose of study medication. Such AEs will be presented in a patent listing.

The table below presents the preferred terms identified to be of special interest for lidocaine treatment. Since lidocaine has a short half-life, for these AEs to be considered of special interest for lidocaine treatment and to be further summarized in a table they need to occur on or after the day of IP insertion and up to the day after the IP removal. For Treatment 1 period it will be up to the day after the 2nd IP removal while for Treatment 2 it will be the day after the IP removal. The summary table will present such events by treatment group and overall. This table will be updated prior to database lock for consistency with the MedDRA version (version presented below is 18.1) that will be used for the analysis.

MedDRA v18.1 PT for AEs associated with of lidocaine toxicity

MedDRA Preferred term
Dizziness

Somnolence
Nervousness
Feeling cold
Feeling hot
Confusional state
Cardiac arrest
Circulatory collapse
Seizure
Vision blurred
Diplopia
Hypoaesthesia
Paraesthesia oral

Hypoaesthesia oral
Hypotension
Bradycardia
Respiratory arrest
Respiratory depression
Tinnitus
Tremor
Muscle twitching
Loss of consciousness
Vomiting

12.2   CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented by treatment group for the following laboratory parameters:

Hematology:	red blood cells (RBC); RBC indices: mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration, RBC morphology; white blood cells (WBC); WBC differential (% and absolute): neutrophils, lymphocytes, monocytes, eosinophils, basophils, hematocrit, hemoglobin, and platelets
Chemistry:	albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total and direct bilirubin, blood urea nitrogen, calcium, chloride, creatinine, gamma glutamyltransferase, globulin, nonfasting glucose, potassium, total protein, and sodium
Urinalysis:	color, appearance of urine, 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

Shift tables from baseline to end of study for clinical laboratory parameters will be presented by treatment group for the following categories: low, normal, and high, which are provided by lab vendor.

## 12.3	**VITAL SIGNS**

Descriptive statistics for vital signs (systolic and diastolic blood pressures, respiratory rate, pulse rate, body temperature) and changes from baseline values at each visit and at the end of each treatment phase and study will be presented by treatment group.

## 12.4	**ELECTROCARDIOGRAM**

Not Applicable.

## 12.5	**OTHER SAFETY PARAMETERS**

### 12.5.1	**Bladder Post-Void Residual**

Post-void residual (PVR) volume measurement and change from baseline volume measurements will be will be summarized by treatment phase for each visit (for visits where PVR assessment is done) using descriptive statistics.

12.5.2   Physical Examination

Complete Physical examinations are performed at the baseline and at the end of each treatment phase. Abnormal findings at these visits will be summarized by treatment phase. The complete and abbreviated physical examinations results will be presented in a patient listing

12.5.3   Cystoscopic Exam

All patients will undergo a cystoscopic examination on the days of insertion and removal of the IP, Treatment 1 Week 4 Follow-up and at study exit if the patient does not continue into Treatment 2 period. Abnormal findings will be summarized by treatment phase.

12.5.4   Investigational Product

The investigational product will be assessed prior to insertion and after the removal from the bladder. The findings on the condition of the IP prior to insertion and after the removal will be presented in a listing.

12.5.5   Pregnancy Test

Pregnancy test results for patients will be provided in a data listing.

12.5.6   Urine Cytology

Urine Cytology test will be performed at screening. The results of this tests will be presented in patient listing.

12.5.7   Urine Culture

A listing of patient's urine culture results will be presented by treatment group and visit.

12.5.8   Suicidality Assessment

Not applicable.

