Cover page for Statistical Analysis Plan

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	07 November 2018

STATISTICAL ANALYSIS PLAN
(SAP)

PROTOCOL rAd-IFN-CS-003

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)

Investigational Product:	INSTILADRIN (rAd-IFN/Syn3)
Protocol Number:	rAd-IFN-CS-003
Development Phase:	3
Sponsor:	FKD Therapies Oy
Protocol Version:	Version 6.0
Version Date:	05 October 2018
SAP Version:	V2.0
SAP Date:	07 Nov 2018

SAP SIGNATURE 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)

This Statistical Analysis Plan has been reviewed and approved by the representatives listed below:

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SAP SIGNATURE 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)

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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)

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SUMMARY OF REVISIONS

- Updated the SAP to reflect changes made in protocol amendment version 6.0 (dated 05 October 2018).
- Updated Section 3.6.1.2 to clarify the definitions of the secondary efficacy endpoints
- Added definition of the 2 patients cohorts in Section 5.1
- Updated Section 6.3 to include more details of the baseline disease charateristics summary
- Added details for “Determination of Complete Response (CIS)” in Section 6.8.1.

TABLE OF CONTENTS

ABBREVIATIONS & TERMS

AE	Adverse event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BCG	Bacillus Calmette-Guerin
BMI	Body mass index
BUN	Blood Urea Nitrogen
CI	Confidence interval
CIS	Carcinoma in situ
CR	Complete response
CRO	Clinical research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic case report form
ECOG PS	Eastern Clinical Oncology Group Performance Status
GGT	Gamma-glutamyl transferase
HCT	Hematocrit
HEENT	Head, eyes, ears, nose, throat
HGRF	High-grade-recurrence-free
INR	International Normalized Ratio
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NMIBC	Non-muscle Invasive Bladder Cancer
OS	Overall survival
PT	Prothrombin time
PTT	Partial thromboplastin time
Q1	First Quartile
Q3	Third Quartile
RBC	Red Blood Cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation(s)
SOC	System organ class
TEAE	Treatment-emergent adverse event
WBC	White Blood Cell
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is created based on Protocol rAd-IFN-CS-003 (Version 6.0, dated 05 October, 2018) and describes in detail the statistical methodology and the statistical analyses to be conducted for the above-mentioned protocol. Any deviations to the planned analyses specified within the SAP, will be justified in writing and presented within the final Clinical Study Report (CSR).

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

The secondary objectives of this study are as follows:

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 the long term follow up period

2.3 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

3 STUDY OVERVIEW

3.1 Overall Study Design

This is a multi-center, open label, repeat dose study to investigate the safety and efficacy of INSTILADRIN administered intravesically to Bacillus Calmette-Guerin (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.

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 4 years from first dose.

3.2 Study Duration

The duration of the study is potentially up to 4 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 3 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 will continue from month 24 onwards for these patients, 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.

3.3 Sample Size

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 at any time (response rate of 37%, two-sided 95% Clopper-Pearson CI = [27.5%, 47.3%]) are sufficient to reject the hypothesis.

3.4 Randomization and Blinding

Not Applicable.

3.5 Study Assessments

Time and events schedule for the study is presented in Table 1.

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	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	M10D1 +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	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	M10D1 +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
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 etc	
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 4 years 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

i. Hematology and clinical chemistry samples may be taken the previous day to ensure results are available before dosing. 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

k. Urinalysis on dosing days to be taken pre-dose

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

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

3.5.1 Efficacy Assessments

Efficacy assessments include:

- Assessment of the recurrence of high-grade disease during the treatment period by cystoscopy, cytology and biopsy if clinically indicated at 3 Monthly intervals,
- 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,
- Assessment of the incidence and time to cystectomy, and
- Assessment of overall survival.

The efficacy assessments (cystoscopy and cytology, and biopsy if applicable) can be conducted up to 14 days prior to re-treatment. INSTILADRIN cannot be instilled for at least 2 weeks following each biopsy to allow time for the bladder to heal. The details of the disease assessment by cystoscopy, cytology, and biopsy during the study are provided below.

