CYST-SLZ-7001

CLINICAL INVESTIGATION PLAN (PROTOCOL)

Protocol Title	Real-world evidence observational study to evaluate performance and safety of intravesical sodium hyaluronate (Cystistat®) in the treatment of patients with interstitial cystitis (IC)/bladder pain syndrome (BPS).
Short Title	Real-world evidence study on Cystistat
Protocol Number	CYST-SLZ-7001
Product	Cystistat
Study Type	Non-interventional study (NIS)
Version	1.0
Protocol Date	06-Apr-2022
Legal/Filing Sponsor	MEDA Pharma GmbH & Co. KG (A Viatris Company) Benzstrasse 1, 61352 Bad Homburg, Germany

Confidentiality:

DOCUMENT HISTORY

Document Version, Date	Summary of Changes with Rationale
1.0 06-Apr-2022	NA

PROTOCOL SYNOPSIS

Protocol Title	Real-world evidence observational study to evaluate performance and safety of intravesical sodium hyaluronate (Cystistat®) in the treatment of patients with interstitial cystitis (IC)/bladder pain syndrome (BPS)
Short Title	Real-world evidence study on Cystistat
Protocol Number	CYST-SLZ-7001
Study Sites	European multicenter study with approximately 15 study sites (approximately up to 15 patients per site)
Co-ordinating Investigator	[redacted]
Study Period Planned	Period from start of recruitment till end of study: Q2 2022 to Q3 2023
Duration of Individual Treatment	For assessment of performance and safety the intended duration of observation per patient is approximately 6 months
End of Study	Date of the last visit of the last patient included in the study
Background and Rationale	Hyaluronan, the biologic form of hyaluronic acid, is found in numerous tissues in the human body. It is part of interstitial fluids in connective tissues and is also an important contributor to surface barriers. Specifically, the importance of hyaluronan as the predominant substance of the Glycosaminoglycan (GAG) layer that protects the urothelial surface of the urinary bladder has been well investigated and documented (1, 2). The impact of a GAG layer defect in Bladder Pain Syndrome (BPS)/Interstitial Cystitis (IC), a chronic bladder disease characterized by bladder pain and a variety of voiding symptoms was recognized about two decades ago. The protective effect of the GAG layer on the transitional surface of the bladder is explained as follows: The hydrophilic glycosaminoglycans bind water molecules in preference to other cations and thus form a molecular layer of water at the bladder surface which acts as a barrier to urinary solutes, crystals and bacteria. Relevant components of the GAG layer include hyaluronic acid, chondroitin sulphate, heparin, heparin sulfate, dermatan sulfate and keratan sulfate. Impairment of this specific layer maybe an initial etiologic event in IC/BPS resulting in a leaky epithelium which is permeable to urinary solutes. An increased uptake of potassium through the leaky surface may induce urgency

	and pain, damage tissue and promote the pathogenesis of IC/BPS. This postulated pathogenetic mechanism may explain the main disease symptoms. The benefit of GAG substitution therapy in such cases of GAG layer injury has been well documented in several clinical studies since then. Various investigators have reported clinically significant remission rates for intravesical hyaluronan instillation therapy. Several uncontrolled as well as a controlled study have shown remission rates between 60 and 85% (3-8). In addition to its efficacy, Cystistat is known to have a good safety profile with a low level of adverse events (9). In the past years the term IC has become misleading since inflammatory changes have not been detected in all symptomatic patients and was therefore replaced by an expert panel with the term BPS. This name is in line with recent recommendations by the European Association of Urology and is based on the axial structure of the International Association for the Study of Pain classification. To facilitate this name change, the European Society for Studies of Interstitial Cystitis (ESSIC) agreed to include IC in the overall term during a transition period (10). Based on that, the aim of this study is assessment of Cystistat therapy in IC/BPS patients. This study will be conducted with the aim of ensuring the continued acceptability of the benefit-risk ratio and confirming the safety and performance of the device throughout its expected lifetime. Real-world evidence observational studies are considered as an expedient tool to reflect the use of a product under real life conditions. However, due to the known difficulties with the diagnosis of IC/BPS, only clinical sites using state of the art diagnostic measures according to current therapeutic guidelines will be selected for this study. A previous randomized, placebo-controlled trial with Cystistat showed limitations of using a placebo group. In this study, the initial response rate in the placebo group was higher than in the Cystistat group, with a turnaround of results at a later timepoint. Several possible explanations for these unexpected findings have been published (8). As the most likely reason for the placebo efficacy the possible beneficial effect from the alkalizing placebo solution has been assumed. Based on these considerations and on the known difficulties in recruiting high number of patients in this indication, an observational real world evidence study was chosen as the best feasible way to collect additional data to demonstrate the benefit/risk profile of Cystistat and compliance with the safety and performance requirements of the Medical Device Regulation (MDR) (11, 12).
Primary Objective	To collect data on the performance of Cystistat on patients' overall IC/BPS condition at end of treatment or latest at week 12 in routine clinical practice.
Primary Endpoint	Responder rate to treatment at end of treatment or latest at week 12 as indicated by improvement on a seven-point Patient Global Assessment (PGA) scale where the patient is able to evaluate the overall change in her/his IC/BPS condition as markedly improved, moderately improved, slightly improved, no change, slightly worse, moderately worse or markedly worse. For the primary analysis, a responder is defined as a patient who has experienced an improvement on the PGA scale (i.e., PGA evaluated as markedly improved, moderately improved, or

	slightly improved. In case of slightly improved, patients will only be considered as responders if the question "Did therapy have a positive effect on your life and would you undergo this treatment again?" is answered with "Yes".).
Secondary Objectives	• Evaluation of the change of morning voiding volume over time (until month 6) • Evaluation of the change of 24-hour urinary frequency and voiding volume (daytime and nighttime) over time (until month 6) • Evaluation of change from baseline in Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) (at end of treatment or latest at week 12 and at month 6) • Evaluation of patients' overall IC/BPS condition at month 6 (using the same approach as for the primary objective) • Evaluation of patients' overall IC/BPS condition at end of treatment or latest at week 12 and at month 6 (using the PGA but with an alternative responder definition) • Evaluation of the change from baseline in bladder pain and urinary urgency on Visual Analogue Scale (VAS) (until month 6) • Evaluation of the change from baseline in quality of life (QoL) on Visual Analogue Scale (VAS) (until month 6) • Evaluation of concomitant IC/BPS and pain medication use (until month 6) • Evaluation of flares (symptom deterioration) (until month 6) • Evaluation of premature termination of treatment • Assessment of tolerability and safety (until month 6)
Secondary Endpoints	• Morning voiding volume over time (from patient diaries, until month 6). • Total number of voids and total voiding volume (daytime and nighttime) over the last 24 hours (from patient diaries, until month 6) • Change from baseline to end of treatment or latest to week 12 and to month 6 in Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS). • Percent responders at month 6 as indicated by improvement on the 7-point Patient Global Assessment (PGA) scale using the same responder definition as for the primary endpoint. • Percent responders at end of treatment or latest at week 12 and at month 6 as indicated by improvement on the 7-point Patient Global Assessment (PGA) scale using an alternative responder definition (i.e. a responder is defined as a patient who experiences moderate or marked improvement). • Change from baseline to end of treatment or latest to week 12 and to month 6 in bladder pain and urinary urgency on Visual Analogue Scale (VAS) scored from 0 to 100. • Change from baseline to end of treatment or latest to week 12 and to month 6 in quality of life (QoL) on Visual Analogue Scale (VAS) scored from 0 to 100.

	• Use of concomitant IC/BPS and pain medication count (until month 6). • Occurrence of flares (documented as adverse events) and additional BPIC-SS (at the time of occurrence) (until month 6). • Premature termination of treatment. • Safety assessments: Adverse events and incidents (until month 6).
Methodology	Multinational, multicenter, prospective, real-world evidence (RWE) observational study. Patients will be enrolled in the study upon signing an Informed Consent. Cystistat will be instilled into the bladder according to the instructions for use. The observation period for this study will end approximately 6 months after start of treatment (irrespective of the duration of treatment). If required, treatment will be continued thereafter under regular medical care.
Investigational Medical Device	This non-interventional study (NIS) refers only to the regular prescription of commercially available Cystistat according to instructions for use (IFU). Cystistat is a clear colorless solution presented in a 50 mL glass vial containing 40 mg sodium hyaluronate. It is manufactured by Mylan [redacted] and distributed by third companies in some countries.
Inclusion/ exclusion criteria	To be eligible for inclusion, a patient must comply with all of the following criteria: • First prescription of Cystistat according to instructions for use. • Female patients of any ethnic origin with clinical diagnosis of interstitial cystitis (IC)/bladder pain syndrome (BPS). If in accordance with routine clinical practice at the site, ESSIC diagnostic criteria will be used. • Age: 18 years and older. • At least 6 months duration of bladder pain/discomfort symptom(s), e.g. constant bladder pain/discomfort or bladder pain/discomfort when voiding or as a burning sensation between voids as the bladder fills with urine. • At least one accompanying intermittent or persistent lower urinary tract symptom, such as urinary frequency, urgency, or nocturia during the previous 6 months. • Bladder Pain/ Interstitial Cystitis Symptom Score (BPIC-SS) > 18 prior to first treatment. • Written informed consent. The patient is not eligible for participating in this study, if one or more of the following criteria are met: • Known hypersensitivity reactions to sodium hyaluronate. • Pregnancy / planned pregnancy or breastfeeding during the course of this NIS. • Known history of any GAG substitution therapy within the last 2 years. • Known history of fulguration or resection of Hunner's lesions. • Known diagnosis of recurrent urinary tract infection or overactive bladder. • Any other conditions or diseases that can cause similar symptoms, using information from medical history, physical examination findings, laboratory studies (e.g., urine bacterial culture), and other previously performed