12.5.9   Potential Hy's Law

Not applicable.
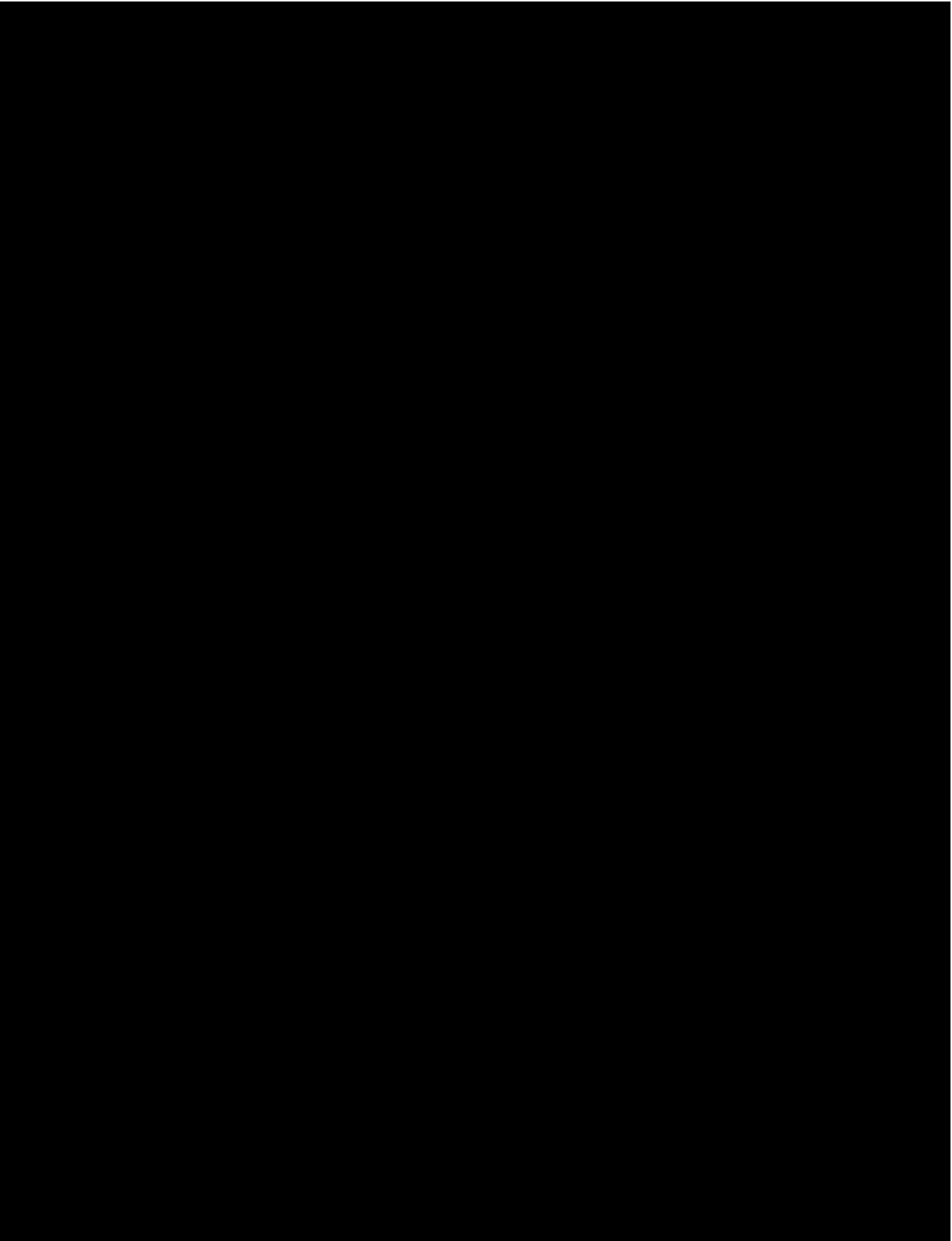