Cover page for Protocol

Sponsor name	Ferring Pharmaceuticals A/S
NCT Number	NCT02773849
Sponsor trial ID:	rAd-IFN-CS-003
Official title of study	A Phase III, Open Label Study to Evaluate the Safety and Efficacy of INSTILADRIN® (rAd-IFN)/Syn3) Administered Intravesically to Patients With High Grade, BCG Unresponsive Non-Muscle Invasive Bladder Cancer (NMIBC)
Document Date	01 February 2022

CLINICAL STUDY PROTOCOL

A Phase III, Open Label Study to Evaluate the Safety and Efficacy of INSTILADRIN® (rAd-IFN/Syn3) Administered Intravesically to Patients with High-Grade, BCG Unresponsive Non-Muscle Invasive Bladder Cancer (NMIBC).

IND No.: **12,547**
Protocol No.: **rAd-IFN-CS-003**

Current: **Version 8.0**
Date of Protocol: **1st February 2022**

Protocol History: Supersedes Version 7.0 24th November 2020
Supersedes Version 6.0 5th October 2018
Supersedes Version 5.0 29th January 2018
Supersedes Version 4.0 16th August 2017
Supersedes Version 3.0 16th December 2016 and Amendment 1 to Version 3.0 7th April 2017
Supersedes Version 2.0 25th August 2016
Supersedes Version 1.1 16th February 2016

Confidentiality Statement:

This study will be conducted in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), in accordance with local legal and regulatory requirements and in compliance with the applicable parts of the United States Code of Federal Regulations.

Dr Stephen Boorjian
Coordinating Investigator Name

[redacted]
Signature

Feb 17, 2022
Date

SPONSOR AND INVESTIGATOR SIGNATURE PAGE

Sponsor: Ferring Pharmaceuticals A/S

Study Acknowledgement

A Phase III, Open Label Study to Evaluate the Safety and Efficacy of INSTILADRIN® (rAd-IFN/Syn3) Administered Intravesically to Patients with High-Grade, BCG Unresponsive Non-Muscle Invasive Bladder Cancer (NMIBC).

This protocol has been approved by Ferring Pharmaceuticals A/S. The following signature documents this approval.

[redacted] [redacted]

Medical Monitor Name (printed) Signature

Feb 21, 2022

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and the Investigator Brochure, and I agree that it contains all necessary details to enable me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. Further, I agree to conduct this study in accordance with Good Clinical Practice and applicable regulatory requirements.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by Ferring Pharmaceuticals A/S. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

[redacted]

Principal Investigator Name (printed) Signature

Feb 17, 2022

Date Study Center Number

Institution Name City, State

Please forward the original signed Protocol Acceptance Statement to your Clinical Research Associate /Designee.

Retain a copy of this form with the study protocol in your regulatory file.

PROTOCOL APPROVAL PAGE

A Phase III, Open Label Study to Evaluate the Safety and Efficacy of INSTILADRIN® (rAd-IFN/Syn3) Administered Intravesically to Patients with High-Grade, BCG Unresponsive Non-Muscle Invasive Bladder Cancer (NMIBC).

[redacted] Senior Vice President Global Research & Development Ferring Pharmaceuticals A/S	[redacted]	Date Feb 21, 2022
[redacted] Associate Vice President Global Regulatory Affairs Ferring Pharmaceuticals A/S	[redacted]	Date Feb 21, 2022
[redacted] Vice president Global Biometrics Ferring Pharmaceuticals A/S	[redacted]	Feb 21, 2022 Date
[redacted] Medical Officer Vice President, TA Urology Ferring Pharmaceuticals A/S	[redacted]	Feb 22, 2022 Date

1. SUMMARY OF CHANGES TO PROTOCOL VERSIONS

Version Number	Summary of Changes
8.0	• Information on a ready-to-use presentation of the investigational product has been added. • Administrative change to correct inconsistency by aligning the wording of secondary endpoints in the synopsis with the endpoints in Section 8.2 • Administrative changes to clarify/update addresses and reflect change in sponsor personnel
7.0	• Change of Sponsor from FKD Therapies Oy to Ferring Pharmaceuticals A/S • Extend the annual follow up period to 60 months for patients post treatment • Minor alterations to wording
6.0	• Extended dosing for patients who continue to benefit from treatment with INSTILADRIN until either the study results (risk / benefit) are shown to be unfavorable or the treatment receives FDA approval. • Additional details regarding management of patients after month 24 Minor alterations – typographical corrections
5.0	• Revision to the protocol primary objectives and endpoints to assess complete response from 3 months onwards in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease) • Addition of a secondary objective and endpoint to assess durability of the complete response in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease) post 3 months • Revision to the protocol secondary objectives and endpoints to assess event free survival and durability in patients with high-grade Ta or T1 papillary disease (without concomitant CIS) post 3 months respectively. • Revision to the sample size needed to recruit the intended CIS population for the primary endpoint • Revised statistical estimation of sample size based on patients with CIS achieving a complete response from 3 months onwards. • Revisions consistent with FDA guidelines on the definition of a complete response • Other changes to relevant sections affected by the changes to the primary statistical analysis
4.0	• Consolidation of the visit windows that apply to procedures at the screening visit • Clarification on the timing and number of biopsies at efficacy and M12 visits • Timelines for dosing after month 12 and visits to month 21 • Schedule of events amended to include anomalies with procedure section of the protocol • Formatting of schedule of assessments table • Formatting of text including introduction of links and ensuring consistency in format used • Reference to appendix A – full hematology and clinical chemistry panel in the procedures section

	• Incorporation of correction of errors outlined in Amendment 1 to version 3.0
3.0	• Change to inclusion criterion 4 regarding the type of Bacillus Calmette-Guerin (BCG) courses for eligibility • Change to inclusion criterion 4 on the timing to tumor recurrence before entry into the study • Clarifications to inclusion criterion 9 and exclusion criterion 10 • Change to exclusion criterion 12 , deletion of creatinine and introduction of estimated GFR • Change to exclusion criterion 13 on timing of previous BCG therapy before entering the study • Study design schematic redrawn to highlight the timing of procedures and previous BCG therapy before study entry • Additional information added to prohibited medications
2.0	• Minor changes to inclusion criterion 4 • Clarification on treating patients after month 12 complete response up to month 24 • Clarification on patients withdrawing from treatment and withdrawing for the study • Study design redrawn to highlight dosing days and visits • Addition of Visit windows to the dosing days • Collating procedures and assessments into separate sections • Additional wording for the use of Interactive Response system (IXRS) in drug accountability • Administrative contract research organization information added to reporting of AEs and SAEs

2. PHASE III PROTOCOL SYNOPSIS

TITLE OF STUDY:

A Phase III, Open Label Study to Evaluate the Safety and Efficacy of INSTILADRIN® (rAd-IFN/Syn3) Administered Intravesically to Patients with High-Grade, BCG Unresponsive, Non-Muscle Invasive Bladder Cancer (NMIBC).

PRINCIPAL INVESTIGATOR:

[redacted]

SPONSOR:

Ferring Pharmaceuticals A/S
Amager Strandvej 405
DK-2770 Kastrup
Denmark

CLINICAL PHASE: III

BACKGROUND & RATIONALE:

INSTILADRIN® (herein INSTILADRIN, rAd-IFN/Syn3) is a gene-based therapy designed to improve delivery of, and hence prolong the exposure of non-muscle invasive bladder cancer (NMIBC) cells to interferon-alfa2b (IFNalfa2b). Intravesical administration of INSTILADRIN delivers the gene encoding IFNalfa2b to the cells on the luminal surface of the bladder safely and efficiently. Within hours of administration of a single dose of INSTILADRIN, the anti-tumor IFNalfa2b protein can subsequently be detected in the urine.

Extensive nonclinical safety and efficacy studies were conducted to support clinical investigation of INSTILADRIN. A Phase I study with INSTILADRIN in 17 patients who had failed prior Bacillus Calmette-Guerin (BCG) therapy has been completed at the University of Texas MD Anderson Cancer Center and the University of Iowa. The treatment was well tolerated and seven of the 17 patients achieved a complete response (CR) at 3 months. Five of the seven patients who achieved CR received a second intravesical dose of INSTILADRIN.

A Phase II multi-center, randomized, parallel arm, open label study to investigate the safety and efficacy of INSTILADRIN administered intravesically to patients with high-grade BCG refractory or relapsed NMIBC has been completed. The primary objective of the study was to evaluate the incidence of high-grade-recurrence-free survival at 12 months. Secondary objectives included but were not limited to the evaluation of the incidence of high-grade-recurrence-free survival at 3, 6 and 9 months, to the determination of the time to progression to muscle invasive disease, and safety of INSTILADRIN.

This study enrolled 40 patients (two treatment groups of up to 20 patients each). Patients were randomized to receive a 75 mL intravesical administration of INSTILADRIN at a dose of either 1×10^{11} vp/mL or 3×10^{11} vp/mL on day 1 of the study.

Three, 6 and 9 months after the start of treatment all patients were evaluated for recurrence of high-grade disease. Cytology, cystoscopy and, if clinically indicated, biopsies were performed to obtain accurate staging. If no evidence of recurrence of high-grade disease was detected, a further dose of INSTILADRIN was administered. The final efficacy evaluation was performed at 12 months. Patients could receive up to four intravesical administrations of INSTILADRIN over the 12 month period of the study. Patients who had recurrence of high-grade disease were withdrawn from treatment. Overall, 14 subjects (35.0%;

90% confidence interval [CI]: 22.6, 49.2) were high-grade recurrence-free at 12 months. The incidence was comparable between dose groups with seven subjects (33.3%) in the $1x10^{11}$ vp/mL dose group and seven subjects (36.8%) in the $3x10^{11}$ vp/mL dose group. This showed that the study met its primary objective and endpoint.

The study concluded that:

- Intravesical administration of INSTILADRIN was well tolerated at both doses. Two INSTILADRIN related serious adverse events (SAEs) were reported, one each for diarrhea and urinary tract infection leading to acute renal failure. All SAEs were resolved.
- Fourteen (14) of the 40 patients achieved a CR, seven at the low dose and seven at the high dose. This represented a 35% response rate in high-grade BCG refractory or relapsed patients.

In addition to the bladder cancer studies described above, rAd-IFN (without the additional use of Syn3) has been investigated intrapleurally for the treatment of mesothelioma and has completed a study in 40 patients.

PHASE III STUDY DESIGN:

A multi-center, open label, repeat dose study to investigate the safety and efficacy of INSTILADRIN administered intravesically to BCG unresponsive patients with high-grade NMIBC.

Patients will receive a 75 mL intravesical administration of INSTILADRIN at a dose of 3×10^{11} vp/mL on Month 1 day 1 (M1D1) of the study.

In the first 12 months, before the start of each subsequent treatment all patients will be evaluated for recurrence of high-grade disease with cytology and cystoscopy to determine accurate staging. These visits will occur up to 2 weeks prior to dosing. Biopsies should be performed if clinically indicated or if there is a positive cytology. If no evidence of high-grade disease is observed, then a further dose of INSTILADRIN will be administered at month 4 (M4) (day 90), M7 (day 180) and M10 (day 270), respectively. Patients can receive up to four intravesical administrations of INSTILADRIN over the initial 12 month observed period.

At month 12 from the date of the first administration of INSTILADRIN (i.e., M1D1 +365 days), all patients who have not been withdrawn from dosing will undergo cystoscopy, cytology and biopsies.

All patients with an absence of high-grade disease recurrence at month 12 will be offered continued treatment every 3 months after M12.

Assessments at months 15, 18, 21, and 24 will be performed by cytology, cystoscopy and biopsy(ies) if clinically indicated before dosing.

From month 24 onwards, assessments will be performed on a 3 monthly basis by the investigator in accordance with usual clinical practice, confirming the suitability of the patient to continue to receive INSTILADRIN prior to each treatment.

Dosing with INSTILADRIN may continue until either the study results (risk / benefit) are shown to be unfavorable or the treatment becomes available following FDA approval.

Patients who have evidence of high-grade disease after receiving at least one dose of INSTILADRIN will be withdrawn from the study schedule, but will be followed for survival and time to cystectomy with data collected on an annual basis.

Long term follow-up safety and survival data will be collected for all patients dosed, including information regarding progression to invasive disease and cystectomy for up to 5 years (Month 60) from first dose.

OBJECTIVES:

Primary Objectives

1. To evaluate the complete response rate in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease)

Secondary Objectives

2. To evaluate the durability of complete response in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease) who achieve a complete response
3. To evaluate the rate of event-free survival, where event-free survival is defined as high-grade recurrence free survival in patients with high-grade Ta or T1 papillary disease (without concomitant CIS)
4. To evaluate the durability of event-free survival in patients with high-grade Ta or T1 papillary disease (without concomitant CIS), no recurrence of high-grade Ta or T1 papillary disease. For comparison purposes, this will also be evaluated in patients with CIS.
5. To determine the incidence of and time to cystectomy.
6. To determine the overall survival in all patients
7. To determine the anti-adenoviral antibody levels for correlation to response rate
8. To evaluate the safety of INSTILADRIN
9. To monitor durability of response during the long term follow up period

Exploratory Objective

10. To identify predictive blood, tissue and urine biomarkers for absence or presence of high-grade disease, including tissue PD-L1 and, if feasible, tissue PD-1 and CDK-N2A

ENDPOINTS:

Primary Endpoints

1. Whether or not a patient with CIS (with or without concomitant high-grade Ta or T1 papillary disease) responds to treatment, defined as complete response at any time after first administration of INSTILADRIN

Secondary Endpoints

Key Secondary endpoint

1. Durability of complete response in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease) who show a complete response at any time after first administration of INSTILADRIN

Other Secondary endpoints

2. Whether or not a patient with high-grade Ta or T1 papillary disease (without concomitant CIS) responds to treatment, defined as absence of recurrence of high-grade disease
3. Event-free survival in patients with high-grade Ta or T1 papillary disease (without concomitant CIS) disease and in patients with CIS (with or without papillary disease)
4. Incidence of and time to cystectomy
5. Overall survival
6. Measurement of anti-adenoviral antibody levels at each dosing period, withdrawal, and at 12 months
7. Type, incidence, relatedness and severity of treatment emergent adverse events (AEs) as assessed by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI-CTCAE V4.03)

Other exploratory endpoints

8. Pre- and post-treatment tissue levels of PD-L1 and, if feasible, PD-1 and CDK-N2A, and treatment outcomes

NUMBER OF PATIENTS:

The study will recruit patients both CIS and with papillary disease. Enrolment will end when approximately 100 evaluable CIS (with and without papillary tumor) patients are dosed. It is anticipated that the total number of patients recruited will be approximately 150.