	procedures (e.g., urodynamics, cystoscopy, laparoscopy, radiological studies). • Patients are not able to fulfil study requirements according to physician's opinion.
Planned Number of Patients	Approximately 74 patients (including approximately 10% drop-outs). [redacted] [redacted] Accounting for approximately 10% drop-outs, further 7 patients and a total of 74 patients should be included in this study.
Statistical Methods	All analyses will be exploratory in character and all assessed measures will be analyzed. Continuous variables will be summarized by number (N), mean, standard deviation (SD), minimum, 5% percentile (P5), lower quartile (Q1), median, upper quartile (Q3), 95% percentile (P95) and maximum. Categorical variables will be presented in frequency distribution tables with number (N) and percentage. All endpoint assessments with more than two time points will be tabulated by timepoint and displayed graphically for absolute values and change from baseline values. [redacted] If there is a substantial rate of patients with rescue medication (n> 20), explorative subgroup analyses will be provided for patients with and without rescue medication. **Populations for statistical analyses:** Safety (SAF) population: All enrolled patients who received at least one instillation of Cystistat and validity of data is confirmed by the physician. Full analysis set (FAS) population: All patients of the SAF, who have at least one post baseline assessment.

	Interim analysis: [redacted]

Table 0-1 Study Schedule

	Baseline[1)]	During Treatment	End of Treatment[2)]	Follow-up[3)]
STUDY DAY	Before first treatment	Week 1-11 (as per standard of care)	Latest Week 12 (Month 3)	Approximately Month 6
Written informed consent	X			
Demography and medical history[4)]	X			
In-/exclusion criteria	X			
Patient Global Assessment of overall IC/BPS condition improvement[5)]			X	X
Assessment of BPIC-SS[6)]	X		X	X
Assessment of VAS[7)]	X		X	X
Instillation of Cystistat[8)]		X	X	(X)
Dispense of diary card[9)]	X		X	
Review of diary card		X	X	X
Collection of diary card			X	X
Assessment of concomitant medications[10)]		X	X	X
Assessment of adverse events, incidents[11)]	X	X	X	X

1 Baseline assessments may be performed on the first treatment visit prior to instillation of Cystistat according to routine clinical practice.

2 This assessment will be performed on the last treatment day or latest at week 12; if required, treatment will be continued after week 12 under regular medical care.

3 Follow-up will be performed as an on-site visit if in accordance with routine clinical practice; if not possible as an on-site visit, the information will be collected remotely (e.g., via phone and postal mail) from the patient.

4 Demography and medical history:
- Patients' demographic and anamnestic background data
- Diagnostic criteria of IC/BPS diagnosis
- Previous and current treatments

5 Patient Global Assessment of overall IC/BPS condition improvement: To be completed at end of treatment or latest at week 12 and at month 6.

6 Bladder Pain/ Interstitial Cystitis Symptom Score (BPIC-SS): To be completed prior to the first treatment, at end of treatment or latest at week 12, and at month 6.

7 Visual Analogue Scale (VAS) for bladder pain, urinary urgency, and quality of life (QoL): To be completed prior to first treatment, at end of treatment or latest at week 12, and at month 6.

8 Instillation of Cystistat: Cystistat will be instilled into the bladder according to the instructions for use; the regimen and duration of treatment will depend on the investigators' discretion; each instillation of Cystistat until month 6 will be recorded in the eCRF; the observation period for this study will end approximately at month 6 (irrespective of the duration of treatment); if required, treatment will be continued after month 6 under regular medical care.

9 Diary card: The following assessments are to be filled out by the patient:
- Morning voiding volume once a week, preferably on the treatment day (until end of treatment or latest week 12) and once at month 6
- Urinary voids and the respective volumes over a period of 24 hours once a week, preferably starting the day before the treatment day (until end of treatment or latest week 12) and once at month 6
- Use of concomitant IC/BPS medication, pain medication, and other relevant concomitant medication (until month 6)
- Adverse events (until month 6)

10 The use of concomitant IC/BPS medication, pain medication, and other relevant concomitant medication will be recorded; it is not required to collect all concomitant medication

11 Adverse events and incidents will be recorded after first instillation of Cystistat; prior to first instillation of Cystistat only adverse events will be recorded.

SIGNATURE PAGE

Protocol Title	Real-world evidence observational study to evaluate performance and safety of intravesical sodium hyaluronate (Cystistat®) in the treatment of patients with interstitial cystitis (IC)/bladder pain syndrome (BPS)
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Not applicable.

LIST OF COMMONLY USED ABBREVIATIONS

Abbreviation	*Description*
AE	Adverse Event
ANCOVA	Analysis of Covariance
BPS	Bladder Pain Syndrome
BPIC-SS	Bladder Pain/Interstitial Cystitis Symptom Score
CE	European Conformity (*Conformité Européene*)
CI	Confidence Interval
CIP	Clinical Investigation Plan (synonymous with Protocol)
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
DMP	Data Management Plan
DVP	Data Validation Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEA	European Economic Area
ESSIC	European Society for the Study of Interstitial Cystitis
FAS	Full Analysis Set
GAG	Glycosaminoglycan
GDPR	General Data Protection Regulation
IC	Interstitial Cystistis
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFU	Instructions for Use
IMDRF	International Medical Device Regulators Forum
IRB	Institutional Review Board
ISF	Investigator's Site File
ISO	International Organization for Standardization
LEC	Local Ethics Committee
MDCG	Medical Device Coordination Group
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
N	Number
NIS	Non-interventional Study
NSAID	Non-steroidal Anti-inflammatory Drug
PDF	Portable Document Format
PGA	Patient Global Assessment
P5	5% Percentile
P95	95% Percentile
PI	Principal Investigator
Q1	Lower Quartile
Q3	Upper Quartile
QA	Quality Assurance

QoL	Quality of Life
RWE	Real World Evidence
SAF	Safety (Population)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
TMF	Trial Master File
USA	United States of America
VAS	Visual Analogue Scale
WHO	World Health Organization

1.0 INTRODUCTION

1.1 Indication

Interstitial Cystitis (IC)/Bladder Pain Syndrome (BPS) is a chronic bladder disease characterized by bladder pain and a variety of voiding symptoms.

The impact of a glycosaminoglycan (GAG) layer defect in this indication was recognized about two decades ago. The protective effect of the GAG layer on the transitional surface of the bladder is explained as follows: The hydrophilic glycosaminoglycans bind water molecules in preference to other cations and thus form a molecular layer of water at the bladder surface which acts as a barrier to urinary solutes, crystals and bacteria. Relevant components of the GAG layer include hyaluronic acid, chondroitin sulphate, heparin, heparin sulfate, dermatan sulfate and keratan sulfate.

Impairment of this specific layer maybe an initial etiologic event in IC/BPS resulting in a leaky epithelium which is permeable to urinary solutes. An increased uptake of potassium through the leaky surface may induce urgency and pain, damage tissue and promote the pathogenesis of IC/BPS. This postulated pathogenetic mechanism may explain the main disease symptoms.

In the past years the term IC has become misleading since inflammatory changes have not been detected in all symptomatic patients and was therefore replaced by an expert panel with the term BPS. This name is in line with recent recommendations by the European Association of Urology and is based on the axial structure of the International Association for the Study of Pain classification. To facilitate this name change, the European Society for Studies of Interstitial Cystitis (ESSIC) agreed to include IC in the overall term during a transition period (10). Based on that, the aim of this study is assessment of Cystistat therapy in IC/BPS patients.

1.2 Background and Rationale

Cystistat is supplied as a 50 mL solution containing 40 mg of sodium hyaluronate. It is indicated for the temporary replacement of the GAG layer in the bladder.

Hyaluronan, the biologic form of hyaluronic acid, is found in numerous tissues in the human body. It is part of interstitial fluids in connective tissues and is also an important contributor to surface barriers. Specifically, the importance of hyaluronan as the predominant substance of the GAG layer that protects the urothelial surface of the urinary bladder has been well investigated and documented (1, 2).