3.5.1.1 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.

3.5.1.2 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.

3.5.1.3 Biopsy

During the course of the study, biopsies will be obtained for all patients at the Screening visit and at the End of Month 12. Biopsies at other visits (Months 3 to 24) will be taken if there is evidence of suspicious lesions during cystoscopy or if there is a positive cytology.

Patients with a positive cytology or with findings on cystoscopy that are suspicious for recurrent cancer will undergo a biopsy to confirm a response. If the biopsy is positive for high-grade bladder cancer, then the patient will be withdrawn from the trial and offered alternative therapy by their treating physician. If the biopsy is negative or shows only low grade recurrence, then patient will continue on the treatment regimen as defined in the trial protocol.

3.5.2 Definitions

Definition of High-Grade Disease

A patient is defined as having a tumor with high-grade histology 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

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.

Definition of Durability of Complete Response

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 recurrence, disease progression or death.

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.

3.5.3 Safety Assessments

Safety assessments include assessment of treatment emergent adverse events (AEs), clinical laboratory assessments, vital signs, physical examinations, resting 12-lead electrocardiogram (ECG), and measurement of the levels of anti-adenoviral antibodies.

3.5.3.1 Adverse Events

An AE is 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 in the electronic case report form (eCRF), 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. 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. All serious adverse events (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 4 years from first dose. All SAEs (initial and follow-up information) will be reported via the eCRF AE page within 24 hours of the discovery of the event.

All adverse Events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, version 19.0). The severity of AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) for Cancer Clinical Trials, Version 4.03.

3.5.3.2 Clinical Laboratory Evaluations

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. Hematology and clinical chemistry samples may be taken on the day prior to dosing to ensure results are available before dosing. The following clinical laboratory tests will be performed by the local laboratory:

- Clinical chemistry: Sodium, Potassium, Chloride, Bicarbonate (HCO3-), Phosphate, Magnesium, Calcium, Glucose, BUN, Creatinine, Albumin, Protein, Alkaline Phosphatase, LDH, AST, ALT, GGT, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Cholesterol and Triglycerides
- Hematology: Hemoglobin, HCT, RBC, WBC, Platelets, Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils, Reticulocytes
- Coagulation assessments: PT, PTT, INR
- Urinalysis: Specific Gravity, PH, Protein, Glucose, Ketones, Blood, Leukocytes, Nitrites, Bilirubin, Urobilinogen.

3.5.3.3 Vital Signs

Vital signs including systolic blood pressure, diastolic blood pressure, hear rate, temperature, and respiration rate will be measured at scheduled time points according to the Schedule of Study Assessments. Measurements will be made after the patient has been resting supine or semi-supine for a minimum of 5 minutes.

3.5.3.4 12-lead electrocardiogram (ECG)

A resting 12-lead ECG will be performed at time points as outlined in the Schedule of Study Assessments.

3.5.3.5 Physical Examination

Routine physical examination will 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 following body systems will be examined: general appearance, dermatologic, head, eyes, ears, nose, throat (HEENT), abdomen/pelvis, respiratory, cardiovascular, gastrointestinal, neurologic and musculoskeletal.

Each body system will be determined to be Normal, Abnormal not Clinically Significant and Abnormal Clinically Significant at each visit. The patient's weight and a neurological exam should be measured and recorded as part of the physical examination.

3.5.3.6 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.

3.5.3.7 Urinary Symptoms

Urinary symptoms including urinary frequency, presence of urgency, severity of dysuria, presence of nocturia, and number of nocturnal voids will be collected throughout the study period as outlined in the Schedule of Study Assessments.

3.5.4 Assessment of Exploratory Biomarkers

Urine samples and biopsy tissues 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 (Section 10 of the protocol) 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.

A blood sample will be collected for possible exploratory gene expression profiling and sequencing and other immunological assays.