PRINCIPAL INCLUSION & EXCLUSION CRITERIA:

Inclusion criteria

1. Aged 18 years or older at the time of consent
2. Able to give written informed consent
3. Have at entry, confirmed by a pathology report:
   - Carcinoma *in situ* (CIS) only
   - Ta/T1 high-grade disease with concomitant CIS or
   - Ta/T1 high-grade disease without concomitant CIS [(4)]
4. Are "BCG Unresponsive" which refers to patients with high-grade NMIBC who are unlikely to benefit from and who will not be receiving further intravesical BCG. The term "BCG unresponsive" includes patients who did not respond to BCG treatment and have a persistent high-grade recurrence within 12 months after BCG was initiated, and those who despite an initial CR to BCG, relapse with CIS within 12 months of their last intravesical treatment with BCG or relapse with high-grade Ta/T1 NMIBC within 6 months of their last intravesical treatment with BCG. The following criteria define the patients who may be included in the study:
   a. Have received at least two previous courses of BCG within a 12 month period – defined as at least five of six induction BCG instillations and at least two out of three instillations of maintenance BCG, **or** at least two of six instillations of a second induction course, where maintenance BCG is not given
      i. Exception: those who have T1 high-grade disease at 1st evaluation after induction BCG alone (at least 5 of 6 doses) may qualify in the absence of disease progression
   b. At the time of tumor recurrence, patients with CIS alone or high-grade Ta/T1 with CIS should be within 12 months of last exposure to BCG and patients with high-grade Ta/T1 without CIS should be within 6 months of last exposure to BCG
   c. No maximum limit to the amount of BCG administered
   d. All visible papillary tumors must be resected and those with persistent T1 disease on transurethral resection of bladder tumor (TURBT) should undergo an additional re-TURBT within 14 to 60 days prior to beginning study treatment. Obvious areas of CIS should also be fulgurated
5. Available for the whole duration of the study
6. Life expectancy >2 years, in the opinion of the investigator
7. Eastern Cooperative Oncology Group (ECOG) status 2 or less
8. Absence of concomitant upper tract urothelial carcinoma or urothelial carcinoma within the prostatic urethra. Freedom from upper tract disease (if clinically indicated) as indicated by no evidence of upper tract tumor by either intravenous pyelogram, retrograde pyelogram, computed tomography (CT) scan with or without urogram, or magnetic resonance imaging (MRI) with or without urogram performed within 6 months of enrollment

9. Patients with prostate cancer on active surveillance at low risk for progression, defined as prostate-specific antigen (PSA) <10 ng/dL, Gleason score 6 and cT1 are permitted to be included into the study at the discretion of the Investigator (see exclusion criterion 10)
10. Female patients of childbearing potential must use maximally effective birth control during the period of therapy, must be willing to use contraception for 1 month following the last study drug infusion and must have a negative urine or serum pregnancy test upon entry into this study. Otherwise, female patients must be postmenopausal (no menstrual period for a minimum of 12 months) or surgically sterile Maximally effective birth control' means that the patient, if sexually active, should be using a combination of two methods of birth control that are approved and recognized to be effective by regulatory agencies
11. Male patients must be surgically sterile or willing to use a double barrier contraception method upon enrolment, during the course of the study, and for 1 month following the last study drug instillation
12. Adequate laboratory values
    - Hemoglobin ⩾10 g/dL
    - White blood cells (WBC) ⩾ 4000/μL
    - Absolute neutrophil count (ANC) ⩾2000/μL
    - Platelet count ⩾100,000/μL
    - International normalized ratio (INR)* below institutional upper limit of normal (ULN)
    - Activated partial thromboplastin time (aPTT)* below institutional ULN
    - Aspartate aminotransferase (AST) ⩽1.5 x ULN
    - Alanine aminotransferase (ALT) ⩽1.5 x ULN
    - Total bilirubin ⩽1.5 x ULN
    - Estimated glomerular filtration rate (eGFR) ⩾ 30 mL/min/1.73m^2

*It is accepted that patients receiving anticoagulation therapy would not have INR and aPTT results that fall within 'normal limits'. It is not intended to exclude these patients and therefore medical discretion is permitted for patients who have clinically acceptable results in regards to their current concomitant anticoagulant therapy.

Exclusion criteria

1. Current or previous evidence of muscle invasive (muscularis propria) or metastatic disease presented at the screening visit. Examples that increase the risk of metastatic disease are (but not limited to):
    - Presence of lymphovascular invasion and / or micropapillary disease as shown in the histology of the biopsy sample.
    - Patients with T1 disease accompanied by the presence of hydronephrosis secondary to the primary tumor
2. Current systemic therapy for bladder cancer
3. Current or prior pelvic external beam radiotherapy within 5 years of entry
4. Prior treatment with adenovirus-based drugs
5. Suspected hypersensitivity to Interferon Alfa2b (IFN alfa2b)
6. Symptomatic urinary tract infection or bacterial cystitis (once satisfactorily treated, patients can enter the study)
7. Clinically significant and unexplained elevated liver or renal function tests
8. Women who are pregnant or lactating or refuse to commit to use contraception at anytime during the study
9. Any other significant disease or clinical findings which in the opinion of the investigator would prevent study entry
10. History of malignancy of other organ system within past 5 years, except treated basal cell carcinoma or squamous cell carcinoma of the skin and ≤pT2 upper tract urothelial carcinoma

at least 24 months after nephroureterectomy. Also patients with genitourinary cancers other than urothelial cancer or prostate cancer that are under active surveillance are excluded (see inclusion criterion 9)

11. Patients who cannot hold instillation for 1 hour
12. Patients who cannot tolerate intravesical dosing or intravesical surgical manipulation
13. Intravesical therapy within 8 weeks prior to beginning study treatment with the exception of:
    - Cytotoxic agents (e.g., Mitomycin C, doxorubicin and epirubicin) when administered as a single instillation immediately following a TURBT procedure which is permitted between 14 to 60 days prior to beginning study treatment
    - Previous intravesical BCG therapy, which can be given at least 5 weeks before the diagnostic biopsy required for entry into the study

STUDY DRUG ADMINISTRATIONS:

The investigational product, INSTILADRIN, consists of rAd-IFN and Syn3 for intravesical administration. The product is presented as either rAd-IFN vector concentrate and Syn3 (lyophilized powder for reconstitution in sterile water) to be mixed with a diluent before use (presentation available at study initiation) or a ready-to-use product including both components and the diluent (presentation developed after study initiation). The two presentations contain identical constituents in the same proportions and strengths and are thus interchangeable.

For the purposes of this study both presentations of the investigational product are termed INSTILADRIN, however, this will not be the name of the potential future marketed product.

Patients will receive 75 mL intravesical administration of INSTILADRIN at a dose of 3×10^{11} viral particles (vp)/mL.

The dose will be given as a single, 1-hour intravesical administration which may, depending on the clinical response, be repeated every 3 months up to a maximum of four instillations in the first 12 months. After M12, patients will be assessed on a 3 monthly basis for further treatment at the discretion of the treating physician.

Biosafety Level 2 precautions will be used in handling INSTILADRIN and in caring for patients receiving INSTILADRIN.

Admixture (rAd-IFN + Syn3) Presentation

rAd-IFN vector concentrate will be supplied in frozen vials and Syn3 (120 mg/vial) will be supplied as a lyophilized powder. The powder is reconstituted with 20 mL of sterile water for injection to form a 5.8 mg/mL solution. rAd-IFN and Syn3 will be reconstituted in a diluent to a volume of approximately 80 mL. The final instillation volume will be 75 mL.

Ready-to-use Presentation

The ready-to-use presentation of the investigational product is an aqueous suspension of rAd-IFN for intravesical administration including the functional excipient Syn3 and diluent. The ready-to-use presentation will be supplied in frozen vials, each one containing 20 mL suspension. The instillation volume will be 75 mL.

STUDY ASSESSMENTS AND CRITERIA FOR EVALUATION:

Details of the study assessments are provided in Table 1; the Schedule of Assessments.

Pre-study efficacy evaluations and procedures: cystoscopy, cytology, TURBT/fulguration and biopsy (all patients).

Efficacy Assessments:

1. Assessment of the recurrence of high-grade disease by cystoscopy and cytology
2. Assessment of muscle invasive disease by biopsy will be done if clinically indicated or if there is a positive cytology at the efficacy safety assessment visits

3. Assessment of the incidence and time to cystectomy
4. Assessment of survival

Safety Assessments:

1. Assessment of Treatment Emergent AEs
2. Clinical chemistry/hematology
3. Vital signs and physical examination
4. Resting 12-lead electrocardiogram (ECG)
5. Measurement of the levels of anti-adenoviral antibodies

Criteria for Efficacy Evaluation:

1. A patient has achieved a complete response at an efficacy assessment when urine cytology is negative and there are no lesions on cystoscopy; if random biopsies of the bladder are performed, these should be negative. Once a complete response is achieved, recurrence of low grade disease only at any subsequent time point is not considered a treatment failure.

2. The cystectomy rate is defined as the number or percentage of patients who have undergone radical cystectomy for any reason

Criteria for Safety Evaluation

The safety and tolerability of INSTILADRIN will be evaluated based on AE reports, vital signs, clinical laboratory values, ECG measurements, anti-adenoviral antibody levels, and results of physical examination.

Efficacy Statistical Methods:

The primary efficacy endpoint is rate of complete response at any time in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease). A patient with CIS has achieved a complete response if cystoscopy, cytology and biopsy (if clinically indicated) show no evidence of CIS.

The proportion of patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease) achieving a complete response at any time will be reported together with an exact 95% CI for the proportion.

The durability of complete response in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease) who achieve a complete response at any time will be presented. Kaplan-Meier methods will be used to provide estimates of median duration and of the probability of duration at 3 monthly intervals.

The proportion of patients with high-grade Ta or T1 papillary disease (without concomitant CIS) achieving high-grade-recurrence-free survival will be reported together with an exact 95% CI for the proportion.

High-grade-recurrence-free survival in patients with high-grade Ta or T1 papillary disease (without concomitant CIS), in patients with CIS (with or without concomitant high grade Ta or T1 papillary disease), and in both cohorts combined will be presented using Kaplan-Meier methods to provide estimates of median duration and of the probability of duration at 3 monthly intervals.

Estimation of Sample Size and Operating Characteristics of Design: The observed complete response rate at any time in CIS +/- papillary subjects in the Phase II study was equal to 50%. Assuming the Phase III study retains 87.5% of that efficacy, the true response rate will be 43.75%. One hundred CIS +/- papillary subjects provide 90% power to reject the hypothesis that the true response rate is 27% at a one-sided alpha of 2.5%. Thirty-seven responding patients (response rate of 37%, two-sided 95% Clopper-Pearson CI = [27.5%, 47.3%]) are sufficient to reject the hypothesis.

Appropriate summaries for the other efficacy endpoints will be presented.

DURATION OF STUDY FOR EACH PATIENT:

The duration of the study is potentially up to 5 years:

- The initial treatment period of 12 months, with dosing occurring every 3 months at M4, M7 and M10 after the initial dose at M1.

Patients that have not withdrawn from treatment will have an efficacy assessment at 12 months (i.e., M1D1+365 days) after the first dose of treatment.

A follow up period consisting of :

- Patients with no evidence of recurrence of high-grade disease at month 12 will be offered continued treatment if considered appropriate by their treating physician. INSTILADRIN will be administered every 3 months to a maximum of 4 doses. Further assessments at months 15, 18, 21, and 24 will be performed by cytology, cystoscopy and a biopsy if clinically indicated.
- Further assessments for patients with no evidence of high-grade disease at month 12 but who decline treatment will take place at months 15, 18, 21, and 24 and will be performed by cytology, cystoscopy and a biopsy if clinically indicated.
- Dosing with INSTILADRIN may continue from month 24 onwards on a 3 monthly basis for patients with no evidence of high grade disease recurrence, until either the study results (risk / benefit) are shown to be unfavorable or the treatment becomes available following FDA approval. Assessments will be performed in accordance with usual clinical practice, the suitability of the patient to continue to receive INSTILADRIN should be confirmed by the investigator prior to each treatment.

Patients who have recurrence of high-grade disease having received at least one dose of INSTILADRIN will be withdrawn from treatment, but will have data collected for long term survival and time to cystectomy on an annual basis for up to 5 years (month 60) from first dose.

NUMBER OF STUDY CENTERS:

Maximum 33

3. TABLE OF CONTENTS

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BCG	Bacillus Calmette-Guerin therapy
BP	Blood pressure
CFR	Code of Federal Regulations
CI	Confidence interval
CIS	Carcinoma *in situ*
CR	Complete response
CRA	Clinical Research Associate
CRO	Clinical research organization
CSR	Clinical study report
CT	Computed tomography
CTCAE V4.03	Common terminology criteria for adverse events version 4.03
DNA	Deoxyribose nucleic acid
ECG	Electrocardiogram
eCRF	Electronic Clinical Report Form
ECOG	Eastern Cooperative Oncology Group
EEAF	Eligibility Enrollment Authorization Form
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
GCP	Good clinical practice
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
IXRS	Interactive cross communication (X) Response System

MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
N	Number of observations
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMIBC	Non-muscle invasive bladder cancer
NCI	National Cancer Institute
PDL-1	Programmed death ligand 1
PGE2	Prostaglandin E2
PSA	Prostate-specific antigen
QTc_F	Corrected QT interval according to Fridericia's correction
rAd-IFN/Syn3	INSTILADRIN®, generic name nadofaragene firadenovec
RR	Respiration rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
TCC	Transitional cell carcinoma
TURBT	Transurethral Resection of Bladder Tumor
ULN	Upper limit of normal
vp	Viral particles
WBC	White blood cells
WHO	World Health Organization

5. INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

Coordinating Investigator
Dr. Stephen Boorjian MD

[redacted]

Ferring Pharmaceuticals A/S
Medical Monitor

[redacted]

FKD Study Operational Head

[redacted]

Statistician

[redacted]

Contract Research Organization:

[redacted]

Clinical Laboratories:

[redacted]

Clinical Investigational Product Distribution:

[redacted]

6. INTRODUCTION

Transitional cell carcinoma (TCC) is the predominant type of urinary tract cancer, comprising approximately 90% of all bladder cancers in the US. Transitional cell carcinoma is comprised of two major types: papillary (Stages Ta and T1) and carcinoma *in situ* (CIS). Carcinoma *in situ* and T1 (invasive into lamina propria) are usually high-grade and can progress to invasive and metastatic disease, while Ta disease is usually low-intermediate grade. In patients with recurrent Non-muscle invasive bladder cancer (NMIBC), recurrence is associated with an increased risk of invasive disease. [(1)]

The goal of treatment for NMIBC is to prevent progression to muscle invasion and metastatic disease. Surgical removal of the bladder (cystectomy) in high risk patients can be curative but is associated with significant morbidity. Any medical treatment that can lead to the prevention of tumor progression, and thus, preservation of the bladder, is the optimal choice. These patients are candidates for intravesical chemotherapy or intravesical immunotherapy. Typically, these agents are instilled into the bladder through a urethral catheter for 2 hours at weekly intervals for 6 to 8 weeks. Occasionally, long-term maintenance treatment regimens are employed.

Bacillus Calmette-Guerin (BCG) immunotherapy is the standard front line therapy for the treatment of NMIBC bladder cancer and has been used since the 1970s. However, for patients with no response to BCG therapy or therapy failure, the likelihood of a positive response to more than two courses of BCG is low, and the risk of invasive or metastatic disease is greatly increased. [(2)] Cystectomy may be indicated for high-risk patients who are not amenable to transurethral resection of the bladder tumor or who have failed BCG therapy. Thus, new treatment modalities need to be developed for patients with recurrent NMIBC who have failed standard therapy.