The benefit of GAG substitution therapy in such cases of GAG layer injury has been well documented in several clinical studies since then. Various investigators have reported clinically significant remission rates for intravesical hyaluronan instillation therapy. Several uncontrolled as well as a controlled study have shown remission rates between 60 and 85% (3-8). In addition to its efficacy, Cystistat is known to have a good safety profile with a low level of adverse events (9).

Cystistat was first CE marked in 1998 and has been on the European market for >20 years and is available in more than 20 international markets outside Europe. This study will be conducted with the aim of ensuring the continued acceptability of the benefit-risk ratio and confirming the safety and performance of the device throughout its expected lifetime.

1.3 Investigational Medical Device

This non-interventional study (NIS) refers only to the regular prescription of commercially available Cystistat according to the instructions for use (IFU) (13).

1.4 Ethics and Benefit-Risk Considerations

This represents a NIS, meaning that the investigator will document ongoing medical care, without conducting any intervention beyond normal medical practice.

The decision to prescribe Cystistat must be previous and independent from the decision to include the patient in the NIS. Before the study is started, the sponsor will comply with all national regulations, regarding notifications, approvals, or any other required administrative obligation.

Cystistat can be considered a well-established medical device; it was first CE marked in 1998 and has been on the European market for >20 years and is available in more than 20 international markets outside Europe. Cystistat has a good safety profile and low level of adverse events (incidents/serious incidents).

Complete information for Cystistat may be found in the Single Reference Safety Document, which for this study is the instructions for use (13).

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

To collect data on the performance of Cystistat on patients' overall IC/BPS condition at end of treatment or latest at week 12 in routine clinical practice.

2.1.2 Secondary Objectives

- Evaluation of the change of morning voiding volume over time (until month 6)
- Evaluation of the change of 24-hour urinary frequency and voiding volume (daytime and nighttime) over time (until month 6)
- Evaluation of change from baseline in Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) (at end of treatment or latest at week 12 and at month 6)
- Evaluation of patients' overall IC/BPS condition at month 6 (using the same approach as for the primary objective)

- Evaluation of patients' overall IC/BPS condition at end of treatment or latest at week 12 and at month 6 (using the PGA but with an alternative responder definition)
- Evaluation of the change from baseline in bladder pain and urinary urgency on Visual Analogue Scale (VAS) (until month 6)
- Evaluation of the change from baseline in quality of life (QoL) on Visual Analogue Scale (VAS) (until month 6)
- Evaluation of concomitant IC/BPS and pain medication use (until month 6)
- Evaluation of flares (symptom deterioration) (until month 6)
- Evaluation of premature termination of treatment
- Assessment of tolerability and safety (until month 6)

2.1.3 Other Objectives

Not applicable.

2.2 Endpoints

2.2.1 Primary Endpoint

Responder rate to treatment at end of treatment or latest at week 12 as indicated by improvement on a seven-point Patient Global Assessment (PGA) scale where the patient is able to evaluate the overall change in her/his IC/BPS condition as markedly improved, moderately improved, slightly improved, no change, slightly worse, moderately worse or markedly worse. For the primary analysis, a responder is defined as a patient who has experienced an improvement on the PGA scale (i.e., PGA evaluated as markedly improved, moderately improved, or slightly improved. In case of slightly improved, patients will only be considered as responder if the question "Did therapy have a positive effect on your life and would you undergo this treatment again?" is answered with "Yes".).

2.2.2 Secondary Endpoints

The secondary endpoints of the study are:

- Morning voiding volume over time (from patient diaries, until month 6).
- Total number of voids and total voiding volume (daytime and nighttime) over the last 24 hours (from patient diaries, until month 6)
- Change from baseline to end of treatment or latest to week 12 and to month 6 in Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS).
- Percent responders at month 6 as indicated by improvement on the 7-point Patient Global Assessment (PGA) scale using the same responder definition as for the primary endpoint.
- Percent responders at end of treatment or latest at week 12 and at month 6 as indicated by improvement on the 7-point Patient Global Assessment (PGA) scale using an alternative responder definition (i.e. a responder is defined as a patient who experiences moderate or marked improvement).

- Change from baseline to end of treatment or latest to week 12 and to month 6 in bladder pain and urinary urgency on Visual Analogue Scale (VAS) scored from 0 to 100.
- Change from baseline to end of treatment or latest to week 12 and to month 6 in quality of life (QoL) on Visual Analogue Scale (VAS) scored from 0 to 100.
- Use of concomitant IC/BPS and pain medication count (until month 6).
- Occurrence of flares (documented as adverse events) and additional BPIC-SS (at the time of occurrence) (until month 6).
- Premature termination of treatment.
- Safety assessments: Adverse events and incidents (until month 6).

2.2.3 Other Endpoints (Efficacy)

Not applicable.

3 STUDY DESIGN

3.1 Overall Design

The present study is a prospective, multicenter, non-interventional study to be conducted in several European countries. It is planned to include approximately 15 study sites. The recruitment will be competitive, with a maximum of approximately 15 patients per site.

Due to the known difficulties with the diagnosis of IC/BPS, only clinical sites using state of the art diagnostic measures according to current therapeutic guidelines will be selected for this study.

3.2 Rationale for Study Design

Real world evidence observational studies are considered as an expedient tool to reflect the use of a product under real life conditions. However, due to the known difficulties with the diagnosis of IC/BPS, only clinical sites using state of the art diagnostic measures according to current therapeutic guidelines will be selected for this study.

A previous randomized, placebo-controlled trial with Cystistat showed limitations of using a placebo group. In this study, the initial response rate in the placebo group was higher than in the Cystistat group, with a turnaround of results at a later timepoint. Several possible explanations for these unexpected findings have been published (8). As the most likely reason for the placebo efficacy the possible beneficial effect from the alkalizing placebo solution has been assumed.

Based on these considerations and on the known difficulties in recruiting high number of patients in this indication, an observational real world evidence study was chosen as the best feasible way to collect additional data to demonstrate the benefit/risk profile of Cystistat and compliance with the safety and performance requirements of the Medical Device Regulation (MDR) (11, 12).

3.3 End of Study Definition

The end of study is defined as the date of the last visit (or remote contact) of the last patient included in the study.

Cystistat will be instilled into the bladder according to the instructions for use (13). The observation period for a patient in this study will end approximately 6 months after start of treatment (irrespective of the duration of treatment). If required, treatment will be continued thereafter under regular medical care.

4 STUDY POPULATION

4.1 Study Population

Approximately 74 female patients with IC/BPS should be included in the study.

4.2 Inclusion and Exclusion Criteria

4.2.1 Inclusion Criteria

To be eligible for inclusion, a patient must comply with all of the following criteria:

- First prescription of Cystistat according to instructions for use.
- Female patients of any ethnic origin with clinical diagnosis of interstitial cystitis (IC)/bladder pain syndrome (BPS). If in accordance with routine clinical practice at the site, ESSIC diagnostic criteria will be used.
- Age: 18 years and older.
- At least 6 months duration of bladder pain/discomfort symptom(s), e.g. constant bladder pain/discomfort or bladder pain/discomfort when voiding or as a burning sensation between voids as the bladder fills with urine.
- At least one accompanying intermittent or persistent lower urinary tract symptom, such as urinary frequency, urgency, or nocturia during the previous 6 months.
- Bladder Pain/ Interstitial Cystitis Symptom Score (BPIC-SS) > 18 prior to first treatment
- Written informed consent.

4.2.2 Exclusion Criteria

The patient is not eligible for participating in this study, if one or more of the following criteria are met:

- Known hypersensitivity reactions to sodium hyaluronate.
- Pregnancy / planned pregnancy or breastfeeding during the course of this NIS.
- Known history of any GAG substitution therapy within the last 2 years.

- Known history of fulguration or resection of Hunner's lesions.
- Known diagnosis of recurrent urinary tract infection or overactive bladder.
- Any other conditions or diseases that can cause similar symptoms, using information from medical history, physical examination findings, laboratory studies (e.g., urine bacterial culture), and other previously performed procedures (e.g., urodynamics, cystoscopy, laparoscopy, radiological studies).
- Patients are not able to fulfil study requirements according to physician's opinion.

4.2.3 Criteria for Study Treatment Termination, Withdrawal from the Study and Study Termination

Patients may terminate the treatment with the investigational medical device or withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or the study center. When available, a reason for not completing the study will be recorded in the electronic case report form (eCRF).

After enrolling in the study, patients will come to the study site on a weekly basis up to week 12 for the instillation of Cystistat according to the instructions for use (13). If required, treatment will be continued thereafter under regular medical care. A follow-up visit is scheduled for approximately month 6 as an on-site visit if in accordance with routine clinical practice. If not possible as an on-site visit, the information will be collected remotely (e.g., via phone and postal mail) from the patient.