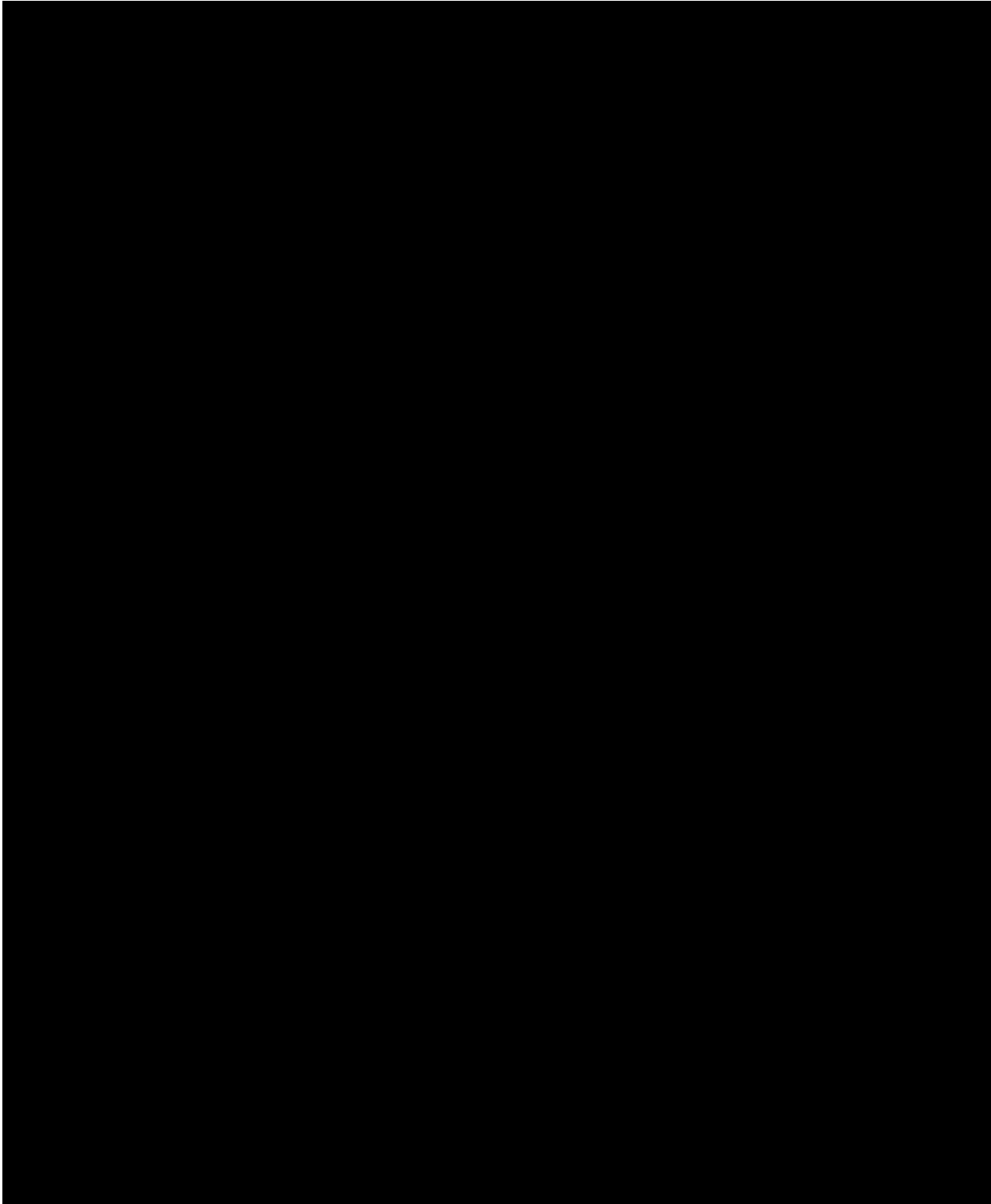
14.0   **INTERIM ANALYSIS**