Recombinant IFNalfa2b (INTRON® A) has pleiotropic effects that contribute to antitumor activity (antiproliferation, apoptosis, angiogenesis inhibition, and immune augmentation) and it has been approved in the United States and Europe for the treatment of a number of human cancers (malignant melanoma, hairy cell leukemia, non-Hodgkin's lymphoma, acquired immunodeficiency syndrome (AIDS)-related Kaposi's sarcoma). INTRON A has been studied in clinical trials involving patients with NMIBC with some success; however, since patients are unable to retain the INTRON A for more than the 1- to 2-hour dwell time, exposure of bladder tumors to INTRON A following intravesical treatment is limited by the duration of instillation.

rAd-IFN is a replication deficient adenovirus-based IFNalfa2b gene transfer vector that is being developed for the treatment of NMIBC. The purpose of using a gene transfer approach is to improve exposure of the bladder urothelium and tumors to IFNalfa2b, minimizing dosing frequency, and enhancing the duration of exposure. The bladder epithelium of the patient is expected to function as a bioreactor for the synthesis and secretion of sustained local concentrations of IFNalfa2b protein, resulting in an improved antitumor effect. Studies in animal models support the hypothesis that prolonging local exposure of IFNalfa2b protein in NMIBC leads to significantly improved antitumor activity. In addition, significant levels of IFNalfa2b are observed in the urine consistent with expression of the protein from the uroepithelium.

A complete summary of the preclinical activity is provided in the Investigator's Brochure for INSTILADRIN.

Clinical Trial Summaries

Three clinical trials have been completed to assess the safety and efficacy of INSTILADRIN (rAd-IFN/Syn3). A summary of these trials is presented below.

A Phase 1 first-in-human study was performed to determine the safety and tolerability of intravesical administration of INSTILADRIN in patients with TCC of the bladder. The protocol allowed for a second intravesical administration of INSTILADRIN at the same dose as the first administration if the evaluation 3 months after the first dose showed complete response (CR) as measured by cystoscopy cytology, and biopsy. Seventeen patients were dosed intravesically with INSTILADRIN. Five of the seven patients who achieved CR received a second intravesical dose of INSTILADRIN. The maximum tolerated dose (MTD) was not reached in this study.

The study concluded that:

- Intravesical administration of INSTILADRIN was well tolerated.
- The maximum dose administered was 3 x 10^{11} viral particles (vp)/mL in a dose volume of 75 mL. The MTD was not achieved in this study.
- Seven of the 17 patients achieved a CR following a single intravesical administration of INSTILADRIN.
- Urinary IFN protein was measurable for up to day 10 post-dose suggesting sustained expression of IFN in the bladder.
- There was no indication of systemic exposure to rAd-IFN-specific DNA following intravesical administration of INSTILADRIN

A second Phase 1 study was performed, under an investigator-sponsored investigational new drug (IND) application, to determine the safety and tolerability of intravesical administration of INSTILADRIN in patients with TCC of the bladder. The protocol allowed for a second intravesical administration of INSTILADRIN® at the same dose as the first administration 4 days following the initial administration. If the evaluation 3 months after the first dose showed CR as measured by cystoscopy, cytology, and biopsy, then a third intravesical administration was allowed. Although transient rises in urine IFN were seen after day 4 treatments, in three patients, sustained IFN at the 12 week retreatment time point was not demonstrated with the additional dose.

A recently completed Phase II study at 14 centers in the US was designed to assess the safety and efficacy of INSTILADRIN in patients with high-grade BCG refractory or relapsed NMIBC. The primary objective of the study was to evaluate the incidence of high-grade-recurrence-free survival at 12 months. Secondary objectives included but were not limited to the evaluation of the incidence of high-grade-recurrence-free survival at 3, 6 and 9 months, the determination of the time to progression to muscle invasive disease, and the safety of INSTILADRIN. The multi-dose study enrolled 40 patients (two treatment groups of up to 20 patients each). Patients were randomized to receive a 75 mL intravesical administration of INSTILADRIN at a treatment dose of either 1 x 10^{11} vp/mL or 3 x 10^{11} vp/mL on day 1 of the study. Patients received subsequent doses at months 4, 7, and 10 if there was no evidence of high-grade disease as determined by

cystoscopy, cytology and, where indicated, biopsy. Final assessments at 360 days following the first dose required cystoscopy, cytology and biopsy to determine if a patient was considered a complete response (CR). Patients that demonstrated recurrence of high-grade disease at months 3, 6, and 9 were removed from the study. Overall, 14 subjects (35.0%; 90% confidence interval (CI): 22.6, 49.2) were high-grade recurrence-free at 12 months. The incidence was comparable between dose groups with seven subjects (33.3%) in the $1x10^{11}$ vp/mL dose group and seven subjects (36.8%) in the $3x10^{11}$ vp/mL dose group. This showed that the study met its primary objective and endpoint.

The study concluded that:

- Intravesical administration of INSTILADRIN was well tolerated. Two drug related SAEs were reported, one each for urinary tract infection leading to acute renal failure, and diarrhea, and all SAEs were resolved
- Fourteen of the 40 patients achieved a CR, defined as no recurrence of high-grade disease, following four intravesical administrations of INSTILADRIN over a course of 360 days. This represents a 35% response rate
- Urinary IFN protein was measurable up to day 10 post-dose demonstrating sustained expression of IFN in the bladder
- There was no indication of systemic exposure to rAd-IFN-specific DNA following intravesical administration of INSTILADRIN

Unlike the Phase II protocol in which the inclusion criteria focused on BCG-refractory or relapsed patients, the Phase III protocol will use the terminology of BCG-Unresponsive as defined in the inclusion criteria section. [(3)]

In addition to the bladder cancer studies described above, rAd-IFN (without the additional use of Syn3) has been studied intrapleurally for the treatment of mesothelioma and has recently completed a study in 40 patients. In summary for this study, subjects with unresectable malignant pleural mesothelioma who had good performance status were enrolled. Subjects received two doses of rAd-IFN intrapleurally ($3x10^{11}$ vp per dose, without Syn3) concomitant with a 14-day course of cyclo-oxygenase-2 inhibitor to reduce side effects and to modify the tumor microenvironment by decreasing prostaglandin E2 (PGE2) levels. Of the 40 subjects treated, 18 received first line pemetrexed-based chemotherapy and 22 received second line chemotherapy with pemetrexed (seven) or gemcitabine –based chemotherapy (15). Treatment was well tolerated and adverse events (AEs) were comparable to historical controls.

7. OBJECTIVES

7.1. Primary Objectives

1. To evaluate the complete response rate in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease)

7.2. Secondary Objectives

2. To evaluate the durability of complete response in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease) who achieve a complete response.
3. To evaluate the rate of event-free survival, where event-free survival is defined as high-grade recurrence free survival, in patients with high-grade Ta or T1 papillary disease (without concomitant CIS)
4. To evaluate the durability of event-free survival in patients with high-grade Ta or T1 papillary disease (without concomitant CIS), who have no recurrence of high-grade Ta or T1 papillary disease. For comparison purposes, this will also be evaluated in patients with CIS.
5. To determine the incidence of and time to cystectomy
6. To determine the overall survival in all patients
7. To determine the anti-adenoviral antibody levels for correlation to response rate
8. To evaluate the safety of INSTILADRIN
9. To monitor durability of response during long term follow-up period

7.3. Exploratory Objective

10. To identify predictive blood, tissue and urine biomarkers for absence or presence of high-grade disease, including tissue PD-L1 and, if feasible, tissue PD-1 and CDK-N2A

8. STUDY ENDPOINTS

8.1. Primary Endpoint

1. Whether or not a patient with CIS (with or without concomitant high-grade Ta or T1 papillary disease) responds to treatment, defined as complete response at any time after first administration of INSTILADRIN

8.2. Secondary Endpoints

Key Secondary Endpoint

1. Durability of complete response in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease) who show a complete response at any time after first administration of INSTILADRIN

Other Secondary Endpoints

2. Whether or not a patient with high-grade Ta or T1 papillary disease (without concomitant CIS) responds to treatment, defined as absence of recurrence of high-grade disease
3. Event-free survival in patients with high-grade Ta or T1 papillary (without concomitant CIS) disease and in patients with CIS (with or without papillary disease)
4. Incidence of and time to cystectomy
5. Overall survival
6. Measurement of anti-adenoviral antibody levels at each dosing period, withdrawal, and at 12 months
7. Type, incidence, relatedness and severity of treatment emergent AEs as assessed by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI-CTCAE V4.03)

Other exploratory endpoints

8. Pre- and post-treatment tissue levels of PD-L1 and, if feasible, PD-1 and CDK-N2A, and treatment outcomes

9. SELECTION CRITERIA

9.1. Inclusion Criteria

1. Aged 18 years or older at the time of consent
2. Able to give written informed consent
3. Have at entry, confirmed by a pathology report:
   - Carcinoma *in situ (*CIS) only
   - Ta/T1 high-grade disease with concomitant CIS or
   - Ta/T1 high-grade disease without concomitant CIS [4]
4. Are "BCG Unresponsive" which refers to patients with high-grade NMIBC who are unlikely to benefit from and who will not be receiving further intravesical BCG. The term "BCG Unresponsive" includes patients who did not respond to BCG treatment and have a persistent high-grade recurrence within 12 months after BCG was initiated, and those who despite an initial CR to BCG, relapse with CIS within 12 months of their last intravesical treatment with BCG or relapse with high-grade Ta/T1 NMIBC within 6 months of their last intravesical treatment with BCG. The following criteria define the patients who may be included in the study:
   a. Have received at least two previous courses of BCG within a 12 month period – defined as at least 5 of 6 induction BCG instillations and at least two out of three instillations of maintenance BCG, **or** at least two of six instillations of a second induction course, where maintenance BCG is not given.
      i. Exception: those who have T1 high-grade disease at 1st evaluation after induction BCG alone (at least 5 of 6 doses) may qualify in the absence of disease progression

b. At the time of tumor recurrence, patients with CIS alone or high-grade Ta/T1 with CIS should be within 12 months of last exposure to BCG and patients with high-grade Ta/T1 without CIS should be within 6 months of last exposure to BCG
c. No maximum limit to the amount of BCG administered
d. All visible papillary tumors must be resected and those with persistent T1 disease on transurethral resection of bladder tumor (TURBT) should undergo an additional re-TURBT within 14 to 60 days prior to beginning study treatment. Obvious areas of CIS should also be fulgurated

5. Available for the whole duration of the study
6. Life expectancy >2 years, in the opinion of the investigator
7. Eastern Cooperative Oncology Group (ECOG) status 2 or less[5]
8. Absence of concomitant upper tract urothelial carcinoma or urothelial carcinoma within the prostatic urethra. Freedom from upper tract disease (if clinically indicated) as indicated by no evidence of upper tract tumor by either intravenous pyelogram, retrograde pyelogram, evidence of upper tract tumor by either intravenous pyelogram, retrograde pyelogram, computed tomography (CT) scan with or without urogram, or magnetic resonance imaging (MRI) with or without urogram performed within 6 months of enrollment
9. Patients with prostate cancer on active surveillance at low risk for progression, defined as prostate-specific antigen (PSA) <10 ng/dL, Gleason score 6 and cT1 are permitted to be included into the study at the discretion of the Investigator (see exclusion criterion 10)
10. Female patients of childbearing potential must use maximally effective birth control during the period of therapy, must be willing to use contraception for 1 month following the last study drug infusion and must have a negative urine or serum pregnancy test upon entry into this study. Otherwise, female patients must be postmenopausal (no menstrual period for a minimum of 12 months) or surgically sterile. Maximally effective birth control means that the patient, if sexually active, should be using a combination of two methods of birth control that are approved and recognized to be effective by regulatory agencies
11. Male patients must be surgically sterile or willing to use a double barrier contraception method upon enrolment, during the course of the study, and for 1 month following the last study drug instillation
12. Adequate laboratory values.
    - Hemoglobin ≥10 g/dL
    - White blood cells (WBC) ≥4000/µL
    - Absolute neutrophil count (ANC) ≥2000/µL
    - Platelet count ≥100,000/µL
    - International normalized ratio (INR)* below institutional upper limit of normal (ULN)
    - Activated partial thromboplastin time (aPTT)* below institutional ULN
    - Aspartate aminotransferase (AST) ≤1.5 x ULN
    - Alanine aminotransferase (ALT) ≤1.5 x ULN

- Total bilirubin ≤1.5 x ULN
- Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2

* It is accepted that patients receiving anticoagulation therapy would not have INR and aPTT results that fall within 'normal limits'. It is not intended to exclude these patients and therefore medical discretion is permitted for patients who have clinically acceptable results in regards to their current concomitant anticoagulant therapy

9.2. Exclusion Criteria

1. Current or previous evidence of muscle invasive (muscularis propria) or metastatic disease presented at the screening visit. Examples of increased risk of metastatic disease include but are not limited to:
   - Presence of lymphovascular invasion and / or micropapillary disease as shown in the histology of the biopsy sample
   - Patients with T1 disease accompanied by the presence of hydronephrosis secondary to the primary tumor
2. Current systemic therapy for bladder cancer
3. Current or prior pelvic external beam radiotherapy within 5 years of entry
4. Prior treatment with adenovirus-based drugs
5. Suspected hypersensitivity to IFNalfa2b
6. Symptomatic urinary tract infection or bacterial cystitis (once satisfactorily treated, patients can enter the study)
7. Clinically significant and unexplained elevated liver or renal function tests
8. Women who are pregnant or lactating or refuse to commit to use contraception throughout during the study
9. Any other significant disease or other clinical findings which in the opinion of the investigator would prevent study entry
10. History of malignancy of other organ system within past 5 years, except treated basal cell carcinoma or squamous cell carcinoma of the skin and ≤pT2 upper tract urothelial carcinoma at least 24 months after nephroureterectomy. Also patients with genitourinary cancers other than urothelial cancer or prostate cancer that are under active surveillance are excluded (see inclusion criterion 9)
11. Patients who cannot hold instillation for 1 hour
12. Patients who cannot tolerate intravesical dosing or intravesical surgical manipulation
13. Intravesical therapy within 8 weeks prior to beginning study treatment with the exception of:
    - Cytotoxic agents (e.g., Mitomycin C, doxorubicin and epirubicin) when administered as a single instillation immediately following a TURBT procedure which is permitted between 14 to 60 days prior to beginning study treatment
    - Previous intravesical BCG therapy, which can be given at least 5 weeks before the diagnostic biopsy required for entry into the study

9.3. Patient Withdrawal/Study Discontinuation

Patients may withdraw from the study at any time without stating a reason and without prejudice to further treatment.

The investigator may also withdraw a patient at anytime from the study. The Sponsor's Medical Monitor should be contacted to discuss the reason for withdrawal and further follow up that maybe required relevant to the study. The Sponsor reserves the right to request the withdrawal of a patient due to protocol violation, administrative or other reasons. All patient withdrawals must be conducted in line with the patient withdrawal/discontinuation procedures in this protocol.

Specific reasons for discontinuing a patient from the study are:

- Disease recurrence and progression. (see Section 12)
- Protocol non-compliance (all documentation concerning the patient must be as complete as possible. Withdrawals due to non-attendance must be followed-up by the Investigator to obtain the reason for non-attendance if possible.)
- Patient request and withdrawal of consent
- Safety reasons including deterioration in renal and hepatic function

Once further treatment of INSTILADRIN is withdrawn due to disease progression, the visit should be noted as a Withdrawal from study\End of treatment visit. Procedures should be completed as soon as possible but no later than 30 days after the progression is noted. Further treatment (i.e., standard therapy, surgery etc) will be at the discretion of the treating physician and will be documented in the patient notes.

For those patients that have disease progression and are in agreement, follow-up data will be collected annually for up to 5 years or until consent is withdrawn. Information will be sought from the investigator by a written communication as to the disease status at last follow-up, what additional therapies the patient might have received, if progression to invasive disease has occurred, if the patient is still alive and to record the date of any cystectomy.