Possible reasons for not completing the study may include, but are not limited to, the following:

- The patient withdraws consent.
- Diagnosis of pregnancy or stated intention to become pregnant.
- At the investigator's discretion, if it is in the patient's best interest due to occurrence of an AE or other finding (e.g. pregnancy, other exclusion criteria) considered to present a safety concern to continued treatment with the medical device, and warrants treatment withdrawal.
- Lost to follow-up.

The principal investigator and/or sponsor reserves the right to terminate the study for any reason.

4.3 Replacement Policy

Patients who are withdrawn from the study will not be replaced.

4.4 Lifestyle Guidelines

There are no special requirements as this is a non-interventional study.

4.5 Contraception

There are no special requirements as this is a non-interventional study.

4.6 Pregnancy Testing

Pregnancy testing will be at the discretion of the investigator and as per site's routine practice.

5 STUDY TREATMENT

5.1 Investigational Medical Device

This NIS refers only to the regular prescription of commercially available Cystistat according to the instructions for use (13).

Cystistat is a clear colourless solution presented in a 50 mL glass vial containing 40 mg sodium hyaluronate. It is manufactured by Mylan [redacted] and distributed by third companies in some countries.

5.2 Administration of Investigational Medical Device

Cystistat will be instilled into the bladder according to the instructions for use (13). Instillation is intended to be performed by a qualified healthcare professional with the use of a sterile catheter and sterile syringe using appropriate hygienic technique, to minimize risk of infection.

At instillation, the clinician will check that the content of the instructions for use (13), warnings and precautions especially, are followed before and during each treatment.

If in accordance with routine clinical practice at the site, a single-shot oral antibiotic will be given on instillation day.

In the event of any incident, the CRA, or sponsor study contact should be contacted immediately, and the event must be reported as described in Section 10.4.1.

5.3 Supply of Investigational Medical Device

Commercially available Cystistat will be prescribed as per routine clinical practice (i.e., the investigational medical device will not be supplied by the sponsor).

5.4 Storage, Disposition of Unused Investigational Medical Device and Accountability

Not required in this non-interventional study.

5.5 Randomization

Not applicable.

5.6 Breaking the Blind

Not applicable.

5.7 Rescue Medication

Not applicable.

5.8 Concomitant Medications

It is not required to collect all concomitant medication taken during this non-interventional study. The use of IC/BPS medication, pain medication, and other relevant concomitant medication (e.g. if in context with an adverse event or incident) will be captured by the patient in the diary card and the investigator will provide documentation in the eCRF, including at least indication, daily dose, and start and stop dates of administration.

5.9 Treatment Compliance

Not applicable.

5.10 Therapy at End of Study for Compassionate Use

Not applicable.

6 STUDY CONDUCT

When the clinical decision has been made to prescribe Cystistat for the first time to a patient according to the instructions for use (13), the investigator will consider enrolling the patient into this NIS. The decision to prescribe Cystistat must be previous and independent from the decision to include the patient in the NIS.

Patients eligible for study recruitment will have the nature, purpose, and risks of the study explained to them by the investigator. They will be provided with a written copy of the informed consent form (ICF) for the study and given sufficient time to consider the study's implications before deciding to participate. Patients agreeing to participate in the study will sign the ICF and be given a duplicate copy before recording any personal data.

In cases where the patient does not return to the next routine treatment, the site should make every effort to contact the patient so that they can appropriately be withdrawn from the study. All contact attempts should be documented in the patient's medical record. Should the patient continue to be unreachable, then she will be considered to have withdrawn from the study as "Lost to Follow-up." For all other patients withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF. Patients may voluntarily withdraw from the trial for any reason and at any time.

In this NIS, the intended duration of observation per patient is approximately 6 months after start of treatment (irrespective of the duration of treatment). For details and timings of assessments, refer to Section 7.0 and Table 0-1.

6.1 Baseline (before first treatment)

Patients for whom Cystistat is prescribed by the treating investigator will be enrolled in the study after signing a written informed consent form. No personal data will be recorded for the study before the consent procedure. Once eligible patients provide written informed consent, baseline assessments will be completed (this may be performed on the first treatment visit prior to instillation of Cystistat according to routine clinical practice):

- The investigator will review and document the patient's demography and medical history. This includes patients' demographic and anamnestic background data, diagnostic criteria of IC/BPS diagnosis, and previous and current treatments.
- Patients will be asked to complete the Bladder Pain/ Interstitial Cystitis Symptom Score (BPIC-SS). If the score is ≤18, the patient will not be suitable for entering this NIS.
- The investigator will evaluate if the patient meets the inclusion/exclusion criteria.
- Patients will be asked to complete the Visual Analogue Scale (VAS) for bladder pain, urinary urgency, and quality of life (QoL).
- The investigator will assess and record any adverse events that occurred during this visit after signing the informed consent form.
- The investigator will provide the patient with the diary card and instruct her on how to record study related data at home. The following assessments are to be filled out by the patient:
    1. Morning voiding volume (once a week, preferably on the treatment day)
    2. Urinary voids and the respective volumes over a period of 24 hours (once a week, preferably starting the day before the treatment day)
    3. Use of concomitant IC/BPS medication, pain medication, and other relevant concomitant medication
    4. Adverse events
- A date for the next visit for the first treatment with Cystistat will be arranged and the investigator will remind the patient not to forget to take the diary card with her that day (not required if the first treatment with Cystistat is performed during the same visit according to routine clinical practice).
- The investigator will enter all required data from this visit in the eCRF within 5 business days.

6.2 During Treatment (Week 1-11, as per standard of care)

The patient will visit the site on a weekly basis for the instillation of Cystistat according to the instructions for use (13). The first treatment with Cystistat may be performed during the same visit as for the baseline assessments according to routine clinical practice (in this case not all of the below mentioned procedures need to be performed at the first treatment visit).

At each visit, procedures will be completed in the following order:

- The investigator will review the paper diary card, copy new entries, and transcribe the information recorded by the patient into the eCRF (not required at first treatment visit if performed on same visit as for the baseline assessment).
- The investigator will assess and record any adverse events that occurred since the last visit (not required at first treatment visit if performed on same visit as for the baseline assessment).
- The investigator will record any concomitant use of IC/BPS medication, pain medication, and other relevant concomitant medication that were taken since the last visit; it is not required to collect all concomitant medication (not required at first treatment visit if performed on same visit as for the baseline assessment).
- Cystistat will be instilled into the bladder according to the instructions for use and as per standard of care.
- The investigator will assess and record any adverse events and incidents, including any related adverse events (side effects), use errors, and malfunction (see "incident" definition, Section 10.1), that occurred during or between the visits. All adverse events and incidents must be transmitted to the sponsor via the eCRF (see Section 10.4.1 for reporting requirements).

  Special focus will be posed on the side effects listed in the instructions for use of the investigational medical device: allergic reaction (local rash and/or itching), bladder/urethral pain and discomfort, or urinary tract infection.
- The investigator will re-dispense the diary card to the patient and instruct her on how to record study related data at home. The following assessments are to be filled out by the patient:

  1. Morning voiding volume (once a week, preferably on the treatment day)
  2. Urinary voids and the respective volumes over a period of 24 hours (once a week, preferably starting the day before the treatment day)
  3. Use of concomitant IC/BPS medication, pain medication, and other relevant concomitant medication
  4. Adverse events

  (not required at first treatment visit if performed on same visit as for the baseline assessment)
- A date for the next visit for the next treatment with Cystistat will be arranged and the investigator will remind the patient not to forget to take the diary card with her that day.
- The investigator will enter all required data from this visit in the eCRF within 5 business days. Specific reporting requirements for AEs and incidents are described in Section 10.4.1.

6.3 End of Treatment (or latest at Week 12, Month 3)

This assessment will be performed at end of treatment or latest at week 12. Procedures will be completed in the following order:

- The investigator will collect the paper diary card and transcribe the information recorded by the patient into the eCRF. The paper diary card will be stored with the patient's medical record.
- The investigator will assess and record any adverse events that occurred since the last visit.
- The investigator will record any concomitant use of IC/BPS medication, pain medication, and other relevant concomitant medication that were taken since the last visit; it is not required to collect all concomitant medication.
- Patients will be asked to complete the Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS).
- Patients will be asked to complete the Patient Global Assessment (PGA).
- Patients will be asked to complete the Visual Analogue Scale (VAS) for bladder pain, urinary urgency, and quality of life (QoL).
- Cystistat will be instilled into the bladder according to the instructions for use.
- The investigator will provide the patient with the diary card and instruct her on how to record study related data at home. The following assessments are to be filled out by the patient:
    1. Morning voiding volume (once at month 6)
    2. Urinary voids and the respective volumes over a period of 24 hours (once at month 6)
    3. Use of concomitant IC/BPS medication, pain medication, and other relevant concomitant medication
    4. Adverse events
- The investigator will assess and record any adverse events and incidents, including any related adverse events, use error, and malfunction (see "incident" definition, Section 10.1), that occurred until or during this visit. All adverse events and incidents must be transmitted to the sponsor via the eCRF (see Section 10.4.1 for reporting requirements).