Assuming that 5% of the randomized patients will not be evaluable for the primary analysis, to ensure that there are 72 evaluable patients approximately 76 patients will be randomized into the study. At a randomization ratio of 2:1:1, 72 evaluable patients ensures that there will be about 36 patients in the treatment group that gets two consecutive LiRIS 400 mg (LiRIS 400 mg/LiRIS 400 mg), 18 patients in the treatment group that gets Placebo and then LiRIS 400 mg (Placebo/LiRIS 400 mg), and 18 patients in the treatment group that gets two consecutive Placebo (Placebo/Placebo).

15.0   **DETERMINATION OF SAMPLE SIZE**

A sample size of 36 patients in the LiRIS 400 mg/LiRIS 400 mg group versus 18 patients in the Placebo/Placebo group has 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 two sample t-test with a type 1 error rate of 0.05. The calculation was performed using the commercial software ███████████ The standard deviation assumption is based on the TAR-100-105 open label study, where the SD is the Week 4 Follow-Up raw average daily NRS.

17.0   **DATA HANDLING CONVENTIONS**

17.1   **VISIT TIME WINDOWS**

Table 17.1–1 presents, for both treatments periods, the derived visits for efficacy (excluding efficacy based on daily pain diary) and safety analyses and the corresponding range of study days (window) during which an actual visit may occur.

Following SDTM and ADaM standard, the date of first IP insertion will be considered as Treatment 1 Day 1. Similarly, the date of 2nd IP insertion will be considered Treatment 2 Day 1. However, in the assessment tables of the protocol and in Section 4 of this document and in the eCRF pages this is considered to be Treatment 1 Day 0 and Treatment 2 Day 0, respectively. For by visit analysis tables and listings the visit label will follow these protocol and eCRF visit definitions (3rd column in table 17.1-1). Some listing will also display study day using the SDTM definition. Hence, using SDTM and ADaM standards study day is calculated as follows (see 2nd column in Table 17.1-1):

Screening & baseline period (prior to IP insertion)

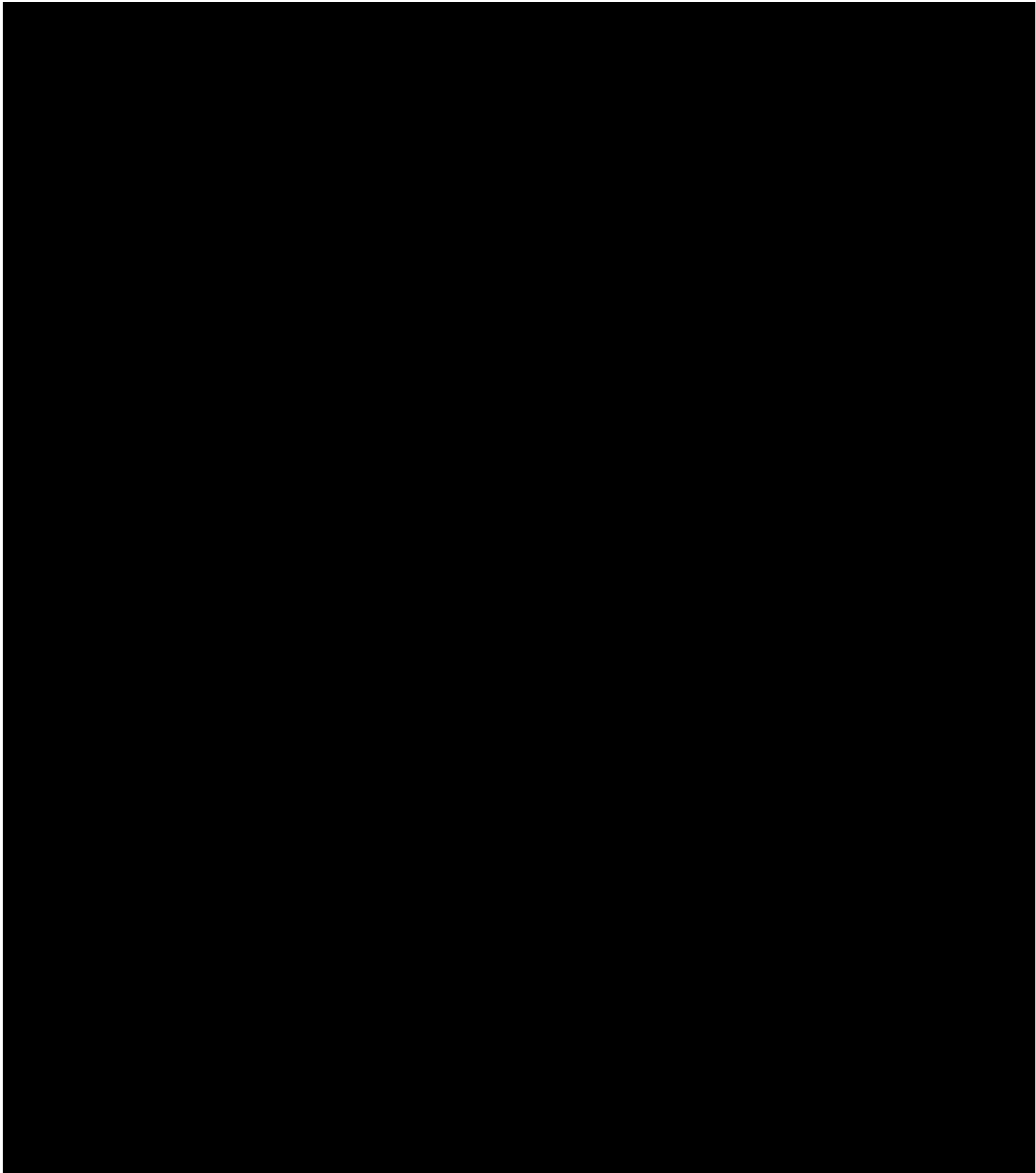study day = visit date - 1st IP insertion date