3.6 Study Variables

3.6.1 Efficacy Variables

3.6.1.1 Primary Efficacy Variable

Complete Response (CIS)

The primary efficacy variable is the rate of complete response at any time in patients with CIS (with or without concomitant high grade Ta or T1 papillary disease) after first administration of INSTILADRIN.

A patient will be deemed not to have achieved a complete response if there are insufficient data to determine whether or not a complete response has occurred.

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.

3.6.1.2 Secondary Efficacy Variables

The key secondary efficacy variable is the 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 efficacy variables are as follows:

- Incidence of high-grade-recurrence-free survival at 3, 6, 9, and 12 months
- High-grade-recurrence-free survival for all patients
- Incidence of cystectomy,
- Cystectomy-free survival
- Overall survival (OS)

Durability of Complete Response in patients with CIS

Durability of complete response in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease) 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 recurrence, progression, or death, whichever occurs earlier. If none of the three-monthly assessments show treatment failure then durability will be censored at the last disease assessment not showing treatment failure.

Incidence of High-Grade-Recurrence-Free Survival at 3, 6, 9 and 12 Months

The proportion of patients who are alive and without documented recurrence of high grade disease or muscle-invasive disease progression at 3, 6, 9 and 12 months following the first administration of INSTILADRIN will be presented for patients with high grade Ta or T1 papillary disease (without concomitant CIS), for patients with CIS (with or without concomitant high grade Ta or T1), and for both cohorts combined.

Note: Patients who recur with low grade disease post initial dose will be considered as treatment successes. A patient will be deemed not to have achieved high-grade-recurrence-free survival if there are insufficient data to determine whether or not high-grade-recurrence-free survival has occurred. It will be considered sufficient evidence for high-grade-recurrence-free-survival if a subsequent assessment shows high-grade-recurrence-free survival and there has been no intermediate treatment for bladder cancer other than INSTILADRIN.

High-Grade-Recurrence-Free survival for all patients

High-grade-recurrence-free survival is defined as the time (in months) from the first administration of INSTILADRIN until documented recurrence of high grade disease, muscle-invasive disease progression, or death due to any cause, whichever occurs earlier. A patient is defined as having a documented recurrence of tumor with high-grade histology, if on cystoscopy or cytology examination it is shown that there is evidence of CIS, Ta or T1 lesions and which on biopsy are evaluated as high-grade.

Patients who were alive with no documented recurrence of high grade disease or progression by the data cut-off date will be censored at the date of their last disease assessment.

Incidence of Cystectomy

The proportion of patients undergoing radical cystectomy for any reason after the first dose of INSTILADRIN will be calculated.

Cystectomy-Free Survival

Cystectomy-free survival is defined as the time (in months) from the first dose of INSTILADRIN to the first date of cystectomy or death due to any cause. Patients who were alive with no cystectomy performed by the data cut-off date will be censored at their last contact date with known status for cystectomy.

Overall Survival

Overall survival is defined as the time (in months) from the first dose of INSTILADRIN to death due to any cause. Patients who are still alive by the data cut-off date will be censored at the last date the patient is known to be alive.

3.6.2 Safety Variables

Safety variables include the following:

- Treatment emergent adverse events (TEAEs)
- Clinical laboratory values
- Vital signs
- ECG measurements
- Physical examinations
- Urinary symptoms
- Anti-adenoviral antibody levels

3.6.3 Biomarkers and Exploratory Variables

Exploratory gene expression profiling and sequencing and other immunological assays may be performed for urine samples and biopsy tissues. These will include a correlation between

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

4 ANALYSIS SETS

4.1 Safety Analysis Set

The Safety Analysis Set will consist of all patients who have received at least one dose of INSTILADRIN.

The Safety Analysis Set will be used for all safety analyses.

4.2 Efficacy Analysis Set

The Efficacy Analysis Set comprises all members of the Safety Analysis Set with a diagnosis of High Grade, BCG Unresponsive Non-Muscle Invasive Bladder Cancer.