  Special focus will be posed on the side effects listed in the instructions for use of the investigational device: allergic reaction (local rash and/or itching), bladder/urethral pain and discomfort, or urinary tract infection.
- The investigator will enter all required data from this visit in the eCRF within 5 business days. Specific reporting requirements for AEs and incidents are described in Section 10.4.1.
- If required, treatment with Cystistat will be continued thereafter under regular medical care. For all patients, a follow-up visit will be scheduled for approximately month 6.

6.4 Follow up (approximately at Month 6)

Follow-up will be performed as an on-site visit if in accordance with routine clinical practice; if not possible as an on-site visit, the information will be collected remotely (e.g., via phone and postal mail) from the patient.

Procedures will be completed in the following order:

- The investigator will collect the paper diary card and transcribe the information recorded by the patient into the eCRF. The paper diary card will be stored with the patient's medical record.
- The investigator will assess and record any adverse events that occurred since the last visit.
- The investigator will record any concomitant use of IC/BPS medication, pain medication, and other relevant concomitant medication that were taken since the last visit; it is not required to collect all concomitant medication.
- Patients will be asked to complete the Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS).
- Patients will be asked to complete the Patient Global Assessment (PGA).
- Patients will be asked to complete the Visual Analogue Scale (VAS) for pain.
- The investigator will assess and record any adverse events and incidents, including any related adverse events, use error, and malfunction (see "incident" definition, Section 10.1), that occurred until or during this visit. All adverse events and incidents must be transmitted to the sponsor via the eCRF (see Section 10.4.1 for reporting requirements).

  Special focus will be posed on the side effects listed in the instructions for use of the investigational device: allergic reaction (local rash and/, or itching), bladder/urethral pain and discomfort, or urinary tract infection.
- The investigator will enter all required data from this visit in the eCRF within 5 business days. Specific reporting requirements for AEs and incidents are described in Section 10.4.1.

6.5 Withdrawal and Early Termination

Patients may request termination of the treatment with the investigational medical device or withdrawal from the study at any time or be required to withdraw or terminate treatment with the investigational medical device by the investigator or sponsor for reasons as per Section 4.2.3. If the patient terminates early, withdraws or is withdrawn, the reason for early termination/withdrawal should be established and recorded.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document the outcome of patient contact attempt, if possible. The investigator will contact sponsor or designee in the event that a patient fails to complete the study.

Every effort should be made to complete the following procedures and obtain the data from the patients:

- The investigator will collect the paper diary card and transcribe the information recorded by the patient into the eCRF. The paper diary card will be stored with the patient's medical record.

- The investigator will assess and record any adverse events that occurred since the last visit.
- Patients will be asked to complete the Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS).
- Patients will be asked to complete the Patient Global Assessment (PGA).
- Patients will be asked to complete the Visual Analogue Scale (VAS) for bladder pain, urinary urgency, and quality of life (QoL)
- The investigator will enter all required data for withdrawal/early termination in the eCRF within 5 business days. If withdrawal is due to an AE or incident, please consider specific reporting requirements described in Section 10.4.1.

If the patient withdraws from the study and also withdraws consent for disclosure of future information, no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7 TREATMENT PROCEDURES AND ASSESSMENT CRITERIA

Cystistat will be instilled into the bladder according to the instructions for use (13) and in line with the routine clinical practice.

7.1 Performance Assessments

For timing of methods and assessments see also the study schedule in Table 0-1.

7.1.1 Patient Global Assessment (PGA)

The PGA is a patient reported outcome (PRO) which has been used widely in recent IC/BPS studies. PROs are encouraged by the FDA guidance for IC/BPS studies (14).

The patient will evaluate the overall change in her IC/BPS condition on the following seven-point scale:

- markedly improved
- moderately improved
- slightly improved
- no change
- slightly worse
- moderately worse
- markedly worse

In case of “slightly improved”, the following additional question will be given to the patients: “Did therapy have a positive effect on your life and would you undergo this treatment again? (Yes/No)”.

The PGA will be provided in local language. It will be completed by the patient at the end of treatment or latest at week 12 and at month 6. Data will be transferred into the eCRF by the site staff.

7.1.2 Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS)

The BPIC-SS is a validated questionnaire for the measurement of IC/BPS symptoms. It contains 8 questions and the total score ranges from 0 to 38 (15).

The BPIC-SS will be provided in local language. It will be completed by the patient at baseline, at end of treatment or latest at week 12, and at month 6. Additional BPIC-SS will be completed in case of flares (see Section 7.1.7). Data will be transferred into the eCRF by the site staff.

7.1.3 Visual Analogue Scale (VAS)

The VAS will be provided to assess disease-related symptom severity and general quality of life (QoL). It has been widely used in clinical studies with the indication IC/BPS (e.g. 8, 16, 17,).

The related question for the VAS will be provided in local language. It will be completed by the patient at baseline, at the end of treatment or latest at week 12, and at month 6. Data will be transferred into the eCRF by the site staff.

7.1.3.1 Bladder Pain

Patients will be asked to assess their bladder pain on the VAS using the question “How was your bladder pain over the last 3 days?”. The VAS will be an unmarked line ranging from 0 to 100 mm, where 0 = “no pain” and 100 = "worst possible pain".

7.1.3.2 Urinary Urgency

Patients will be asked to assess their urinary urgency on the VAS using the question “How intense was urinary urgency over the last 3 days?”. The VAS will be an unmarked line ranging from 0 to 100 mm, where 0 = “no urgency” and 100 = “worst possible urgency”.

7.1.3.3 Quality of Life (QoL)

Patients will be asked to assess QoL on the VAS using the question “How good or bad would you rate your overall health condition throughout the last 3 days?”. The VAS will be an unmarked line ranging from 0 to 100 mm, where 0 = “the worst health you can imagine” and 100 = “the best health you can imagine”.

7.1.4 Morning Voiding Volume

The morning voiding volume will be measured by the patients at home once a week (preferably in the morning of the treatment day) until end of treatment or latest week 12. One additional measurement will be performed at month 6. The patients will be provided with a

measuring cup and the measured voiding volume will be captured in the diary card. The entries from the diary cards will be transferred into the eCRF by the site staff.

7.1.5 24-hour Urinary Frequency and Voiding Volume

The patients will document each urinary void and the respective volume over a period of 24 hours in the diary at home once a week (preferably starting the day before the treatment day) until end of treatment or latest week 12. One additional documentation will be performed at month 6. The total number of voids and the total voiding volume over the 24-hour period (daytime and nighttime) will be transferred into the eCRF by the site staff.

7.1.6 Use of Concomitant IC/BPS and Pain Medication

The use of concomitant IC/BPS and pain medication during the treatment will be captured by the patient in the diary card and the investigator will provide documentation in the eCRF, including at least indication, daily dose, and start and stop dates of administration.

Relevant IC/BPS medication includes amitriptyline, pentosan polysulfate, antihistamines, anticholinergics, pain medication (e.g. Tramadol (retard formulation) or NSAID followed by Tramadol), H2 blockers/antacids.

In addition, the use of all other pain medication (irrespective of indication) will be documented.

7.1.7 Occurrence of Flares

Flares are defined as symptom deteriorations and will be considered as adverse events. Adverse events will be recorded by the patient in the diary and also assessed and recorded by the investigator at the weekly controls/instillations and at the follow-up visit. In case of a flare, and additional BPIC-SS (see Section 7.1.2) will be completed by the patient at the time of occurrence.

7.1.8 Premature Termination of Treatment

Treatment with Cystistat may be terminated prematurely by the patient or investigator (see Section 4.2.3). In such a case, the investigator will provide documentation in the eCRF, including at least the date of last treatment and the reason for premature termination.

7.2 Safety Assessment

7.2.1 Adverse Events and Incidents

Relevant medical conditions from baseline (i.e. before signature of the ICF) will be recorded as medical history. Clinically significant worsening from these conditions will be recorded as adverse events (causality to be assessed).

Before first instillation of Cystistat, AEs should be assessed as not related to investigational device.

After first treatment, the patients will be routinely queried regarding the presence or absence of adverse events using open ended questions.

At each visit, clinic will also assess if any incident occurs during the instillation. The clinic will document any incident, including any related adverse events, use errors, malfunctions (see "incident" definition, Section 10.1) in the patient's eCRF.

All AEs, incidents and serious incidents should be reported to the Sponsor as described in section Section 10.4.1 "Reporting of Adverse Events and Incidents"

The investigator should forward any event to the sponsor, including an investigator's causality assessment in the notification (eCRF form). The sponsor will check and assess the events as well.

Special focus will be posed on the expected side effects as mentioned in the instructions for use: allergic reaction (local rash and/or itching), bladder/urethral pain and discomfort, or urinary tract infection.

8 STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

8.1 Sample Size Determination-

Approximately 74 patients (including approximately 10% drop-outs). [redacted]

Accounting for approximately 10% drop-outs, further 7 patients and a total of 74 patients should be included in this study.