Treatment 1 period :

   study day = visit date - 1st IP insertion date +1

Treatment 2 Period :

   study day = visit date - 2st IP insertion date +1

Throughout this document ,unless otherwise stated, this definition of study day is used.

If not stated otherwise, all by visit analysis will be using the visit windows specified above. The target day for each treatment period is referenced to days after first IP insertion within each treatment period. Treatment 1 Day 1 refers to the first IP insertion date while Treatment 2 Day 1 refers to the IP insertion date in Treatment 2 period. In contrast, if the assessment date is before date of Treatment 1 IP insertion, the study day is calculated as follows:

assessment date – date of Treatment 1 IP insertion.

The visit window for each treatment period is defined as follows:

[(target day of current visit + target day of previous visit)/2+1] to [(target day of current visit + target day of next visit)/2]

If a patient has 2 or more visits within the same visit window, the last visit with a non-missing value will be used for the analysis.

For laboratory and vital signs analysis, baseline refers to study baseline, i.e. the baseline information collected at the start of Study 201025-001.

17.2   DERIVED VARIABLES

The data derivations and definitions listed in this section are to be applied to all analyses described in this analysis plan, unless otherwise stated.

- In this study there are two treatment periods:

    - Treatment period 1: for patients that just receive treatment in the randomized and blinded phase of the trial, it covers the period from the first Treatment 1 IP insertion to study exit. In contrast, for patients that receive IP insertions in both the randomized phase of the study (Treatment 1) and the open label phase of the study (Treatment 2) it covers the period from first Treatment 1 IP insertion up to Treatment 2 IP insertion,

    - Treatment period 2: covers the period from Treatment 2 IP insertion to study exit.

- Study days for each treatment period X (X=1 or 2) will be calculated as:

    - Study day of Treatment X = visit date – (day 1 of Treatment X) + 1.

- The baseline value of an assessment will be the last value recorded prior to the patient being inserted with first Treatment 1 IP on Day 1.

- Unless otherwise stated no imputation will be performed for missing data. All analyses will be based on the observed data.

- For analyses that are by stratification factor, actual stratification levels rather than randomization stratification levels will be used.

- Data will be pooled across the investigational sites.