Where possible, patients who withdraw consent should complete a Withdrawal from Study\End of Treatment visit within 30 days. Procedures are at the discretion of the treating physician as per Section 11.4.

Patients will be classed as 'withdrawn from treatment' when they have not attended more than two consecutive scheduled clinic visits and 'lost to follow-up' if completely unresponsive to contacts either via phone, fax or email for over a 1 month period post missed visit/ contact, unless there is evidence previously provided by the patient to explain their absence.

9.3.1. Procedures for Discontinuation

If a patient withdraws from the study for reasons other than disease progression or tolerability, the reason for withdrawal should be sought and recorded on the case report form. For all patients, Serious Adverse Events (SAEs) should be followed up until resolution and AEs to a maximum of 30 days post the withdrawal from study visit.

9.3.2. Replacement of Patients

Patients who enter the study (sign informed consent) but are not enrolled (dosed) may be replaced. No other replacements will be allowed.

10. INVESTIGATIONAL PLAN

10.1. Overall Study Design

A multi-center, open label, repeat dose study to investigate the safety and efficacy of INSTILADRIN administered intravesically to BCG unresponsive patients with high-grade NMIBC.

Patients will receive a 75 mL intravesical administration of INSTILADRIN® at a dose of 3 x 10^{11} vp/mL on each dosing day of the study. Anti-cholinergic drugs are permitted during the instillation procedure to aid in maintaining the instillation for up to 1 hour.

The duration of the study is up to 5 years:

- The initial treatment period of 12 months, All patients will be evaluated for evidence of disease with cytology and cystoscopy to determine accurate staging. Biopsies should be performed if clinically indicated. If no evidence of recurrence of high-grade disease is detected at any efficacy assessment visits, then a further dose of INSTILADRIN will be administered at day 90 (M4), 180 (M7) and 270 (M10) Patients that have not withdrawn from treatment will have an efficacy assessment at 12 months (i.e., M1D1+365 days) after the first dose of treatment.

A 4 year follow up period consisting of :

- Patients with no evidence of high-grade disease at month 12 will be offered continued treatment if considered appropriate by their treating physician. INSTILADRIN will be administered every 3 months to a maximum of 4 doses. Further assessments at months 15, 18, 21, and 24 will be performed by cytology, cystoscopy and a biopsy(ies) if clinically indicated.
- Further assessments for patients with no evidence of high-grade disease at month 12 but who decline treatment will take place at months 15, 18, 21, and 24 and will be performed by cytology, cystoscopy and a biopsy(ies) if clinically indicated,
- Dosing with INSTILADRIN may continue from month 24 onwards, on a 3 monthly basis, for patients with no evidence of high grade disease recurrence, until either the study results (risk / benefit) are shown to be unfavorable or the treatment becomes available following FDA approval. Assessments at these visits will be performed in accordance with usual clinical practice; the suitability of the patient to continue to receive INSTILADRIN should be confirmed by the investigator prior to each treatment.

Patients who have recurrence of high-grade disease having received at least one dose of INSTILADRIN will be withdrawn from treatment, but will have data collected for long term survival and time to cystectomy on an annual basis for up to 5 years (month 60) from first dose.

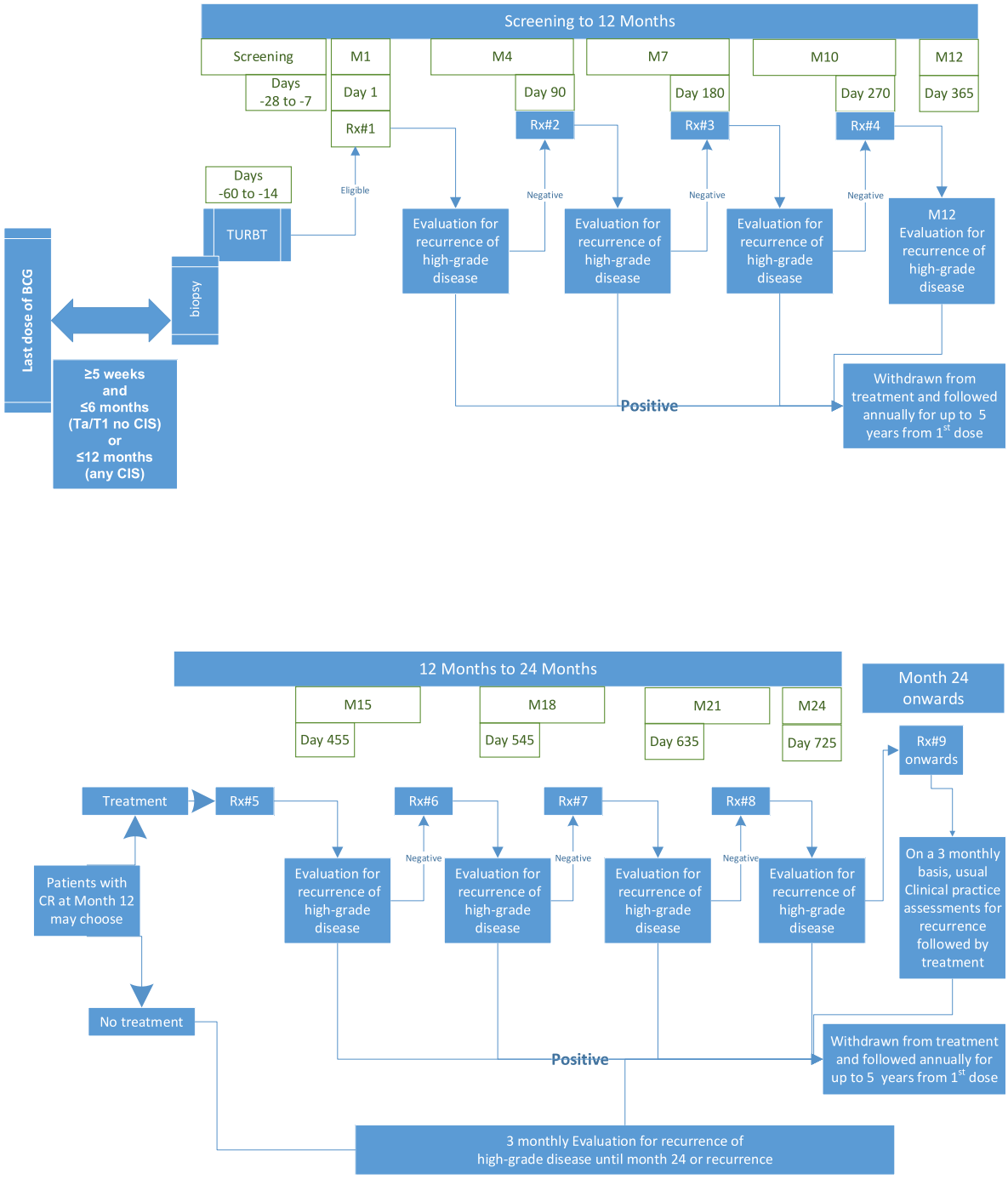
Withdrawal procedures should be conducted on an annual basis from date of withdrawal in accordance with Sections 9.3 and 11.4.

The primary analysis of the study will be performed when the required number of evaluable CIS (with or without concomitant high-grade Ta or T1 papillary disease) patients have either completed the month 12 (M12) assessment or have been withdrawn from the study and undergone a withdrawal from treatment\study assessment.

10.1.1. Number of Patients Planned

It is anticipated that the total number of patients required for the study will be approximately 150. However, enrolment will cease when approximately 100 evaluable CIS patients have been dosed. Patients who have already given informed consent will be treated, if eligible.

10.1.2. Study Flow Chart



11. STUDY SCHEDULE PROCEDURES

All procedures are performed as per the schedule of assessment outlined in Table 1.

- **The initial treatment phase (up to Month 12)**

Patients who have given informed consent will attend the clinic for a screening visit. The first dose of INSTILADRIN will be administered intravesically on month 1, day 1.

Assessments for disease progression (efficacy assessment visit) will be made up to 2 weeks (14 days) before the re-treatment target date at M4, M7 and M10. Dosing should occur within ±5 days of the target timepoint e.g., for dosing at M4D1, the target date for dosing should be between day 85 and 95. The efficacy assessments can be performed up to 14 days prior to the actual date within this window.

Following the table of study assessments (Table 1), at M1 and M4 (the first two treatments), patients will also attend the clinic on day 3 for safety assessments. Where day 3 falls on a non working day, the visit can be delayed by up to 2 days. The day 3 visit at M7 and M10 will be conducted by telephone.

Patients will also be contacted monthly by phone (approx. every 30 days) between visits according to the table of study assessments (Table 1) to provide information regarding AEs and concomitant medications.

At 12 months from the date of the first administration of INSTILADRIN (i.e., M1D1 +365 days), all patients who have not been withdrawn from dosing will undergo cystoscopy, cytology and biopsy.

- **Further follow up and treatment after Month 12 Assessment**

Further treatment in patients with no evidence of high-grade disease will be at the discretion of the investigator after M12.

Safety assessments will be performed up to 2 weeks before dosing at months 15, 18 and 21 (M15, M18, M21 and M24) in accordance with the schedule and include cytology, cystoscopy and a biopsy if clinically indicated to exclude tumor recurrence. At M24, treatment may continue for patients who are responding to INSTILADRIN and assessments will be performed as per usual clinical practice.

Those patients who are withdrawn from treatment at any time and withdraw consent will complete the Withdrawal from study\End of Treatment visit as per the schedule and will discontinue treatment with INSTILADRIN if applicable.

Patients who are withdrawn from treatment and are in agreement, will have follow-up long term safety and survival data, including information regarding progression to invasive disease and

cystectomy (conducted as per normal clinical practice), collected every 12 months for up to 5 years (month 60) from the 1st dose.

Table 1: Schedule of Study Assessments

Visit Number	1	2	3		4	5	6		7	8			9	10			11
Month (4 weeks) and Day of Month	Screening	M1 D1	M1 D3[t]	Phone Calls[j]	Efficacy Assessments[f]	M4 D1	M4 D3 [t]	Phone Calls[j]	Efficacy Assessments[f]	M7 D1	M7 D3 [t]	Phone Calls[j]	Efficacy Assessments[f]	M10 D1	M10 D3 [t]	Phone Calls [j]	M12
Day relative to initial dosing (days)[s]	D-28 to D-7	Day 1	+2 days	Mthly[u]	M4D1 -14days	M1D1 +90 ±5 days	M4D1 +2 days	Mthly [u]	M7D1 -14days	M1D1 +180 ±5 days	M7D1 +2 days	Mthly [u]	M10D1 -14 days	M1D1 +270 ±5 days	M10 D1 +2 days	Mthly [u]	M1D1 +365 ±5 days
Informed consent	X																
Medical history (inc. demographics)	X																
Inclusion/exclusion	X																
Pregnancy test[c]	X	X				X				X				X			X
Physical examination[d]	X	X				X				X				X			X
ECG[o]	X	X	X			X	X			X				X			X
Vital signs[e]	X	X	X			X	X			X				X			X
ECOG performance status[l]	X	X				X				X				X			X
Urinary Symptoms	X	X	X			X	X			X				X			X
TURBT[r] and endoscopic resection	X																
Cystoscopy					X				X				X				X
Biopsy[n,q]					(X)[g]				(X)[g]				(X)[g]				(X)[g]
Urine Cytology	X				X				X				X				X
Blood sample for antibody level[h] assessments		X				X				X				X			X

Visit Number	1	2	3		4	5	6		7	8			9	10			11
Month (4 weeks) and Day of Month	Screening	M1 D1	M1 D3[t]	Phone Calls[j]	Efficacy Assessments[f]	M4 D1	M4 D3 [t]	Phone Calls[j]	Efficacy Assessments[f]	M7 D1	M7 D3 [t]	Phone Calls[j]	Efficacy Assessments[f]	M10 D1	M10 D3 [t]	Phone Calls [j]	M12
Day relative to initial dosing (days)[s]	D-28 to D-7	Day 1	+2 days	Mthly[u]	M4D1 -14days	M1D1 +90 ±5 days	M4D1 +2 days	Mthly [u]	M7D1 -14days	M1D1 +180 ±5 days	M7D1 +2 days	Mthly [u]	M10D1 -14 days	M1D1 +270 ±5 days	M10 D1 +2 days	Mthly [u]	M1D1 +365 ±5 days
Exploratory Urine samples[m]		X	X			X	X			X				X			X
Clinical chemistry[i]	X	X	X			X	X			X				X			X
Hematology[i]	X	X	X			X	X			X				X			X
Blood Sample exploratory analysis		X															X
Urinalysis[k]	X	X	X			X	X			X				X			X
Concomitant medications[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bladder Capacity[p]	X																
Study Drug administration		X				X				X				X			X[v]
Annual updates on patient response and survival																	

Visit Number		12	13
Month (4 weeks) and Day of Month	Withdrawal from Study\ End of treatment [a]	Follow up every 3 months[q]	Long-term follow-up following treatment. Annual data collection[b]
Day relative to initial dosing (days)[s]		M1D1 +M15, +M18, +M21,+M24	
Informed consent			
Medical history (inc. demographics)			
Inclusion/exclusion			
Pregnancy test[c]	X	X	
Physical examination[d]	X	X	
ECG[o]	X	X	
Vital signs[e]	X	X	
ECOG performance status[l]	X	X	
Urinary Symptoms	X	X	
TURBT[r] and endoscopic resection			
Cystoscopy	X	X	
Biopsy[n,q]	X	(X)[g]	
Urine Cytology	X	X	
Blood sample for antibody level[h] assessments	X		
Exploratory Urine samples[m]	X		
Clinical chemistry[i]	X	X	
Hematology[i]	X	X	
Blood Sample exploratory analysis	X		
Urinalysis[k]	X	X	
Concomitant medications[j]	X	X	
Adverse events[j]	X	X	X (Related SAEs Only)
Bladder Capacity[p]			
Study Drug administration		X	
Annual updates on patient response and survival			X

Footnotes to Table 1 Schedule of Study Assessments

a. The assessments detailed in the Withdrawal Visit will only be performed for patients who are withdrawn from treatment

b. After withdrawal from the study, patients will be followed as per clinical practice to determine duration of response, progression to invasive disease, date of cystectomy and survival for up to 5 years (month 60) from first dose

c. Pregnancy test to be performed in women of child bearing potential during screening, prior to commencing treatment, prior to repeat administration, end of month 12 and at Withdrawal visit

d. Physical examination to be performed prior to treatment and should include neurological examination and body weight

e. Vital signs are to be assessed pre- and post-dose. Blood pressure measurements will be made after the patient has been resting supine or semi supine for a minimum of 5 minutes

f. Efficacy assessments (urine cytology and cystoscopy only) must be performed up to 2 weeks (14 days) before re-treatment. Only patients who do not have recurrence of High-Grade disease will receive the next dose

g. Biopsies will be performed if evident or suspicious lesions are seen during cystoscopy at efficacy visits. No instillations are permitted until at least 2 weeks after a biopsy. Biopsies must be done at withdrawal and at the end of month 12 (day 365) for all patients

h. Anti-adenoviral antibodies samples will be taken at M1D1, M4D1, M7D1, M10D1, M12 or at a withdrawal from treatment \study visit. No samples required on withdrawal visits after M12.

i. Hematology and clinical chemistry samples may be taken the previous day to ensure results are available before dosing, up to month 24 See Appendix A for full panel listing

j. Patients will be contacted monthly by phone following each dose to provide information regarding AEs and concomitant medications. Annual follow up will collect Serious Adverse Events only that are considered related

k. Urinalysis on dosing days to be taken pre-dose, up to month 24

l. Eastern Cooperative Oncology Group (ECOG) assessments to be performed pre-dose

m. Urine samples for exploratory work should be taken pre-dose at M1D1, M4D1, M7D1, M10D1, M12 and also post dose at M1D3 and M4D3. Samples should also be collected at a withdrawal visit. No samples required on withdrawal visits after M12.

n. Biopsy slides will be stored centrally for possible correlation to local pathology. Biopsy tissue and/ blocks (if permissible) will also be collected for central storage

o. All ECGs should be performed pre-dose. Clinically significant ECG abnormalities are to be reviewed by the investigator prior to dosing. QTcF measurement will be recorded in the eCRF

p. May be performed at screening if investigator feels it is necessary to determine whether or not a patient can hold an instillation of INSTILADRIN®

q. During the first 12 months of the Long Term Follow Up period for patients having a complete response at month 12, assessments at months 15, 18, 21, and 24 will be performed by cytology, cystoscopy and a biopsy if clinically indicated. Continued dosing at least 14 days from biopsy may take place for patients with no evidence of high grade disease recurrence at month 12, After M24, treatment at 3 monthly intervals may continue for patients who are responding to INSTILADRIN and assessments performed in accordance with usual clinical practice to demonstrate the patient suitability

r. TURBT/fulguration procedure is permitted up 14 to 60 days prior to beginning study treatment

s. Dosing should occur within ±5 days of the target timepoint e.g., M4D1 has a target timepoint of 90 days, therefore the dosing should be scheduled for between day 85 and 95 and the other assessments scheduled to this date.

t. Where day 3 falls on a non working day, the visit can be delayed by up to 2 days.

u. Mthly: Approximately every 30 days, telephone calls after each dose for concomitant medication and adverse event collection

- See Appendix A for full hematology and clinical chemistry laboratory panel
- See Appendix B for Eastern Cooperative Oncology Group performance status (ECOG)
- See Appendix C for Timings of procedures before and after dosing

11.1. Screening

Patients will have been deemed to be BCG unresponsive in accordance with inclusion criterion 4 during the pre-screening review.