8.2 Populations for Analyses

Safety (SAF) population: All enrolled patients who received at least one instillation of Cystistat and validity of data is confirmed by the physician.

Full analysis set (FAS) population: All patients of the SAF, who have at least one post baseline assessment.

8.3 Statistical Analyses

All analyses will be exploratory in character. Continuous variables will be summarized by number (N), mean, standard deviation (SD), minimum, 5% percentile (P5), lower quartile (Q1), median, upper quartile (Q3), 95% percentile (P95) and maximum. Categorical variables will be presented in frequency distribution tables with number (N) and percentage.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in an SAP.

8.3.1 Definition of the Primary Efficacy Endpoint

Responder rate at end of treatment or latest at week 12 as indicated by improvement on a seven-point Patient Global Assessment (PGA) scale where the patient is able to evaluate the overall change in her/his IC/BPS condition as markedly improved, moderately improved, slightly improved, no change, slightly worse, moderately worse or markedly worse. For the primary analysis, a responder is defined as a patient who had an improvement on the PGA scale (i.e. PGA evaluated as markedly improved, moderately improved, or slightly improved. In case of slightly improved, patients will only be considered as responder if the question "Did therapy have a positive effect on your life and would you undergo this treatment again?" is answered with "Yes".).

8.3.2 Primary Analysis of Primary Endpoint

If there is a substantial rate of patients with rescue medication (n>20), explorative subgroup analyses will be provided for patients with and without rescue medication.

8.3.3 Sensitivity Analysis of Primary Endpoint

8.3.4 Missing Data

Missing data will not be imputed. More details will be specified in the SAP.

8.3.5 Sub-Group Analyses

According to the instructions for use, the subgroup of patients who have at least 4 weeks of treatment will be analyzed if relevantly different from the FAS. According to the low sample size, no other subgroup analyses are planned for the study. However, descriptive analyses of subgroups might be relevant and will be described in the SAP.

8.3.6 Definition and Analysis of the Secondary Endpoint(s)

The following secondary endpoints will be analyzed and reported similar to the analysis method and reporting of the primary endpoint as described above (all endpoint assessments will be tabulated by timepoint and in case of more than 2 timepoints additionally be displayed graphically):

- Time course of morning voiding volume, 24-hour urinary frequency and voiding volume (daytime and nighttime) (from patient diaries)
- Change from baseline to end of treatment or latest week 12 and month 6 in Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) will be analyzed by Analysis of Covariance (ANCOVA) using baseline and eventually categories of concomitant IC/BPS and pain medication as covariate.
- Responder rate and CI at month 6 as indicated by improvement on a seven-point Patient Global Assessment (PGA) scale (same responder definition as for the primary endpoint) will be analyzed with the same approach as the primary analysis.
- Responder rate and CI at the end of treatment or latest at week 12 and at month 6 as indicated by improvement on a seven-point Patient Global Assessment (PGA) scale (responder defined as a patient who had moderate or marked improvement on the PGA scale) will be analyzed with the same approach as the primary analysis.
- Change from baseline to end of treatment or latest week 12 and month 6 in Visual Analog Scale (bladder pain, urinary urgency, and quality of life) will be analyzed by Analysis of Covariance (ANCOVA) using baseline and eventually categories of concomitant IC/BPS and pain medication as covariate.
- Number and percentage of premature termination of treatment will be given.
- Use of concomitant IC/BPS and pain medication count will be analyzed by frequency tables.

8.3.7 Safety Analyses

Analysis of all safety data will be performed on the SAF Population.

8.3.7.1 Adverse Events and Incidents

Adverse events and incidents will be coded using current version of Medical Dictionary for Regulatory Authorities (MedDRA). In addition, all incidents (as defined in Section 10.1) will be coded according to IMDRF Problem code A.

The occurrence of AEs will be summarized in terms of affected patients, as well as in terms of total number of AEs. In addition, analysis of AEs by severity and by relatedness will also be provided.

The occurrence of incidents will be summarized in terms of affected patients, as well as in terms of total number of incidents. In addition, analysis of incidents by severity will also be provided.

Additional analysis of side effects mentioned in the IFU will be performed (number and percentage per incident as well as total number/percentage).

Concomitant IC/BPS and pain medications will be coded by the WHO Drug Dictionary Enhanced and will be summarized. Medical history will be listed by patient and coded using the current version of MedDRA and will be summarized.

8.3.8 Planned Interim Analyses

[redacted]

9 ADMINISTRATIVE PROCEDURES

9.1 Source Documentation

All clinical data will be recorded by the clinical staff on the patient's medical record and/or recorded electronically using validated software. If computerized systems are used to create, modify, maintain, archive, retrieve or transmit source data, they must comply with the applicable regulatory regulations and/or guidance.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary.

The nature and location of all source documents will be documented separately. Source data may be directly captured from devices, transferred from 3rd parties (e.g. laboratory data) or entered manually into eCRF/database.

9.2 Access to Data/Source Documentation

The investigator or designated representative will permit full access to data and source documentation for the purpose of clinical monitoring, audits, IRB/IEC review and regulatory inspections.

9.3 Final Clinical Study Report and Case Report Forms (CRFs)

A written study report will be issued within one year after completion of the NIS in all participating countries based on statistical tables. Summaries of related-adverse events as

well as incidents by severity and listed side effects reported in the IFU will be presented as applicable. In the final report, not-related AE will be reported in a summary table, if applicable. An extract (synopsis) of this report will be provided to the participating investigators on request.

Case Report Forms (CRFs) containing data transcribed from subject source documents (as appropriate) and copies of other source documents will be supplied by the clinical site. The principal investigator must sign each patient's CRF after completion of data entry, signifying that the data entered in the CRF is complete and accurate. Electronic CRFs will be provided for this study.

9.4 Adherence to Protocol

The study will be conducted as described in the approved protocol (and amendments, if applicable), and applicable SOPs. In addition, the study will be conducted in compliance with ISO 14155:2020 (19) and any regional or national regulations, as appropriate.

9.5 Monitoring and Site Training

Site initiation visits will be performed before patient enrolment and data documentation is started. Site staff will be trained on study protocol, study background, how to use/access the eCRF, obtaining of Informed Consent, safety reporting and further study requirements and procedures (e.g. Patient Diary).

Central data monitoring will be performed by the CRO on a regular basis and details will be specified in a monitoring plan. Monitoring includes at least enrolment status, completion status, safety data and predefined key data (e.g. Informed Consent, In-/Exclusion Criteria). In case any general issues/misunderstandings are identified, this will be brought to the attention of the Sponsor/the site.

One on-site monitoring visit per study site is planned. Source data verification will include 100% of Informed Consents, 100% of safety data, and predefined key data that will be described in the monitoring plan. An adaptive approach of monitoring will be conducted during the study period based on the risk or critical data/process evaluation at the site.

9.6 Data Handling and Record Retention

All clinical information shall be recorded, handled, and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial patients remains protected.

An eCRF is required to be completed for each enrolled patient. The eCRF is property of the sponsor and the investigator must review and electronically sign all CRFs prior to database lock.

All data collected in the study will be captured and maintained in a secure and validated electronic data capture (EDC) system and provided to clinical data management.

The paper diary cards serve as basis of information for the investigator to transfer relevant information to the eCRF. Completed diary cards will be stored with the patients' source documents.

9.6.1 Data Management

All data will be recorded in a standardized, validated EDC system complying with international quality standards.

Data will be overseen centrally, all data acquired at the participating sites will be entered into the eCRF by the site team. The data will be checked for integrity, consistency and plausibility using preassigned checks, details are described in the Data Validation Plan (DVP). In the case of open queries, the affected site will be immediately informed. Each investigator agrees in providing support on request for clarifying possible queries on contradictions. Any change on data, e.g. due to adjustment of pending queries, will be documented through an audit trail of the database. Prior to database lock, a reconciliation of all adverse events, and incidents with the sponsor's database will be performed.

Details are described in the Data Management Plan (DMP).

9.6.2 Archiving

The sponsor and the investigator will each maintain a Trial Master File (TMF) for the "essential documents". Sponsor or its designated CRO will provide an Investigator's Site File (ISF) as a part of the TMF to each PI containing a cover page with a description of the required contents for each binder section and any project specific standardized forms.

All data including the analysis programs and their description will be archived at the biostatistical department of the sponsor.

Archiving of items pertinent to this study at each site is the responsibility of the participating investigator and should follow national regulations. These items include:

- Signed copy of protocol (principal investigator protocol signature page)
- Signed copy of patients' consent forms (if applicable according to local regulations)
- Patient diary cards
- Patient identification list
- Site personnel delegation list
- Signed clinical study agreement between sponsor and/or CRO and the participating investigator
- Any other document required by specific national regulations (e.g. ethics committee approval)

When a copy is used to replace an original document (e.g., source documents), the copy should fulfil the requirements for certified copies as specified by ISO 14155:2020.