- Descriptive statistics for continuous/ordinal data include the sample size (N), mean, standard deviation (SD), median, minimum (Min), and maximum (Max) and 95% confidence intervals.

- Summary statistics for categorical variables include sample size (N), frequency count (n), and percentage (%).

17.2.1   **Pain Data Derivations**

A pain assessment tool will be utilized in the study to capture the average daily 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 will continue every day up to and including the day prior to the Exit visit.

The patient's baseline average daily pain NRS will be the mean of the 7 day "average pain in your bladder over the last 24 hours" scores from the 7 reported days prior to Treatment 1 Day 1. Similarly, a patient's baseline daily worst pain NRS will be the mean of the 7 day "worst pain in your bladder over the last 24 hours" scores from the 7 reported days prior to Treatment 1 Day 1. Baseline average daily pain and average worst pain will only be calculated if the information is collected for *any* 5 consecutive days in the 7 days prior to Day 1 (i.e., Day -7 to Day -1). If less than 5 consecutive days are available, the baseline score will be set to missing.

Average daily pain NRS and daily worst pain NRS will be summarized for each week post- randomization. Patients are scheduled to have two IP insertion in Treatment 1 period and then Follow-Up visit. However, if a patient receives only one IP insertion in the study the follow up visits follow after the IP removal.

Table 17.2.1–1, presents for patients that receive more than one IP insertion, in days from first IP insertion within each treatment period the days to be included in each weekly summary. For patients that only receive one IP, Table 17.2.1-1 also presents in days from this IP insertion the days to be included in each weekly summary. For the post-baseline weeks that do not cover IP insertion or removal, a patient will be included in each weekly summary if they have at least 5 consecutive days of information within the summary week presented in Table 17.2.1–1 . For the week intervals that cover IP insertion or removal a different rule is applied. For assessment weeks where there is IP insertion, the day of insertion and the two days after the day of insertion will not be included in the weekly average summary. The summary for such a week will be based on all available values, provided there are at least three days of daily assessments to be summarized (the days that are to be removed will be considered in the 5 day criteria). In contrast, for the week where IP removal occurs, the IP removal date and the day after the IP removal will be removed from the weekly average summary. The summary for such a week will be based on all available values provided there are at least three daily assessments to be summarized (the days that are to be removed will be considered in the 5 day criteria). The rational for excluding these IP insertion and removal dates is to reduce the impact of pain or pain medication that is related to the procedure rather than the disease under consideration.

Table 17.2.1–1 presents the weekly pain assessment windows.

17.2.2   **Void Data Derivations**

- For baseline and posttreatment visits, analyses on void diary efficacy variables will be based on the diary data collected during a 3-day interval for each visit. Each 3-day interval consists of 3 consecutive 24-hour periods, with the first period starting from the time of the first urinary episode on the first of the 3 days.

- A valid diary day is defined as any of the three 24-hour periods with 2 or more urinary episodes. Data collected from a 24-hour period with less than 2 urinary episodes (i.e., an invalid diary day) will be set to missing.

- For baseline and posttreatment visits, the 3-day diary will be determined based on the following algorithm:

  - Apply visit windows defined in Section 17.1, which are based on days from the date of study first treatment in each treatment period.

  - Determine the time of the first urinary episode that is within the visit window (in the example below, 7:30 am on April 3). Count forwards for 3 consecutive days. Note: the last 24-hour period should end within the window, i.e., prior to or on the last day specified in the window definition; otherwise, the 24-hour data will not be used for the corresponding window. For baseline diary data, the urinary episodes that occurred on the day of first IP insertion but before the IP insertion time will be counted as baseline diary data.

  - Using the example below, the first 24-hour time period starts from 7:30am on April 3 and ends at 7:29 am on Apr 4. The second 24-hour time period starts from 7:30am on Apr 4 and ends at 7:29 am on Apr 5. Note that this 24-hour is considered as an invalid diary day since it has just one episode during the 24 hours. The third or the last 24-hour time period starts from 7:30 am on Apr 5 and ends at 7:29 am on Apr 6.