Patients are expected to have a confirmed tissue diagnosis of NMIBC made by cystoscopy and biopsy taken at least 5 weeks after the last intravesical dose of BCG. The patient will also have undergone tumor removal/treatment by TURBT, fulguration or endoscopic resection, conducted between 14 and 60 days prior to study treatment.

The screening procedures below will be conducted after the patient has signed the informed consent for the study and up to 28 days prior to the start of dosing. All patients with a signed consent must be entered into the interactive response system (IXRS) system. The Eligibility Enrollment Authorization Form (EEAF) must be submitted to the Medical Monitor prior to dosing for review and approval, ideally 5 days in advance of dosing.

In exceptional circumstances, where procedures are required as part of care or patient safety are repeated, and with prior approval of the Medical Monitor, the screening window maybe extended to allow patients to enter the study.

The following procedures will be carried out during screening:

- Medical history, including all previous, now resolved, significant medical conditions, date of diagnosis, extent of disease, disease staging, radiation and oncology surgical history
- Demographic data, including date of birth, sex, height, and race
- Confirmation patient meets the inclusion/exclusion criteria
- Urine pregnancy test, in women of child bearing potential. A serum pregnancy test may be conducted if clinically indicated
- Physical examination (including neurological examination) and weight
- Vital signs, including blood pressure (BP), heart rate, temperature and respiration rate (RR)
- Resting 12-lead electrocardiogram (ECG)
- Eastern Cooperative Oncology Group performance status (see Appendix B)
- Collection of information regarding urinary symptoms
- Urine cytology
- Bladder Capacity: Assessment made via Investigator medical judgment within 6 months of screening. This will be determined to assess the probability that the patient will be able to retain the dose of INSTILADRIN®. This data will not be recorded on the electronic clinical report form (eCRF)
- Collection of blood sample for clinical chemistry and hematology profile and urine for urine analysis. See Appendix A for full clinical chemistry and hematology panel
- Collection of biopsy slides, tissue and blocks. Slides will be collected and held centrally. Biopsy tissue and blocks will be maintained at the sites and if permissible, collected for exploratory analysis (see Section 12.6.3 for collection details)
- Concomitant medication
- Adverse events

11.2. Treatment Cycles

In addition to the assessments below, AEs and concomitant medications will be recorded every day that the patient attends the clinic.

11.2.1. Pre dose assessments at M1, M4, M7 and M10

The following assessments will be conducted pre-dose on day 1 of month 1, month 4, month 7, and month 10:

- Urine pregnancy test, in women of child bearing potential
- Physical examination (including neurological examination) and weight
- Vital signs (pre and post dose)
- Resting 12-lead ECG performed at any time between 24 hours and 1 hour pre-dose
    - Clinically significant ECG abnormalities are to be reviewed by the investigator prior to dosing. QTcF measurements will be recorded in the eCRF
- Eastern Cooperative Oncology Group performance status
- Collection of information regarding urinary symptoms
- Collection of urine sample for exploratory analysis
- Collection of serum for anti-adenoviral antibody assessments
- Collection of blood samples for clinical chemistry and hematology profile (and exploratory analysis on M1D1 only). Samples may be taken the previous working day to ensure results are available before dosing (samples may be taken on the Friday before a Monday/Tuesday scheduled dosing) See Appendix A for full clinical chemistry and hematology panel
- Urinalysis
- Concomitant medication
- Adverse events
- Preparation and Instillation of INSTILADRIN®

11.2.2. Post Dose Assessments at Day 3 at M1, M4, M7 and M10

The following assessments will be conducted on day 3 of month 1 and month 4:

- Collection of information regarding urinary symptoms
- Resting 12-lead ECG,
    - Clinically significant ECG abnormalities are to be reviewed by the investigator. QTcF measurements will be recorded in the eCRF
- Vital signs
- Collection of blood sample for hematology and clinical chemistry profile. See Appendix A for full clinical chemistry and hematology panel

- Collection of urinary samples for biomarker assessments
- Urinalysis
- Concomitant medication
- Adverse events

The following assessments will be conducted on day 3 at M7 and M10 by telephone
- Concomitant medication
- Adverse events

11.2.3. Efficacy Assessments Procedures – 2 weeks before dosing

Up to 2 weeks before the scheduled dose, the following efficacy assessments will be conducted:

Cystoscopy and cytology will be done on all efficacy assessments. Patients with a positive cytology or with findings on cystoscopy that are suspicious for recurrent cancer will undergo a biopsy(ies) to confirm a response.

- If a biopsy is positive for high-grade bladder cancer, then the patient will be withdrawn from treatment, followed as per protocol schedule of events and offered alternative therapy by their treating physician. See Section 12 for definitions.
- If the biopsy is negative or shows low grade recurrence only, then patients will continue on the treatment regimen as defined in the protocol schedule of events. In these cases, patients should be dosed as soon as feasible. Note: INSTILADRIN cannot be instilled for at least 2 weeks following each biopsy to allow time for the bladder to heal. The medical monitor should be consulted if dosing will be outside the visit window.

Concomitant medications and AEs noted during the efficacy assessments will also be documented

Missing Data

A patient will be deemed not to have achieved a complete response or high-grade-recurrence-free survival if there are insufficient data to determine whether or not a complete response or high-grade-recurrence-free survival has occurred. It will be considered sufficient evidence for a complete response or high-grade-recurrence-free-survival if a subsequent assessment shows a complete response or high-grade-recurrence-free survival and there has been no intermediate treatment for bladder cancer other than INSTILADRIN.

11.2.4. Month 12 procedures

The following assessments will be conducted at the end of month 12 visit (i.e., M1D1 +365 days)

- Urine pregnancy test, in women of child bearing potential
- Physical examination (including neurological examination) and weight
- Vital signs
- Resting 12-lead ECG

  - Clinically significant ECG abnormalities are to be reviewed by the investigator prior to dosing. QTcF measurements will be recorded in the eCRF.
- Eastern Cooperative Oncology Group performance status
- Collection of information regarding urinary symptoms
- Urine cytology
- Cystoscopy and biopsy. At least five biopsies will be obtained (dome, trigone, right and left lateral wall, posterior wall) +/- prostatic urethra in men with positive cytology and prior disease in this region, and will be sent for pathology review at the participating institution.

Collection of biopsy slides, tissue and blocks. Slides will be collected and held centrally. Biopsy tissue and blocks will be maintained at the sites and if permissible, collected for exploratory analysis

- Collection of blood sample for clinical chemistry and hematology profile. Samples may be taken the previous working day to ensure results are available before dosing (samples may be taken on the Friday before a Monday/Tuesday scheduled dosing). See Appendix A for full clinical chemistry and hematology panel.
- Collection of blood and urine sample for exploratory analysis
- Collection of serum for anti-adenoviral antibody assessments
- Urinalysis
- Concomitant medication
- Adverse events

11.2.5. Procedures Post M12

The following procedures will be conducted at 3 monthly intervals (months 15, 18, 21 and 24).

- Physical examination (including neurological examination) and weight
- Vital signs
- Resting 12-lead ECG
- ECOG Performance status
- Collection of information regarding urinary symptoms
- Urine cytology
- Cystoscopy cytology and biopsy(ies) if clinically indicated
- Collection of blood sample for clinical chemistry and hematology profile. Samples may be taken the previous working day to ensure results are available before dosing (samples may be taken on the Friday before a Monday/Tuesday scheduled dosing). See Appendix A for full clinical chemistry and hematology panel
- Urinalysis
- Concomitant medication
- Adverse events
- Preparation and instillation of INSTILADRIN

11.2.6. Procedures Post M24

The following procedures will be conducted at 3 monthly intervals post M24.

- Usual clinical practice assessments
- Serious adverse events considered to be related to INSTILADRIN
- Concomitant medication associated with SAEs
- Preparation and instillation of INSTILADRIN, if considered clinically appropriate by the treating physician

11.3. Withdrawal from Study\End of Treatment visit procedures

The Withdrawal from Study/End of Treatment visit should be performed when a patient has recurrent high-grade disease or withdraws for some other reason. Patients withdrawing at a scheduled visit should have their data recorded in the Withdrawal from Study or end of Treatment visit in the eCRF.

Patients withdrawing between visits should have the following procedures conducted within 30 days of withdrawal. Note: procedures are at the discretion of the investigator, e.g., a patient withdraws soon after a scheduled visit, repeat cystoscopy / biopsy(ies) may not be necessary.

The following procedures should be conducted

- Urine pregnancy test, in women of child bearing potential
- Physical examination (including neurological examination) and weight
- Vital signs
- Resting 12 lead ECG. QTcF measurements will be recorded in the eCRF
- Eastern Cooperative Oncology Group performance status
- Collection of information regarding urinary symptoms
- Urine cytology
- Cystoscopy and biopsy(ies) (if clinically indicated). Biopsy tissue blocks, if obtained, will remain on site
- Collection of blood sample for clinical chemistry and hematology profile
- Collection of serum for anti-adenoviral antibody assessment (not required after month 12)
- Collection of urine sample for biomarker assessment (not required after month 12)
- Urinalysis
- Concomitant medication
- Adverse events

11.4. Long Term Follow-Up Visits - Annual Data Collection

Patients who have withdrawn from treatment at any time after receiving at least one dose of INSTILADRIN will be followed as per usual clinical practice and data collected annually for up to 5 years (Month 60) from the 1st dose.

This data will be used to determine duration of response, progression to invasive disease if known, and survival and to record any dates of cystectomy.

11.5. Blood Sampling Volumes

The approximate volumes of blood that will be drawn from each patient during screening and in the month following treatment are provided for guidance only in the tables below. Institutional procedures for volumes required should be followed where required. See Appendix A for full clinical chemistry and hematology panel.

Table 2: Volume of Blood to be drawn per Patient during Screening

Assessment		Sample Volume (mL)	n of Samples	Total Volume (mL)
Safety/ Efficacy	Clinical chemistry	6	2	12
	Hematology	3	2	6.5
Total for screen			**4**	**18**

Table 3: Volume of Blood to be drawn per Patient in Month 1

Assessment		Sample Volume (mL)	n of Samples	Total Volume (mL)
Safety/ Efficacy	Clinical chemistry	6	2	12
	Hematology	3	2	6
	Antibody	6	1	6
Exploratory	Exploratory analysis at M1D1 only	10	1	10
Total			**6**	**34**

Table 4: Volume of Blood to be drawn per Patient in Month 4

Assessment		Sample Volume (mL)	n of Samples	Total Volume (mL)
Safety/ Efficacy	Clinical chemistry	6	2	12
	Hematology	3	2	6
	Antibody	6	1	6
Total			**5**	**24**

Table 5: Volume of Blood to be drawn per Patient in Month 7, Month 10. Month 12 and every 3 months to Month 24 and Withdrawal from Treatment \ End of Study \visit

Assessment		Sample Volume (mL)	n of Samples	Total Volume (mL)
Safety/ Efficacy	Clinical chemistry	6	1	6
	Hematology	3	1	3
	Antibody	6	1	6
Exploratory	Exploratory analysis up to M12 / withdrawal from treatment /end of study only before month 12	10	1	10
Total			**4**	**25**

12. STUDY ASSESSMENTS

Before being entered into the study, patients will be assessed to ensure that eligibility criteria are met. The EEAF must be submitted to the Medical Monitor for each patient. Patients not meeting the criteria must not be entered into the study. Patients will be assessed by the investigator during the study for safety and efficacy.

12.1. Assessment of Efficacy

12.1.1. Urine Cytology

Pre-dose voided urine will be collected in accordance with the Schedule of Study Assessments, processed, and analyzed at the site for cytology using local procedures.

12.1.2. Cystoscopy

Up to 2 weeks before M4, M7, M10 and at months 12 15, 18, 21 and 24 for patients who have no recurrence of high-grade disease (irrespective of whether the patient receives further therapy), the patient will undergo cystoscopy under appropriate anesthesia.

For the purposes of this study, disease progression is defined as:

12.1.3. Definition of High-Grade Disease

A patient is defined as having a tumor with high-grade histology[4] if on cystoscopy or cytology examination it is shown that there is evidence of:

1. CIS or recurrent high-grade Ta or T1 disease
2. Increase in T stage from CIS or Ta to high-grade T1 (lamina propria invasion)
3. Development of T2 or greater or lymph node (N+) disease or distant metastasis (M1)
4. T1 (lamina propria invasion) or T4 (stroma invasion) of the prostate

12.1.4. Definition of Complete Response (CIS)

A patient has achieved a complete response at an efficacy assessment when urine cytology is negative and there are no lesions on cystoscopy; if random biopsies of the bladder are performed these should be negative.
Once a complete response is achieved, recurrence of low-grade disease only at any subsequent time point is not considered a treatment failure.

12.1.5. Definition of High-Grade-Recurrence-Free Survival

A patient has achieved High-Grade-Recurrence-Free Survival if the patient is alive and a cystoscopy, cytology, and biopsy examination (if clinically indicated or mandated) shows either (a) no evidence of progression to CIS, Ta or T1 lesions or (b) show evidence of Ta or T1 lesions which are evaluated as low-grade.

12.1.6. Definition of Durability

The durability of Complete Response is defined as the time from first observed complete response to treatment failure, where treatment failure is defined as high-grade disease rrecurrence, disease progression or death.