All relevant site documents of this study including eCRFs and other patient records will be stored after the end or termination of the study according to the local requirements. Archiving of documents pertinent to this study at each site is the responsibility of the investigator and should follow national regulations.

All study data remain the sole property of the sponsor. The investigator must obtain in writing the sponsor's agreement to dispose of any records, even if the retention period has been reached.

9.7 Data Protection and Confidentiality

Information furnished to clinical investigators and IRBs/Ethics Committees will be maintained in confidence by the clinical investigator and IRB/Ethics Committee. By signing this protocol, the investigator affirms to the sponsor that he/she will maintain, in confidence, information furnished to the IRB/Ethics Committee relevant to this study under appropriate understanding of confidentiality with such IRB/Ethics Committee.

By signing the protocol, the investigator agrees that within local regulatory restrictions and institutional and ethical considerations, the sponsor may consult and/or copy source documents (e.g. laboratory reports, workbooks, medical records) in order to verify CRF data.

Data, including personal data, from source documents may be transferred to sponsor entities or service providers which may be located outside the European Economic Area (EEA) including, but not limited to, the USA. In such cases, sponsor ensures that such transfers are carried out in compliance with all applicable data protection laws and regulations and signed ICF.

Personal study related data will be kept confidential. Study documents submitted to the sponsor, e.g. eCRFs, etc., are only identifiable by pseudonym, i.e. the patient no. The investigator will keep the original of the patient identification list (including complete name and date of birth of each patient). To allow compliance with applicable regulations, each patient will be asked for consent regarding the access to her personal study related data for monitoring, audits, and inspections as well as regarding transmission and storage of his/her pseudonymous data; a respective statement will be part of the informed consent. The patient has the right to access and rectification of his/her personal data according to the General Data Protection Regulation (GDPR) (18).

9.8 Ethics and Regulatory Authorities

This represents a NIS, meaning that the investigator will document ongoing medical care, without conducting any intervention beyond normal medical practice.

The decision to prescribe Cystistat must be previous and independent from the decision to include the patient in the NIS. Before the study is started, the sponsor will comply with all national regulations, regarding notifications, approvals, or any other required administrative obligation.

In this respect, the participating investigator declares consent with the transmission of his/her name and address. National regulations will govern any aspect related to patient's

information and consent. This clinical study protocol together with a sample CRF, if applicable, will be submitted to a competent ethics committee for review and opinion. A copy of their final vote will be included in the investigator's study file.

This clinical study will not begin until the required approval/favorable opinion from the ethics committee has been obtained. Any additional requirements imposed by the ethics committee will be followed, if appropriate.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

9.9 Informed Consent

A properly executed, written informed consent in compliance with current guidelines shall be obtained from each volunteer prior to entering the study. A copy of the informed consent document to be used will be submitted by the investigator to an independent institutional review board (e.g. IRB or ethics committee) and the sponsor and/or its agent for review and approval prior to the start of the study. The investigator shall provide a copy of the signed and dated informed consent to the patient, and a signed and dated copy shall be maintained in the patient's medical record.

9.10 Study Registration

This clinical study will be registered in a publicly accessible database before start of recruitment.

9.11 Disclosure and Publication of Clinical Study Data

The disclosure and publication of clinical study data will be detailed in the clinical trial agreement with the investigators.

9.12 Financing and Insurance

MEDA Pharma GmbH & Co. KG (A Viatris company), Benzstrasse 1, D-61352, Bad Homburg, Germany ("Sponsor") will act as legal sponsor [redacted]

Financial aspects will be subject to the formal agreement with each participating site. Refunds are based on the national fair market value.

[redacted]

9.13 Quality Assurance

This clinical study will be conducted in accordance with Standard Operating Procedures (SOP) of the sponsor and the CRO, as well as in accordance with the applicable national and local laws.

The study sites will receive data collection tools (eCRFs) from Sponsor/CRO. Complete data should be entered into the eCRF within 5 business days after each patient visit and updated as necessary if new information is available. Paper-based questionnaires and diary cards completed by the patients in local language will be collected by sites and data entered into the eCRF accordingly.

The Investigator is responsible for the accurate and complete documentation of study-related data in each patient's eCRF after the patient's Informed Consent has been received. Data should be entered in the eCRF in a timely manner (see special requirements for AEs and incidents, Section 10.4.1).

The investigator must sign off electronically the complete eCRF for each patient, confirming the validity of the data. Sponsor/CRO representatives will instruct investigators on how to use/access the eCRF. They will be responsible for the delivery and collection of study documents. CRO representatives are responsible for Study Monitoring. A Monitoring Plan will be prepared and describing details of remote data monitoring and risk-based approach of source data verification. Auditing in the sense of Good Clinical Practice is not intended. The study will be conducted in compliance with DIN EN ISO 14155:2021-05 (19) and any regional or national regulations, as appropriate.

Data checks regarding incidents and listed adverse events in the IFU reporting may trigger queries. Each participating investigator agrees to provide support on request for clarifying possible queries or contradictions.

In case of an incident during the instillation of Cystistat, the site will provide documentation in the patient's CRF and proceed as described in Section 10.4.1.

9.14 Audits and Inspections

Inspections by regulatory authority representatives and IECs are possible at any time, even after the end of the study. The investigator must notify the sponsor immediately of any such inspection.

Audits are not planned, but for cause audits may be performed by the sponsor's QA or delegates in order to scrutinize the performance and quality at the study site. In this case, the sponsor QA will agree with the contract auditor regarding the timing and extent of the audit(s). In case of audits at the study site, a representative from the CRO will usually accompany the auditor(s).

9.15 End of Trial

The end of trial is considered to be the date of last patient last visit (or remote contact) or the date of early termination of the study whichever is the later.

10 ADVERSE EVENTS AND INCIDENTS REPORTING

The adverse event collection period begins at signing of informed consent and incident collection period begins with the first administration of the investigational medical device. The collection time for adverse events and incidents continues until the end of the last study visit (or (e-)mail contact) of the patient. Adverse events and incidents occurring during this period need to be reported to the sponsor according to Section 10.4.1 'Reporting of Adverse Events and Incidents'. The investigator is also responsible for notifying the sponsor if he/she becomes aware of any adverse event or incident after the study period has ended and it is considered related to the investigational medical device. Once an AE or incident is detected, it should be followed until its resolution or until it is judged by the principal investigator to be stable or permanent.

10.1 Definitions

Adverse Event

For the scope of this document, an adverse event (AE), is an untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device and whether anticipated or unanticipated.

Note to entry: This definition includes events related to the procedures involved.

Note to entry: For users or other persons, this definition is restricted to events related to the use of the investigational medical device.

All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an investigational medical device will be designated as related AEs, thus incidents.

Reasonable causal relationship means that the causal relationship to the investigational medical device is reported as "possible", "probable" or "causal relationship" or similar. If the relationship to the investigational medical device is not given, then the AE must be treated as if the relationship were "possible".

Before the first instillation of Cystistat, AEs are considered not related.

Side Effect

For the scope of this document, side effects are adverse events with a reasonable causal relationship to the investigational medical device.

Incident

Any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the sponsor and any undesirable side-effect (i.e. related adverse event)

For the scope of this document, a ***device malfunction*** is a failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use.

For the scope of this document, a ***use error*** is a user action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user.

It should be noted:

- Use error includes the inability of the user to complete a task.
- Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment.
- Users might be aware or unaware that a use error has occurred.
- An unexpected physiological response of the patient is not by itself considered a use error.
- A malfunction of a medical device that causes an unexpected result is not considered a use error.

Serious Incident

Any incident that directly or indirectly led, might have led or might lead to any of the following:

a) Death, of a patient, user or other person,

b) Temporary or permanent serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:

   1) A life-threatening illness or injury, or

   2) A permanent impairment of a body structure or a body function including chronic diseases, or

   3) In-patient or prolonged hospitalization, or

   4) Medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,

   5) Foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment,

c) Serious public health threat (event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time).

Note to entry: Planned hospitalization for a pre-existing condition, or a procedure required by the Clinical Investigation Plan (CIP), without serious deterioration in health, is not considered a serious incident.

Not Related Serious Adverse Event (SAE)

For the scope of this document, any adverse event (not related to the investigational medical device) that led to any of the following:

a) Death,

b) Serious deterioration in the health of the subject, that resulted in any of the following:

i. life-threatening illness or injury,

ii. permanent impairment of a body structure or a body function,

iii. hospitalisation or prolongation of patient hospitalisation,

iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

v. chronic disease,

c) Foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Preexisting Condition

Any medical condition that is present before signature of the ICF will be considered as baseline medical history and not reported as an AE. A baseline or preexisting condition should be recorded as an adverse event only if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

Any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

10.2 Collection and Recording of Adverse Events and Incidents

During the visits, the investigator will record all adverse events and incidents. At each contact with the patient, the investigator must seek information on adverse events from diary cards, by specific questioning and, as appropriate, by examination. Information on adverse events and incidents should be recorded immediately in the source document and in the respective eCRF forms.