The Efficacy Analysis Set will be the primary analysis set for the analyses of efficacy data.

4.3 Per Protocol Analysis Set

The Per Protocol Analysis Set comprises all patients in the Efficacy Analysis Set who had no major protocol violation and either:

- Completed their 12 months assessment at earliest Day +357 and at latest Day +396; or
- Withdrew before their 12 month assessment because of disease recurrence or progression, death, adverse event related to the disease or treatment, or lack of tolerability.

All criteria for major protocol violations and patient evaluability for Per Protocol Analysis Set will be established by the study team prior to the database lock and will be documented in a memo by the study team. Supportive efficacy analyses will be performed for selected efficacy endpoints using the Per Protocol Analysis Set.

5 GENERAL STATISTICAL CONSIDERATIONS

Descriptive statistics on continuous variables will include the number of observations (n), mean, standard deviation (SD), minimum, first quartile (Q1), median, third quartile (Q3), and maximum, while categorical variables will be summarized using the frequency count and percentage in each category.

All analyses will be performed using SAS® for Windows® (version 9.3 or higher).

5.1 Definition of Patient Cohort

Two cohorts are defined based on patients' diagnosis at enrollment:

- **CIS cohort**: comprising patients with CIS with or without concomitant high-grade Ta or T1 papillary disease;
- **Papillary disease cohort**: comprising patients with high-grade Ta or T1 papillary disease without concomitant CIS

Patients with CIS (with or without concomitant papillary disease) and patients with high-grade Ta or T1 papillary disease (without concomitant CIS) will be summarised separately and if appropriate together with both cohorts combined.

5.2 Baseline and Data Considerations

Baseline Definition

Unless otherwise specified, baseline for efficacy and safety variables is defined as the last measurement obtained prior to the first administration of study medication.

Visit Windows

For the analysis of HGRF survival at Months 3, 6 and 9, the assessment of "recurrence of high grade disease" will be based on the cytology, cystoscopy and biopsy (if applicable) scheduled immediately before the second, third and fourth doses of INSTILADRIN.

For the analysis of HGRF survival at Month 12, the assessment of "recurrence of high grade disease" will be based on the earliest cytology, cystoscopy and biopsy performed on or after Day +357.

For all other study variables, the by-visit summaries will be based on the nominal scheduled visit. The results of all scheduled and unscheduled measurements will be included in the data listings.

5.3 Handling of Dropouts or Missing Data

Missing Response Assessment

A patient will be deemed not to have achieved a complete response if there are insufficient data to determine whether or not a complete response has occurred.

Missing Data for HGRF Survival

A patient will be deemed not to have achieved high-grade-recurrence-free survival at an evaluation visit if there are insufficient data to determine whether or not high-grade-recurrence-free survival has occurred.

It will be considered sufficient evidence for high-grade-recurrence-free-survival if a subsequent assessment shows high-grade-recurrence-free survival and there has been no intermediate treatment for bladder cancer other than INSTILADRIN.

Missing or Partial Dates

- To be conservative in reporting treatment-emergent adverse events (TEAEs), when an adverse event is proven to occur prior to the first dose of the study drug, it is considered as a non-treatment-emergent event. Otherwise, it is considered to be a TEAE. Therefore, if the start date of an adverse event is missing but the stop date is either overlapping into the treatment period or missing, the adverse event will be considered to be a TEAE, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the adverse event started prior to the start of the study drug. If the above cannot be conclusively established based on the partial dates, then the adverse event will be considered as a TEAE.
- For classification of prior and concomitant medications, medications missing both start and stop dates, or having a start date prior to the first dose of the study drug and missing the stop date, or having a stop date after the start of the study drug and missing the start date, will be considered as concomitant medications. When partial dates exist in the data, the same logic to that of the adverse events described above will be used.
- Time from initial diagnosis (months) is calculated as (date of first dose of study drug - date of initial diagnosis + 1)/30.4375. If the month and year of the diagnosis are provided but the day is missing, the missing day is imputed as 15. If only the year is provided, then the missing month and day are imputed as July 1st for the calculation. If the imputation rule specified above yields a date of initial diagnosis after the informed consent date, then the partial date of the initial diagnosis will be imputed as January 1st when only a year is provided and the 1st of the month when only a month and year are provided.