12.2. Safety Assessments

12.2.1. Physical Examination

Routine physical examination should be performed during the course of the study as outlined in the Schedule of Study Assessments and as appropriate for the patient population in this study. The patient's weight and a neurological exam should be measured and recorded as part of the physical examination. A resting 12-lead ECG will be part of this examination.

12.2.2. Vital Signs

For timing of individual measurements, refer to the Schedule of Study Assessments.

On each study day, (BP and heart rate (HR) will be measured using a BP recording device with an appropriate cuff size. The date and time of collection and measurement will be recorded on the appropriate eCRF.

Measurements will be made after the patient has been resting supine or semi-supine for a minimum of 5 minutes.

On each study day, temperature and respiration rate will be measured as per clinical practice.

12.2.3. Subjective Symptomatology

Symptoms reported spontaneously by the patient will be recorded throughout the study period. Symptoms reported will be reviewed by the Investigator and recorded as AEs on the eCRF where this is a change from baseline (i.e., from screening) or a new symptom reported. Patients will be assessed for the presence of AEs up to the end of month 24 or to the safety follow-up visit.

12.3. Priority Order of Study Assessments

At certain time points, several assessments will be required at the same time. In these cases, the following 'priority order' will be followed:

1. Resting 12-lead ECG
2. AEs
3. Concomitant medications
4. Vital signs
5. Samples for clinical chemistry, hematology and urinalysis and Pregnancy test
6. ECOG assessment
7. Urine samples for exploratory analysis
8. Serum for antibody measurements

12.4. Treatment Emergent Adverse Events and Adverse Event Collection

The primary endpoint for safety analysis is treatment emergent AEs.

Following patient consent and completion of the screening medical history assessments, the following events will be recorded in the eCRF as AEs:

- Common terminology criteria for adverse events all grades (including new events post screening and changes from baseline)
- Clinical chemistry, hematology, urinalysis results out of range and considered clinically significant in the opinion of the Investigator. All out of range clinical chemistry, hematology and urinalysis results which meet the definition of an AE of any grade (as defined in the CTCAE) will be reported as AEs
- Abnormal findings during clinical assessments, including physical examination (including neurological examination) and vital signs
- Abnormal ECG readings
- Spontaneous patient reports

Adverse Events will be graded according to the NCI-CTCAEs V4.03.

Adverse events occurring after the initial medical history assessment performed at screening will be listed in the AE section of the eCRF.

Treatment emergent AEs should be captured for those patients who continue to receive treatment until the end of month 24. Any SAEs will be followed until resolution or until stable.

12.5. Laboratory Safety Measurements

Blood samples for determination of clinical chemistry and hematology and urine samples for determination of urinalysis parameters will be taken at the times given in the Schedule of Study Assessments. The hematology, clinical chemistry and urinalysis parameters to be measured are detailed in Appendix A.

The date and time of collection will be recorded on the appropriate eCRF. Hematology and clinical chemistry samples may be taken on the day prior to dosing to ensure results are available before dosing.

Copies of laboratory accreditation certificates and reference ranges will be provided prior to the analysis of the first patient sample.

12.6. Central Lab Collection and Exploratory Samples

12.6.1. Serum for Anti-Adenoviral Antibody Measurements

Six mL of whole blood will be drawn in accordance with the Schedule of Study Assessments for determination of anti-adenoviral antibodies. The blood will be drawn into a red top Vacutainer

tube, allowed to clot at room temperature for 30 minutes and will be centrifuged at 1500*g* for 15 minutes. The resulting serum will be separated into two properly labeled polypropylene tubes and frozen at -70°C until shipped for analysis. Further details are provided in the laboratory manual.

12.6.2. Blood and Urine Samples for Exploratory Analysis

A blood sample will be collected for possible exploratory gene expression profiling and sequencing and other immunological assays. Samples will be collected in accordance with the Schedule of Study Assessments. Whole blood (10 mL) will be drawn into a green top vacutainer tube and will be centrifuged at 1500*g* for 15 minutes. The resulting plasma will be separated into two properly labeled polypropylene tubes and frozen at -70°C until shipped for analysis.

Urine will be collected into a sterile container. Urine samples must be stabilized with the addition of buffer containing 10% bovine serum albumin and 50 mM HEPES. Buffer (2 mL) will be added to each 20 mL of urine as soon as possible after collection of the urine sample. After addition of the stabilization buffer, aliquots will be transferred using sterile pipette tips into cryotubes and the tubes will be frozen at or below -70°C until shipped for analysis.

Further details for blood and urine sample collection are provided in the laboratory manual. Urine for any safety assessments as required will be removed from the collection prior to the addition of the buffer. Urine samples will be stored at each site until instructed to ship to the central depository periodically.

12.6.3. Biopsy slides, Tissues and/Blocks for Analysis

This includes biopsies taken to confirm recurrence of NMIBC after BCG treatment. Slides will be prepared as per local procedures in accordance with the Schedule of Study Assessments from patients who receive INSTILADRIN.

Biopsy slides, biopsy tissue and /blocks will be stored at each site until instructed to ship to the central depository. The site personnel **must** ensure that any slides submitted have the patients' identifiers (name and address etc) redacted before submission.

The plan for these samples will be established separate to this protocol before conducting the analysis.

13. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

13.1. Investigational Product

The investigational product, INSTILADRIN, consists of rAd-IFN and Syn3 for intravesical administration. The product is presented as either rAd-IFN vector concentrate and Syn3 (lyophilized powder for reconstitution in sterile water) to be mixed with a diluent before use (presentation available at study initiation) or a ready-to-use product including both components and the diluent (presentation developed after study initiation). The two presentations contain identical constituents in the same proportions and strengths and are thus interchangeable.

For the purposes of this study, both presentations of the investigational product are termed INSTILADRIN, however, this will not be the name of the potential future marketed product.

Admixture (rAd-IFN + Syn3) Presentation

rAd-IFN is buffered with sodium dihydrogen phosphate hexahydrate and trometamol to a pH of approximately 7.8. Additional ingredients include sucrose, magnesium chloride hexahydrate and glycerol, which act to stabilize the rAd-IFN. The virus concentration is 5.0×10^{11} vp/mL in each vial. rAd-IFN will be prepared as a sterile, single-use liquid viral suspension in a Type 1 glass vial. rAd-IFN is supplied in frozen vials.

rAd-IFN with Syn3 has been used in the Phase I and II trials conducted to date. Syn3 is a polyamide surfactant. Non-clinical studies, described in the Investigator's Brochure, demonstrate that Syn3 facilitates transduction of cells in the urothelium by the adenoviral vector. Syn3 is supplied as a lyophilized powder, 120 mg in a 20 mL, Type 1 glass vial. The powder is reconstituted with 20 mL of sterile water for injection to form a 5.8 mg/mL solution of Syn3 at the clinical site. The Syn3 formulation is buffered with citric acid monohydrate and sodium citrate dihydrate to a pH of approximately 5.7. Additional ingredients include polysorbate 80 and hydroxypropyl-beta-cyclodextrin.

A series of non-clinical studies has been conducted with Syn3 to assess potential effects on the cardiovascular, central nervous and respiratory systems. Studies used the intravenous route to maximize systemic exposure relative to that anticipated following intravesical administration in the clinic. The non-clinical safety profile of Syn3 alone has been evaluated in single dose intravesical, intravenous and intraperitoneal studies in rats, a rising dose tolerance intravenous study in monkeys, an intravesical monkey study, 2-week intravenous studies in rats and monkeys and in bacterial mutagenicity and chromosome aberration assays. In addition, the non-clinical safety profile of rAd-IFN administered with Syn3 has been evaluated in a repeat dose intravesical study in the monkey. These studies are summarized in the Investigator's Brochure and they demonstrate that the non-clinical safety profile of Syn3 alone and in conjunction with rAd-IFN is well characterized and supports its clinical use. This, together with the clinical safety data from the Phase I and II trials, confirm the safety profile of Syn3 and its purpose in the formulation. The rAd-IFN and reconstituted Syn3 are combined with the Diluent to produce an admixture for intravesical administration.

Ready-to-use Presentation

The ready-to-use presentation of the investigational product is an aqueous suspension of rAd-IFN for intravesical administration including the functional excipient Syn3. Additional ingredients include sodium dihydrogen phosphate dihydrate, tromethamine, glycerol, sucrose, magnesium chloride hexahydrate, hydroxypropyl-beta-cyclodextrin, citric acid monohydrate, trisodium citrate dihydrate and polysorbate 80. As stated above, the functional excipient, Syn3, is a polyamide surfactant that has been used with rAd-IFN in the Phase I and II trials conducted to date. Non-clinical studies, described in the Investigator's Brochure, demonstrate that Syn3 facilitates transduction of cells in the urothelium by the adenoviral vector. The suspension has a

concentration of 3 x 10^{11} vp/mL with a fill volume of 20 mL per vial. Each vial contains an appropriate overfill to ensure withdrawal of the correct volume for instillation. The suspension is filled in Type 1 glass vials, closed with a rubber stopper, and sealed with a crimped aluminum seal. The ready-to-use presentation is supplied in frozen vials.

13.2. Investigational Product Preparation

Full details of the preparation of the investigational product are provided in the most recent version of the Pharmacy Manual.

13.2.1. Investigational Product Administration

It is recommended that anticholinergics are used on each dosing day (unless contraindicated) to reduce potential bladder irritation and to prevent product leakage. INSTILADRIN should be administered into the bladder through a urinary catheter; 75 mL will be instilled, and will be left in the bladder for 1 hour. During the dwell time, the patient will be repositioned from left to right, back and abdomen to maximize bladder surface exposure. The patient should be repositioned approximately every 15 minutes. If after dosing, the patient exhibits bladder cramping and/or leakage, turning of the patient may be stopped. All AEs associated with dosing should be recorded in the eCRF.

13.3. Dose Modification

13.3.1. Delays between Treatments

If any toxicity experienced has not recovered to less than Grade 2 in severity as per CTCAE, then treatment may be delayed for a maximum of 14 days.

13.3.2. Dose Reductions

No dose reductions will be permitted. Adjustments to the dwell time or splitting of the dose (e.g., 37.5 mL volume x 2) may be made based upon assessments of local tolerability.

13.3.3. Supportive Care

All patients should continue to receive appropriate supportive care for the treatment of their cancer, including the use of anticholinergic therapeutic agents prior to the instillation of INSTILADRIN if required.

13.3.4. Selection of Doses in the Study

The dose of INSTILADRIN selected for this study is 75 mL at 3 x 10^{11} vp/mL. This dose is based on prior clinical testing of INSTILADRIN in two Phase 1 studies and the most recently concluded Phase II study.

In the initial Phase 1 study titled “A Phase 1 Study of the Safety and Tolerability of Intravesical Administration of SCH 721015 in Patients with Transitional Cell Carcinoma of the Bladder”, five doses of INSTILADRIN were tested including 3x10^{9} vp/mL, 1x10^{10} vp/mL, 3x10^{10} vp/mL, 1x10^{11} vp/mL and 3x10^{11} vp/mL. Patients received only one instillation of INSTILADRIN unless the patient had a CR at day 90. They then had the option of a second dose. Four patients were

instilled with $3x10^{11}$ vp/mL. Efficacy was observed at this dose. The dose was well tolerated and while each patient reported at least one treatment-emergent AE, all were of Grade 1 or Grade 2 in severity.

In a Phase 1B investigator initiated study titled "Intravesical administration of SCH 721015 (IFN alpha) in admixture with SCH 209702 (Syn3) for the Treatment of BCG Refractory Superficial Bladder Cancer", the highest dose of $3x10^{11}$ vp/mL from the initial Phase I study was used to treat seven patients. Patients received two doses of INSTILADRIN, one each on day 1 and day 4 of the study. Of these seven patients, two had a CR and there were no serious side effects observed in the study.

The efficacy and safety of INSTILADRIN in the Phase II study was tested in 40 patients using the two highest doses from the initial Phase I study, $1x10^{11}$ vp/mL and $3x10^{11}$ vp/mL. In this study, 19 patients received the highest dose tested of $3x10^{11}$ vp/mL. Patients exhibiting a CR at month 12 had received a maximum of four doses of INSTILADRIN. At this dose, there were seven CR and no significant safety issues.

In total, 30 of a total of 64 patients in these studies have been treated with a $3x10^{11}$ vp/mL dose of INSTILADRIN. Patients had either a single dose, two doses, or four doses of INSTILADRIN in the three clinical studies. This dose has demonstrated efficacy in this patient population with an acceptable safety profile and no dose limiting toxicities.

13.4. Packaging and Labeling

13.4.1. Primary and Secondary Label

The primary and secondary labels for the investigational product (components and diluent, as applicable [Section 13.1]) will contain the following information:

- Pharmaceutical dosage form
- Quantity per container
- Manufacturing lot number
- Date of manufacture
- Storage conditions
- Study Number
- "New drug limited by Federal (or United States) law to Investigational Use"
- Name and location of manufacturer
- Expiry date

13.5. Storage

The investigational product must be stored in a safe and locked place with no access for unauthorized personnel.

Vials containing rAd-IFN (i.e., vials of rAd-IFN and ready-to-use product) must be stored frozen below -60°C (-76°F).

Prior to use, the investigational product should be thawed protected from light under ambient temperature or refrigerated at 2-8°C (35-46°F). Once the thawing procedure is initiated, the vials may be stored 8 hours at ambient temperature or 24 hours at 2-8°C (35-46°F).

The vials of Syn3 and Diluent must be stored at a nominal 2–8°C (35-46°F).

13.6. Replacement of Unusable Investigational Product

Additional doses of medication will be supplied to each site at the beginning of the study and upon request for patient re-dosing. In cases where a vial is broken or unusable, the vial should be replaced as detailed in the Pharmacy Manual.

13.7. Accountability

Management of INSTILADRIN doses will be performed centrally using an Interactive cross communication (X) Response System (IXRS/ IRT). At the Screening visit, the investigator, or other site personnel under the direction of the investigator, should contact or access the IXRS to register the patient, obtain the patient ID, and record the patient's initials, date of birth or age, gender, and initial screening date. Upon confirmation of a patient's eligibility, the investigator, or designee, will contact the IXRS to register the patient as either eligible or ineligible. At each visit (month 1, 4, 7, 10 and 12), the investigator, or designee, should contact the IXRS to record the patient's visit and status. At the End-of-Treatment/End of Study, the patient's visit and status should also be recorded using the IXRS.

The Clinical Research Associate will be responsible for performing drug accountability for INSTILADRIN by ensuring that the IXRS system is up to date and completed by the site personnel responsible and reconciled with the site accountability logs.

The medication provided for this study is for use only as directed in the protocol. It is the Investigator/Institution's responsibility to establish a system to ensure that:

- Deliveries of such products are correctly received by a responsible person
- Such deliveries are recorded
- Study treatments are handled and stored safely and properly as stated on the label
- Study treatments are only dispensed to study patients in accordance with the protocol
- Any unused product is destroyed following receipt of permission for destruction from Ferring

INSTILADRIN supplies must be stored appropriately under the recommended storage conditions. The recommended storage conditions are detailed in the pharmacy manual.

NOTE: If there is any deviation from the specified storage conditions, the site must not dispense the affected supplies (which should be placed in quarantine) and must contact Ferring to determine if the affected supplies can be used.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed stock. Records of usage should include the identification of the person to whom the study treatment was dispensed and the quantity and date of dispensing. This record is in addition to any drug accountability information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery must be signed, preferably by the Investigator or a pharmacist, and copies retained in the Investigator Site File.