Special focus will be posed in the side effects listed in the instructions for use of the investigational device: allergic reaction (local rash and/or itching), bladder/urethral pain and discomfort, or urinary tract infection.

In the event of an AE and/or incident, as a minimum the following information should be documented in the respective eCRF:

- Study number (pre-filled)
- Investigator/Reporter name and contact details
- Patient number (pre-filled)
- Date of occurrence of incident/AE

- Description of incident (facts)/AE
- AE/incident name or term (in standard medical terminology) and final diagnosis, time and date of onset, clinician's assessment of severity, seriousness,
- Relationship of AE to study product (assessed only by those with the training and authority to make a diagnosis)
- Action taken with the study product, treatment for the event and time (if available) and date of resolution/stabilization of the event.

Additional information and potentially the return of the product may be requested by the Sponsor in order to investigate the AE/incident.

Once these minimum data are entered in the respective eCRF form, the investigator/reporter will submit the information electronically by clicking "Submit & Next" button on the bottom of the eCRF form. An email notification along with a PDF report will be generated informing the sponsor and CRO that an AE/incident is reported in the study. If there is any change in original data entry, again an Email notification will get generated with updated PDF report (marked updates/changes).

All clearly related signs, symptoms, and abnormal results of diagnostic procedures should be grouped under one diagnosis on the eCRF where possible and appropriate.

The clinical course of each (related) adverse event should be followed until resolution or stabilization. Adverse events related to the investigational medical device that are still ongoing at the end of the study period must be followed up to determine the outcome. Any adverse event that occurs after the study period and is related to the investigational medical device or study participation should be recorded and communicated to the sponsor as per already described timelines in Section 10.4.1.

10.3 Classification of Adverse Events and Incidents

10.3.1 Severity

The investigator will assign a severity rating to each AE and incident. For purposes of consistency, the following scale is to be used:

Grade 1 - MILD	Does not interfere with subject's usual function.
Grade 2 - MODERATE	Interferes to some extent with subject's usual function.
Grade 3 - SEVERE	Interferes significantly with subject's usual function.

Severity is a classification of intensity, whereas a serious event meets any of the defined criteria (e.g. hospitalization; see definitions in Section 10.1).

10.3.2 Causality

For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality of each AE.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational medical device caused or contributed to an AE. The investigator must make an assessment of the relationship of each AE to the investigational medical device and record this relationship in the eCRF.

During the causality assessment, clinical judgement must be used and the relevant documents must be consulted, such as the medical device leaflet (instructions for use).

Factors that need to be considered when making a causality assessment include: Temporal relationship, clinical and pathological characteristics of the event(s), exclusion of confounding factors (medical and medication history), de-challenge/re-challenge.

A suspected relationship (causal relationship, probable, possible) between the events and the investigational medical device means, in general, that there are facts (evidence) or arguments to suggest a causal relationship. Receipt of additional or clarifying information may warrant reassessment of causality. The investigator is responsible for assessing relationship of AEs to the investigational medical device in accordance with the following definitions (20):

Category	Causality	Description
CAUSAL RELATIONSHIP	Causal relationship is certain	The event is associated with the investigational device or comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category to which the device belongs or of similar devices and procedures; - the event has a temporal relationship with the use/application or the procedures; - the event affects a site or organ that i. the investigational device or procedures are applied to; ii. the device or investigational procedures have an effect on; - the event follows a known response model of the medical device (if the response model is previously known); - the interruption to application of the medical device (or reduction in the level of activation/exposure) and the reintroduction of its use (or increase in the level of activation/exposure), affect the event (when clinically feasible); - other possible causes (e.g. an underlying or

		concomitant illness/clinical condition and/or an effect of another device, drug or treatment) have been adequately ruled out; - damage to the subject due to use error; - the event depends on a false result provided by the investigational device used for the diagnosis, where applicable.
PROBABLE	High degree of certainty for causal relationship	The relationship with the use of the investigational device or comparator or the relationship with the procedures appears relevant and/or the event cannot be reasonably explained by another cause.
POSSIBLE	Causal relationship is uncertain	The relationship with the use of the investigational device or comparator or the relationship with the procedures is weak but cannot be completely ruled out. Alternative causes are also possible (e.g. an underlying or concomitant illness/clinical condition and/or an effect of another device, drug or treatment). Cases where the correlation cannot be assessed or no information was obtained should be classified as possible.
UNRELATED/NOT RELATED	No possible relationship	The relationship with the device or the procedures may be ruled out when: - the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device; - the adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event; - the event involves a body-site or an organ that cannot be affected by the device or procedure; - the adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

For the purpose of establishing the relationship, all criteria listed above could not be met at the same time, depending on the type of device/procedures and the event.

The sponsor and the investigators shall distinguish between the adverse events related to the investigational device and those related to the procedures (any specific procedure of the clinical investigation). An adverse event may be related to both the procedures and the investigational device. Procedure complications are considered unrelated if those procedures would have been applied to patients even without the use/application of the investigational device.

10.3.3 Expectedness

AEs are expected as mentioned in the instructions for use (allergic reaction (local rash and/, or itching), bladder/urethral pain and discomfort, or urinary tract infection) (13).

10.3.4 Outcome

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to sponsor or its designated representative.

The outcome at the time of last observation will be classified as:

RECOVERED/RESOLVED where the subject recuperated and is free of any pathological conditions resulting from the prior disease or injury.

RECOVERED WITH SEQUELAE where the subject recuperated but retained pathological conditions resulting from the prior disease or injury.

NOT RECOVERED/NOT RESOLVED (i.e. ongoing) where the subject has not recuperated from the condition or injury and the event is still considered ongoing

RECOVERING where the subject has begun to recuperate from the condition or injury but the event is considered ongoing at a reduced intensity

FATAL the condition or injury results in the subject’s death. The investigator should identify the principal cause of death and assign Fatal outcome to that event. Other concurrent ongoing AE/SAEs present at the time of death would remain Not recovered/Not resolved.

UNKNOWN can be selected if none of the other situations apply or are known. Follow-up should be conducted to obtain one of the preceding outcomes.

10.3.5 Action Taken with the Investigational Medical Device

For all adverse events and incidents, the following information should be provided by the investigator.

Action	Description
Treatment interrupted	The treatment was temporarily discontinued
Treatment withdrawn	The treatment was permanently discontinued
Unknown	Not known, not observed, not recorded, or refused
No action taken	The event did not result in any modification of treatment or frequency of treatment
Not applicable	The event occurred prior to first treatment or following last scheduled treatment

10.4 Reporting of Adverse Events and Incidents

10.4.1 Investigator Reporting: Notifying the Study Sponsor

Incidents must be notified by investigator within 5 business days after becoming aware of it. Serious incidents must be notified by investigator within 3 calendar days after becoming aware of it.

For serious incidents, the investigator should provide further information on the serious incident as soon as possible, preferably within 48 hours of awareness.

Supporting documents can be provided by the Investigator/Reporter if applicable via email to the Sponsor: [redacted]

Patient identifying information must not be visible on any documentation provided by the investigator via email. Any information that could be used to identify the patient (e.g. name, address, medical record number) must be de-identified before submission to the sponsor or its designee. The patient's study specific ID number should be recorded on every page of documentation forwarded to the sponsor.

The PI should provide the final diagnosis of serious incidents whenever possible. Not related AEs including an investigator's causality assessment should be forwarded to the sponsor by the investigator within 10 business days.

Once the investigator or designee has entered the minimum data (Section 9.2) in the respective eCRF form, the Investigator/Reporter will submit the information electronically by clicking the "Submit & Next" button on the bottom of the eCRF form. An email notification along with a PDF report will be generated informing the Sponsor and CRO that an AE/incident is reported in the study. If there is any change in original data entry, again an Email notification will get generated with updated PDF report (marked updates/changes).

Sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

10.4.2 Follow-up

New information and any important missing information from prior reports on a serious incident or serious AE, must be provided promptly to the study sponsor by updating and submitting the respective eCRF form. In addition, the investigator may be requested by sponsor/designee to obtain specific additional follow-up information in an expedited fashion. The investigator should respond to targeted follow-up requests as soon as possible and preferably within 48 hours from receipt of the request.

New information for non-serious incidents/AEs should be entered in the respective eCRF form in the same timely manner as for all other CRF entries.

10.4.3 Investigator Reporting: Notification of Ethics Committee

Investigators are responsible for safety reporting to their local Ethics Committee (LEC) and complying with their local EC's reporting requirements. Copies of each report and documentation of LEC notification and receipt will be kept in the investigator's study file.

10.4.4 Investigator Reporting of Pregnancy - notifying the study sponsor

All patients who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation as detailed in the inclusion and exclusion criteria.

Patients who have been enrolled in the study should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

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