  - At least one valid 24-hour diary day within the window is required for the visit. Otherwise, the 3-day diary data will be missing for the visit.
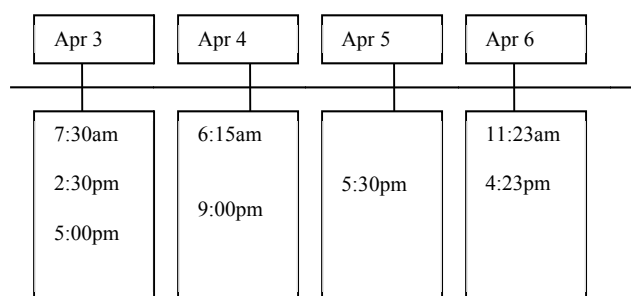
17.3 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a patient has repeated assessments before the start of the first treatment, the results from the final non-missing assessment made prior to the start of the study treatment will be used as baseline.

17.4 MISSING DATE OF THE LAST DOSE OF STUDY TREATMENT

Not applicable.

17.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study treatment, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

17.6 MISSING CAUSAL RELATIONSHIP TO STUDY TREATMENT FOR ADVERSE EVENTS

If the causal relationship to the study treatment is missing for an AE that started on or after the date of the first dose of study treatment, a causality of yes will be assigned. The imputed values for causal relationship to study treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

17.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for AEs is incomplete (i.e., partly missing).

Missing month and day
- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only
- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study treatment, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of study treatment, the date of the first dose of study treatment will be assigned to the missing start date

- If the stop date is before the date of the first dose of study treatment, the stop date will be assigned to the missing start date

17.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including rescue medications, incomplete (i.e., partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a patient, the start date will be imputed first.

17.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day
- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only
- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only
- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study treatment, the first day of the month will be assigned to the missing day

17.8.2   **Incomplete Stop Date**

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date.

Missing month and day
- If the year of the incomplete stop date is the same as the year of the last dose of study treatment, the month and day of the study exit date will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the last dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the last dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only
- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only
- If the month and year of the incomplete stop date are the same as the month and year of the last dose of study treatment, the day of the study exit will be assigned to the missing day

- If either the year of the incomplete stop date is before the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete stop date is after the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of study treatment, the first day of the month will be assigned to the missing day

17.9 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

Table 17.9–1 shows examples of how some possible laboratory results should be coded for the analysis.

Table 17.9–1.   **Examples of Coding Special Character Values for Clinical Laboratory Parameters**

Laboratory Test, SI Unit	Possible Laboratory Results	Coded Value for Analysis
CHEMISTRY		
ALT, U/L	< 5	5
AST, U/L	< 5	5
Bilirubin, total, μmol/L	< 2	2
URINALYSIS		
Glucose, mmol/L	= OR > 55, ≥ 55, > 0	Positive
	≤ 0, negative	Negative
pH	> 8.0, ≥ 8.0	8.0
	≥ 8.5	8.5
Protein	= OR > 3.0, ≥ 3.0, > 0	Positive
	≤ 0	Negative

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SI = *Le Système International d'Unités* (International System of Units).

18.0   <u>CHANGES TO ANALYSES SPECIFIED IN PROTOCOL</u>

- The AE analysis by time of insertion or removal has been removed. It was assessed to be not relevant to this study

- The primary efficacy analysis with LOCF method of imputation has been removed. This has been replaced with repeated measures mixed model analysis.

19.0 **REFERENCES**

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DOCUMENT HISTORY PAGE

Effect Date	Revision Number	Primary Author	Description of Change
01 July 2015	0.1	███████████	Initial Release
06 June 2016	0.2	█████████	Changes to conform with Protocol Amendment 2

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LiRIS 201025-001 Analysis Plan - Amd_2_v_1

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