All unused medication should be destroyed at site following appropriate drug accountability procedures and confirmed by the monitor.

13.8. Biosafety Precautions

All biosafety precautions and procedures required by the Institutional Biosafety Committee and local regulatory authorities will be observed. Patient care will be administered by health care personnel trained in the administration of clinical research protocols and clinical biosafety procedures. The Center for Disease Control has not taken an official position on pregnant or immunosuppressed health care workers. All individuals handling rAd-IFN or caring for patients receiving rAd-IFN must use biosafety Level 2 precautions. Individuals who are immunosuppressed or immunodeficient may place themselves at increased risk upon use or potential exposure to biological agents. It is suggested that individuals in these categories consult with their local physician and/or Institutional Biosafety Committees to determine an appropriate course of action.

13.9. Patient Care and Handling of rAd-IFN Product and Patient Specimens

Universal precautions must be observed in the handling of rAd-IFN product; clinical specimens (e.g., patient blood, tissue, body fluids); and materials or equipment contaminated by these substances following treatment with rAd-IFN.

This includes:

- Wear gloves and wash hands after removing them and before exiting room
- Mucous membrane splash protection
- Needle and sharps precaution and disposal
- Use of a biological safety cabinet to perform any procedures which may result in the generation of an aerosol (Class II/A, II/B1, II/B2, or II/B3 cabinets or at least equivalent should be used)
- Decontaminate biosafety cabinet and other work surfaces with an effective disinfectant upon completion of work with rAd-IFN. Decontaminate overt spills, splashes, or other contamination immediately

- Cleaning/decontamination of patient bedding according to procedures used for blood or body fluid soiled laundry
- Transport and storage of rAd-IFN and patient specimens (blood, tissue and urine) must be in a closed leak proof container
- Disposal of rAd-IFN product and all patient specimens must follow decontamination procedures of the study institution (e.g., autoclave, incineration)

13.10. Decontamination of rAd-IFN Product Spills

Close cabinet sash and immediately initiate the following chemical disinfection procedures:

- Allow aerosol to settle for 15 minutes
- Wearing appropriate protective equipment (eye protection, gloves) place absorbent material onto liquid spill. Pour disinfectant (5% bleach (sodium hypochlorite or hydrogen peroxide disinfectant), or hospital grade disinfectant) onto absorbent
- Allow 20 to 30 minutes contact time. Remove absorbent and contained liquid
- Dispose of absorbent and all other materials used in spill cleanup by autoclave or other appropriate measures

13.11. Accidental Product Exposure

- **Needle Stick:** Wash with soap and water and obtain medical attention
- **Splash to Eyes, Mucous Membranes:** Rinse with water or 1% sterile saline solution for at least 15 minutes and obtain medical attention
- **Inhalation:** Obtain medical attention

13.12. Advice for Patients

Based on results of intracystic studies in monkeys which demonstrated that the majority of monkeys no longer had detectable virus in the urine at 7 days post-dose, patients should be instructed after each instillation to add 4 ounces of bleach (sodium hypochlorite or hydrogen peroxide disinfectant) to the toilet bowl prior to voiding and wait 15 minutes before flushing the toilet. This should be done for the first 7 days after each treatment.

13.13. Treatment Allocation

Patients will be assigned a screening number by the site. The Investigator or designated staff will be responsible for allocating and recording patient numbers at the time of screening. This will include the site number (3 digits) followed by patient number (3 digits).

Example: **Patient: 001– 001**

Denotes the following information:

- Site number 001
- First patient screened at site 001

13.14. Blinding and Procedures for Un-blinding the Study

This is an open-label study and there are no blinding/un-blinding procedures.

13.15. Prohibited and Permitted Concomitant Medications/Treatments

No non-specified systemic anti-cancer therapy or radiotherapy is to be used during the study.

The patient must not have taken the following medications for the length of time specified prior to Screening, or while treatment with INSTILADRIN® is ongoing:

Table 6: Prohibited Medications

Prohibited Medications Prior to Screening, and During the Study	Washout Period
Immunosuppressive Therapy	3 months prior to screening
Investigational drugs	30 days prior to screening
Intravesical therapy	Intravesical therapy within 8 weeks prior to beginning study treatment with the exception of: • Cytotoxic agents (e.g., Mitomycin C, doxorubicin and epirubicin) when administered as a single instillation immediately following a TURBT procedure which is permitted between 14 to 60 days prior to beginning study treatment • Previous intravesical BCG therapy, which can be given at least 5 weeks before the diagnostic biopsy required for entry into the study

All prescription, non-prescription, or over-the-counter medications including herbal remedies given to, or taken by, the patient at entry and during the study must be clearly documented on the appropriate eCRF.

Any medication considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator(s). Anti-cholinergic drugs are permitted during the instillation procedure.

Use of inhaled corticosteroids is permitted during the study. Patients who have received oral or injectable corticosteroids for the treatment of other conditions within 3 months of receiving the first dose of INSTILADRIN are to be discussed with the Medical Monitor.

During the treatment phase, patients who require treatment with corticosteroids will not be withdrawn from the study.

13.16. Dosing Error Instructions (Overdose)

Any dose of study treatment in excess of that specified in this protocol is considered to be an overdose. Regardless of presence or absence of clinical symptoms, an overdose must be reported as an AE to the contract research organization (CRO) in the same timeframe as any SAE. Signs and symptoms of an overdose that meet any SAE criterion also must be reported as an SAE in the appropriate time frame and documented as clinical sequelae to an overdose. Treatment of AEs associated with overdose should be supportive for the underlying symptoms.

14. COMPLETION OF THE STUDY

The primary analysis of the study will be performed when the required number of evaluable CIS (with or without concomitant high-grade Ta or T1 papillary disease) patients have either completed up to the month 12 assessment or have been withdrawn from the study and undergone a withdrawal from treatment\study assessment. Patients may continue dosing and have follow up visits unless shown to have evidence of high-grade disease progression. Long term survival data and information regarding invasive disease and cystectomy will be collected from all patients that received at least one dose of INSTILADRIN for up to 5 years (month 60) from first dose.

15. EVALUATION, RECORDING AND REPORTING OF ADVERSE EVENTS

15.1. Definitions

15.1.1. Adverse Event

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal finding in laboratory tests or other diagnostic procedures), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug and from any route of administration, formulation, or dose, including an overdose.

All AEs which arise during the conduct of this study will be recorded, including pre-existing medical conditions (other than natural progression of the disease being studied) judged by the Investigator or patient to have worsened in severity or frequency or changed in character.

An AE can also be a complication that occurs as a result of protocol mandated procedures (e.g., invasive procedures such as biopsies).

15.1.2. Serious Adverse Event

An AE is considered serious, if in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE

  An AE is considered “life-threatening” if in the view of either the Investigator, or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death

- Inpatient hospitalization or prolongation of an existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious when, based on the appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE. Examples of such medical events are intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or development of drug dependency or drug abuse

The following events do not need to be reported as SAEs

- Disease recurrence
- Treatment failure
- Hospitalization for planned procedures (cystoscopies and sample collection) unless hospitalization is prolonged due to an AE

15.2. Adverse Event Reporting and Description

All treatment-emergent AEs (AEs occurring or worsening after the start of study treatment) either observed by the Investigator or one of his or her medical collaborators, or reported by the patient spontaneously, or in response to the direct question below, will be recorded in the patient notes and in the AEs section of the patient's eCRF.

New AEs will be recorded from patient consent (following the screening assessment of the patient's baseline medical status) until month 24 or withdrawal from Study/end of treatment (see Section 11.3). Screening procedure-related AEs that occur before the start of study treatment will be recorded. If a patient or a patient's partner becomes pregnant, follow requirements stipulated in Section 15.2.3.

Whenever possible, the Investigator should group signs and symptoms (including laboratory tests or other results of diagnostic procedures) into a single diagnosis under a single term. For example, cough, rhinitis, and sneezing might be reported as "upper respiratory infection" or a pulmonary infiltrate, positive sputum culture and fever might be reported as "pneumonia."

In an attempt to optimize consistency of AE reporting across centers, the patient must be asked a standard, general, non-leading question to elicit any AEs (such as "Have you had any new symptoms, injuries, illnesses since your last visit?").

For any change in laboratory results, vital signs, physical examination, radiologic exam or ECG measurements that arises after the baseline assessment (i.e., screening), the Investigator will decide if the finding or result is clinically significant and will determine if it is necessary to repeat the evaluation. If the evaluation is judged to be clinically significant, it must be recorded as an AE, and if applicable, reported as an SAE. Clinically significant laboratory findings include any

lab for which a therapeutic intervention is initiated to correct the abnormality unless the laboratory finding is part of the disease state or disease progression.

Investigators will assess the status of previously reported, and occurrence of new AEs and SAEs at all patient evaluation time points during the study.

15.2.1. Severity

Definitions found in the CTCAE V4.03 will be used for grading the severity (intensity) of AEs. The CTCAE V4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a patient experience any AE not listed in the CTCAE V4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the patient's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the patient, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the patient's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the patient to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in patient death

15.2.2. Relationship to Study Treatment (Suspected Adverse Reactions)

All AEs/SAEs must be assessed for relationship to study drug or if applicable, to study procedure.

If an AE/SAE occurs before the initiation of the investigational product, it should be reported but further consideration is needed to confirm whether it is related to a study specific procedure (e.g., bleeding or local infection after skin punch biopsy). Those events will be recorded in the study database but will not be part of the treatment- emergent AE analysis.

To ensure consistency of AE and SAE causality assessments, Investigators should apply the general guideline shown below. Multi-drug regimens should have a causality assessment of each component to aid in analysis.

Related (Suspected Adverse Reaction)	A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE such as a plausible temporal relationship between the onset of the AE and administration of the drug; and/or the AE follows a known pattern of response to the drug; and/or the AE abates or resolves upon discontinuation of the drug or dose reduction and, if applicable, reappears upon re-challenge. Further examples of type of evidence that would suggest a causal relationship between the drug and the AE: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., acute myocardial infarction in a young woman) • An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group that in a concurrent or historical control group
Not related (Not Suspected)	Adverse events that do not match the above

15.2.3. Pregnancy and Abortion

Report any pregnancy that occurs in a patient or patient's partner from the time of consent to 60 days after the last dose of study drug. Record any occurrence of pregnancy on the Pregnancy Report Form and submit to the [redacted] Clinical Safety within 24 hours of learning of the event. Outcomes of the pregnancy, such as birth of the baby or spontaneous abortion etc will be collected. Abortion and the reason for it, whether therapeutic, elective or spontaneous, will be reported as an SAE.

A patient must immediately inform the Investigator if the patient or patient's partner becomes pregnant from the time of consent to 60 days after the last dose of study drug. Any female patients receiving INSTILADRIN who becomes pregnant should be withdrawn from the study. The Investigator should counsel the patient, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

15.3. Reporting and Evaluation of Serious Adverse Events

15.3.1. Reporting Requirements for Serious Adverse Events

All SAEs regardless of causality will be reported by the Investigator to [redacted] Clinical Safety for all patients during treatment as per the schedule. Patients withdrawn from treatment for any reason and experiencing SAEs that are considered related to study drug or study procedures must also be reported and will be entered into the safety database for up to 5 years (month 60) from first dose. These events will be entered and followed in the clinical database until either resolution or the study database is finally closed.

All SAEs (initial and follow-up information) will be reported via the eCRF AE page within 24 hours of the discovery of the event. The [redacted] Clinical Safety may request follow-up and other additional information from the Investigator (e.g., hospital admission or discharge summary, laboratory results). If the eCRF is not assessable for SAE reporting, the [redacted] SAE hotline must be contacted and the SAE completed using the paper form and submitted using the details below

[redacted] Clinical Safety
[redacted] SAE information: Telephone: [redacted] Facsimile: [redacted] E-mail: [redacted]

All deaths should be reported with the primary cause of death as the AE and SAE term, as death is the outcome of the event, not the event itself. If an autopsy was performed, the primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to [redacted] Clinical Safety, as outlined above.

If INSTILADRIN is discontinued, temporarily suspended or dose reduced because of an SAE, this information must be included in the SAE report.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that qualify for mandatory expedited reporting to regulatory authorities where the SAE is suspected to be caused by the study drug or study regimen and is considered unexpected (i.e., not defined as expected in the current Investigator's Brochure, or clinical study protocol). In this case, [redacted] Clinical Safety will forward a formal notification describing the SAE to all Investigators. Each Investigator must then notify his or her Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of the SAE as required by local regulatory authorities and in accordance with IRB or IEC policy.

15.4. Stopping Criteria

The Stopping Criteria for the study will be based on the occurrence of clinically significant and causally related serious adverse reactions higher than Grade 3 (as defined by the CTCAE criteria)

which are life-threatening and require urgent medical intervention. A Safety Monitoring Committee will be in place for the study and will meet at regular intervals or as events dictate to review any emerging safety data. If serious adverse reactions as highlighted do occur, then the Safety Monitoring Committee will be consulted with respect to stopping the clinical trial.

15.5. Safety Management Committee

The Safety Management Committee will comprise as a minimum, the Ferring Medical Monitor and an independent reviewer to be selected by the Sponsor, and other Ferring representatives. The Committee will meet at regular intervals, and as events dictate, to review emerging safety data. The Committee will, as a minimum, review data from

- The month 1 safety data from the first 20 patients treated in the study
- The month 1 safety data from the first 40 patients treated in the study
- The month 1 safety data from the first 60 patients treated in the study

The Safety Management Committee will be responsible for monitoring safety throughout the study and the composition of the Safety Management Committee is described in the Safety Management Committee plan.

16. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

16.1. Statistical Considerations

Detailed statistical analysis information will be provided separately in the Statistical Analysis Plan (SAP). The SAP will be finalized before the first patient is entered into the study. Any deviations to the planned analyses specified within the SAP, will be justified in writing and presented within the final Clinical Study Report (CSR).

Changes to the analyses specified in this protocol need not trigger a protocol amendment provided they are described in the SAP or CSR as appropriate.

Where continuous data are summarized, the following summary statistics will be presented: number of observations (n), mean, standard deviation (SD), minimum, first quartile, median, third quartile and maximum. For categorical data, a frequency table (showing n and %) replaces this summary.

Where the change from baseline is to be calculated, the baseline is the last planned assessment before the first administration of study medication, unless otherwise specified.

The analyses will be performed using SAS® version 9 or later. The reporting of the analyses will conform to the relevant International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

16.2. Analysis Sets

The **safety analysis set** comprises all patients who have received at least one dose of INSTILADRIN.

The **efficacy analysis set** is identical to the safety analysis set.

The **per protocol analysis set** comprises all patients who had no major protocol violation and either:

- completed their twelve month assessment

or:

- withdrew before twelve months because of disease recurrence or progression, death, AE related to the disease or treatment, or lack of tolerability.

The principal analysis set for the analysis of efficacy data is the **efficacy analysis set**. Supportive efficacy analyses may be performed using the **per protocol analysis set.**

16.3. Demographic and Other Baseline Characteristics

Demographic and disease characteristics will be listed and summarized. Other baseline characteristics will only be listed.

16.4. Statistical Methods for Efficacy Parameters

All efficacy assessments will be based on the efficacy analysis set.

Complete Response (CIS)

The primary efficacy endpoint is: rate of complete response at any time in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease) who show a complete response at any time. The proportion of patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease) achieving a complete response at any time will be reported together with a two-sided 95% Clopper-Pearson CI for the proportion.

The primary part of the study will be complete when all evaluable patients have either completed the month 12 assessment or have been withdrawn from the study and undergone a safety assessment.

Durability of complete response is calculated from the first post-treatment assessment at which complete response is observed to treatment failure, where treatment failure is defined as high-grade disease recurrence, disease progression or death.

The durability of complete response in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease) who achieve a complete response at any time will be presented.

Kaplan-Meier methods will be used to provide estimates of median duration and of the probability of duration at 3 monthly intervals. The confidence interval for median durability is considered substantive if the outcome with respect to the primary endpoint is successful: under other circumstances the confidence interval for median durability is considered indicative.

High-Grade Recurrence Free Survival

The proportion of patients with high-grade Ta or T1 papillary disease (without concomitant CIS) achieving high-grade-recurrence-free survival will be reported together with a two-sided 95% Clopper-Pearson CI for the proportion.

High-grade-recurrence-free survival in patients with high-grade Ta or T1 papillary disease (without concomitant CIS) in patients with CIS (with or without concomitant high grade Ta or T1 papillary disease), and in both cohorts combined will be presented using Kaplan-Meier methods to provide estimates of median duration and of the probability of duration at 3 monthly intervals.

Incidence of and Time-to-Cystectomy

The proportion of patients undergoing cystectomy within 12 months within 2 years and within 5 years will be reported together with an exact 95% CI for the proportion.

Cystectomy-free survival will be summarized by Kaplan-Meier methods. The Kaplan-Meier estimate of the median time to cystectomy or death from any cause and the estimated probability of cystectomy or death from any cause at 3 monthly intervals will be presented. If cystectomy is not performed before end of follow up for alive patients then cystectomy-free survival will be censored at the last contact date with known status for cystectomy before the end of follow-up. Plots of Kaplan-Meier curves will be presented

Overall Survival

Overall survival is defined as the time from first dose of INSTILADRIN to death. If death does not occur before end of follow-up then overall survival will be censored at the last time known to be alive before the end of follow-up.

Overall survival will be summarized by Kaplan-Meier methods.

Missing Data

A patient will be deemed not to have achieved a complete response or high-grade-recurrence-free survival if there are insufficient data to determine whether or not a complete response or high-grade-recurrence-free survival has occurred. It will be considered sufficient evidence for a complete response or high-grade-recurrence-free-survival if a subsequent assessment shows complete response or high-grade-recurrence-free survival and there has been no intermediate treatment for bladder cancer other than INSTILADRIN.

Missing data for other endpoints will be handled conservatively. If appropriate, sensitivity analyses will be performed.

Exploratory Analyses

Exploratory analyses may be performed at the Sponsor's discretion.

Exploratory analyses may include, but are not limited to:

- Investigation for correlation between pre- and post-treatment tissue levels of PD-L1 and, if feasible, PD-1 and CDK-N2A, and treatment outcomes
- Evaluation of all treated patients on the efficacy endpoints
- Evaluation of the effect of baseline demographics and disease characteristics on the efficacy endpoints

16.5. Statistical Methods for Pharmacodynamics Parameters

Pharmacodynamics data will be listed and summarized by dose and time point.

16.6. Statistical Methods Safety Parameters

All safety and tolerability assessments will be based on the safety analysis set.

Vital signs, hematology, clinical chemistry and urinalysis data will be listed by dose and time point.

The number and percentage of patients reporting treatment-emergent AEs will be tabulated by preferred term and system organ class, and summarized by both CTC grade and relationship to study medication. All AEs commencing prior to dosing with study medication (and not worsening during dosing) will be excluded from the tabulation but will be fully listed. Adverse events that have missing onset dates will be considered to be treatment-emergent, unless the stop date is known to be prior to the first administration of the study medication.

All SAEs will be listed separately.

Study drug exposure will be summarized and listed.

The incidence and reasons for study drug interruptions and withdrawals will be summarized and listed.

Laboratory assessments, concomitant medications and physical examinations will be summarized and listed.

16.7. Estimation of Sample Size and Operating Characteristics of Design

The observed complete response rate at any time in CIS +/- papillary subjects in the Phase II study was equal to 50%. Assuming the Phase III study retains 87.5% of that efficacy, the true

response rate will be 43.75%. One hundred CIS +/- papillary subjects provide 90% power to reject the hypothesis that the true response rate is 27% at a one-sided alpha of 2.5%. Thirty-seven responding subjects (response rate of 37%, two-sided 95% Clopper-Pearson CI = [27.5%,47.3%]) are sufficient to reject the hypothesis.

16.8. Statistical Reports and Timing of Analyses

The Final Statistical Report will be written after all patients have completed their M12 assessment or have withdrawn before then.

A follow-up Statistical Report will be written after the last patient has completed the long term follow up.

An administrative analysis may be performed to support discussions with the Regulatory Agencies after all patients have completed their M3 assessment or have withdrawn before then. The conduct of the study will not be changed as a result of this analysis.

17. QUALITY ASSURANCE

17.1. Data Recording

Data will be collected using an eCRF. For each patient enrolled, an eCRF must be completed and signed by the principal investigator or sub-investigator within a reasonable time period after data collection. All data collected in the eCRF will be entered into a validated computerized clinical data management system.

Laboratory data received electronically from a central laboratory will be merged with the database and not entered from the eCRF. Paper copies of laboratory data received will be entered into a validated computerized clinical data management system.

Analysis of the data will only be performed after all queries have been resolved using appropriate software for analysis.

The eCRF will not be regarded as source for any data point.

17.2. Study Monitoring

The CRO will be responsible for the monitoring of the study.

The study monitor will review the progress of the study on a regular basis to ensure adequate and accurate data collections. Monitoring site visits to review eCRF, patient case notes, administrative documentation including the Investigator Site File and frequent telephone communications with site will be performed throughout the study.

At each study monitoring visit the Investigator will make available all records pertaining to the study. To allow sufficient time to assemble documentation for the study monitor, monitoring visits will be confirmed in advance of planned visits.

Communications, between the Sponsor, designated study representative, and Investigator should be documented for the study file.

17.3. Clinical Study Audit

The Sponsor or Sponsor representative or external regulatory agency may at any time during or after completion of the study conduct a Good Clinical Practice (GCP) audit.

Prior notice will be given to each site selected for audit in advance of a planned GCP audit.

17.4. Publication Policy

It is the intent of all parties that the results of the Study be published in a timely manner consistent with academic standards and with due consideration given to the protection of intellectual property rights. Accordingly, each Participating Institution will be free to publish or present the results of research performed by it consistent with the relevant terms of its Clinical Trial Agreement with the Sponsor.

The original eCRFs and all data generated during the study under this protocol will become the property of the Sponsor.

Any proposed publication or presentation (including a manuscript, abstract or poster) for submission to a journal or scientific meeting should be sent to the Sponsor for review at least 1 month prior to submission (7 days for abstracts). Sponsor may delay such submission by a maximum of 90 days. No single center or groups of centers may publish individually. The Sponsor's comments on the proposed publication shall be considered in good faith by the authors. Sponsor may delay such submission by a maximum of 60 days if it reasonably believes that publication of results may compromise its intellectual property rights or else insist that such information or data is removed from the proposed publication. Publication of the results will not include confidential information without the permission of the Sponsor.

The Sponsor may announce quality assured summary data in order to comply with Financial Regulatory Authorities, whilst ensuring so far as possible that such announcements will not compromise the investigator’s ability to publish the data in appropriate scientific forums.

Nothing herein shall be construed to restrict disclosure of results as reasonably necessary to prevent an immediate hazard to the safety, rights or welfare of patients or the public and/or for regulatory compliance.

Sponsor will register the Study on www.clinicaltrials.gov or a substantially equivalent website. Additionally, Sponsor will be exclusively responsible for updating and/or amending such registration as appropriate.

17.5. Clinical Study Report

The results of the study will be presented in an integrated CSR according to GCP.

17.6. Data Retention and Availability

The Investigator is required to maintain all study documentation, including regulatory documents, copies of eCRFs, signed informed consent forms, and records for the receipt and disposition of study medications, for a period of 2 years following approval date of a New Drug Application for the drug, or until 15 years after completion of the study, whichever is later.

During the study, the Investigator must make study data accessible to the Sponsor, IRB and the Food and Drug Administration (FDA). A file for each patient must be maintained that includes the signed informed consent form and copies of all source documentation related to that patient. The Investigator must ensure the availability of source documents from which the information on the eCRF was derived.

17.7. Study Termination

The study may be terminated prior to completion of the specified number of patients at the request of the Sponsor, the Investigator, or by mutual agreement. Conditions that may warrant early termination include, but are not limited to, insufficient adherence to the protocol requirement, the discovery of a significant, unexpected and unacceptable risk to the patients, attainment of study objectives, or at the discretion of the Sponsor. Procedures for terminating the study will be agreed upon by both the Sponsor and the Investigator.

18. INSTITUTIONAL REVIEW BOARD REVIEW

The final study protocol and patient informed consent form will be approved by the IRB for sites in the US. Approval will be received in writing before initiation of the study.

Any changes to the study design will be formally documented in protocol amendments and approved by the IRB prior to implementation, except in the case of changes made to protect patient safety, which will be implemented immediately.

18.1. Ethical Conduct of the Study

The study will be conducted according to ICH, GCP, the Declaration of Helsinki, IRB and in accordance with the U.S. Code of Federal Regulations on Protection of Human Rights (21 CFR 50).

Clinical Trial Authorization will be obtained prior to initiation of the study from the U.S. FDA.

18.2. Informed Consent

The principles of informed consent in the Declaration of Helsinki, in ICH Good Clinical Practice and in US 21 CFR Part 50 (Protection of Human Patients) will be implemented before any protocol-specified procedures or interventions are carried out.

A signed informed consent form (ICF) shall be obtained from each patient or the patient's legally acceptable representative prior to entering the study. The Investigator is responsible for obtaining written informed consent from the patient or the patient's legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any study medications are administered. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB.

Patients will also be asked to consent to allow the Sponsor, Sponsor representative or external regulatory auditor to review their medical records to confirm compliance with GCP.

The patient must give consent to the main information sheet in order to participate in the study. All information sheets and consent forms will be provided in the English language.

The acquisition of informed consent should be documented in the patient's medical record and the ICF should be signed and personally dated by the patient or the patient's legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily by the Investigator). The original signed ICF should be retained in the Investigator Site File and a copy of the signed consent should be provided to the patient or the patient's legally acceptable representative prior to participation in the trial.

18.3. Investigator Responsibilities

By signing the Form FDA 1572 the Investigator agrees to:

1. Conduct the study in accordance with the protocol and make changes only after notifying the Sponsor, except to protect the safety, rights or welfare of patients
2. Personally conduct or supervise the study (or investigation)
3. Inform any patients enrolled in the study that the drug is being used for investigational purposes
4. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet Federal guidelines, as stated in 21 CFR, parts 50 and 56
5. Report to the Sponsor any AEs that occur during the course of the study, in accordance with 21 CFR 312.64, as well as ICH guidelines
6. Have read and understood the Investigator Brochure, including potential risks and side effects of the drug
7. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments
8. Maintain adequate and accurate records, in accordance with 21 CFR 312.62 and to make those records available for inspection with the Sponsor, their designated representative, the prostate-specific antigen or any agency authorized by law
9. Ensure that an IRB that complies with the requirements of 21 CFR 56 will be responsible for initial and continuing review and approval of the clinical study

10. Report promptly to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to patients or others (to include amendments and IND safety reports)
11. Not make any changes in the research study without approval, except when necessary to eliminate hazards to the patients
12. Comply with all other requirements regarding the obligations of the Clinical Investigators and all other pertinent requirements listed in 21 CFR 312

18.4. Patient Data Protection

The Written ICF will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by Ferring will be identified by patient number/study code. The Written ICF will also explain that for data verification purposes, authorized representatives of Ferring, a regulatory authority, an IRB may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

For study sites or where patients' protected health information (patient data) will come into the US through a covered entity (e.g., Central Lab/Reader), the Written ICF will incorporate, or be accompanied by, a separate document incorporating Health Insurance Portability and Accountability Act (HIPAA) compliant wording by which patients authorize the use and disclosure of their Protected Health Information by the Investigator and by those persons who need that information for the purposes of the study.

19. REFERENCES

1. Pashos CL, Botteman MF, Laskin BL, et al. Bladder cancer epidemiology, diagnosis, and management. Cancer Pract 2002;10:311–322.

2. Catalona WJ, Hudson MA, Gillen DP, et al. Risks and benefits of repeated courses of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. J Urol 1987;137:220–224.

3. Lerner SP, Dinney C, Kamat A et al. Clarification of bladder cancer disease states following treatment of patients with intravesical BCG. Bladder Cancer 2015; 1: 29–30.

4. Montrioni, R. and Lopez-Beltran, A. The 2004 WHO Classification of Bladder Tumours, A Summary and Commentary. Int J Surg Path 2005; 13:143–153.

5. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649–655.

20. APPENDIX A - LABORATORY SAFETY MEASUREMENTS

The list of hematology, clinical chemistry and urinalysis parameters to be measured are detailed below:

Clinical chemistry:

Sodium, Potassium, Chloride, Bicarbonate (HCO3-), Phosphate, Magnesium, Calcium, Glucose, BUN, Creatinine, Albumin, Protein, Alkaline Phosphatase, Lactate Dehydrogenase (LDH), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Gamma-Glutamyltransferase (GGT), Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Cholesterol and Triglycerides

Hematology:

Hemoglobin, Hematocrit (HCT), Red Blood Cells (RBC), White Blood Cells (WBC), Platelets, Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils, Reticulocytes

Including the following coagulation assessments: Prothrombin Time (PT), Partial Thromboplastin Time (PTT), International Normalized Ratio (INR)

Urinalysis:

Specific Gravity, pH, Protein, Glucose, Ketones, Blood, Leukocytes, Nitrites, Bilirubin, Urobilinogen.

21. APPENDIX B – ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol:
Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-655.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

22. APPENDIX C – STUDY ASSESSMENTS – ALLOWABLE WINDOWS

The allowable time windows for the following study assessments are listed in the table below:

Study Assessment	Allowable timeframe window
Pregnancy testing	Prior to dosing on dosing days
Physical examination	Prior to dosing on dosing days
Vital signs	Pre-dose: Up to 2 hours prior to dosing Post-dose: after dosing, during that specific visit
ECG	Pre-dose: performed at any time between 24 hours and 1 hour pre-dose
ECOG performance status	Prior to dosing on dosing days
Urine cytology and Cystoscopy	Up to 2 weeks prior to re-treatment to ensure results available prior to planned dosing.
TURBT/ fulguration and endoscopic resection	Between 14 and 60 days prior to the beginning of study treatment (first dose)
Blood sample for antibody levels	Performed at any time between 24 hours and 1 hour pre-dose
Blood and urine sample for exploratory assays	Performed at any time between 24 hours and 1 hour pre-dose
Safety labs (clinical chemistry, and hematology)	Pre-dose: May be taken on day -1 prior to dosing to ensure results are available pre-dose
Safety labs (urinalysis only)	Performed at any time between 24 hours and 1 hour pre-dose

Patients will be contacted by phone monthly (approx. every 30 days) following D1 treatments on months 1, 4, 7, and 10.