No imputations will be made for any of the other endpoints; the data will be treated as missing.

6 STATISTICAL ANALYSIS

The statistical analysis will be performed by [redacted]

6.1 Patient Disposition

Patient disposition information will be summarized for all enrolled patients for the following disposition categories:

- Patients who were enrolled (received first dose),
- Patients who were treated at each 3 months interval
- Patients who completed 12 months assessment
- Patients who did not complete the 12 months assessment,

- Patients who discontinued early from the study

The primary reasons for terminating treatment will be tabulated by number of doses administered. The primary reason for early withdrawal from the study will also be tabulated.

In addition, the number and percentage of patients in each analysis set will be presented.

All disposition data will be listed by patient.

6.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively for the Safety Analysis Set, Efficacy Analysis Set, and the Per-Protocol Analysis Set. If 2 analysis sets are identical to each other, the table will be presented only once.

Categorical baseline variables (e.g., gender, age group, race, ethnicity, and Eastern Clinical Oncology Group Performance Status [ECOG PS]) will be summarized by the number and percentage of patients in corresponding categories. Continuous baseline variables such as age at informed consent, body weight, height, and body mass index (BMI) will be summarized by descriptive statistics (number of observations, mean, standard deviation, median, Q1, Q3, minimum, and maximum).

All demographic and baseline characteristics data will be listed by patient.

6.3 Disease History

Disease history including initial diagnosis of bladder cancer (stage and grade), current status (refractory or relapsed) at study entry, current tumor stage, urine cytology result at screening, prior cancer therapy (yes, no), type of most recent prior cancer therapy, number of prior regimens, line of the most recent prior cancer therapy, best overall response to the most recent line of prior cancer therapy, prior cancer surgeries (yes, no), and prior radiation therapy (yes, no) will be collected at screening and will be summarized using descriptive statistics for the Safety Analysis Set, Efficacy Analysis Set, and the Per-Protocol Analysis Set. If 2 analysis sets are identical to each other, the table will be presented only once. Time from initial diagnosis of bladder cancer and time from the last TURBT/endoscopic resection will also be summarized using descriptive statistics.

In addition, recurrence history including the number of previous recurrences, stage and grade of the most recent recurrence, best overall response of the most recent recurrence, and the time from the diagnosis of the most recent recurrence will be summarized descriptively for the Safety Analysis Set, Efficacy Analysis Set, and the Per-Protocol Analysis Set.

BCG history including the number of courses of BCG administered and time from last exposure to BCG to the first dose of INSTILADRIN will also be summarized descriptively for the Safety Analysis Set, Efficacy Analysis Set, and the Per-Protocol Analysis Set.

Individual disease history, recurrence history, and BCG history data will be presented in separate data listings.

6.4 Medical History

Medical/surgical history will be listed by patient.

6.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the most current version of World Health Organization (WHO) Drug Dictionary (Version DDE B2, March 2018 or later) to give the Anatomical Therapeutic Chemical (ATC) classes and preferred term for each medication. Prior medications are medications used and stopped before the first dose of study drug. Concomitant medications are medications that were taken on or after the first dose of study drug.

Concomitant medications will be summarized for the Safety Analysis Set by ATC class and preferred term. Although a patient may have taken two or more medications, the patient is counted only once within an ATC classification. The same patient may contribute to two or more preferred terms in the same classification.

All prior and concomitant medications will be listed by patient.

6.6 Study Drug Exposure and Compliance

INSTILADRIN will 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.

The number of INSTILADRIN doses administered will be presented. The number and percentage of patients with a dose split and the number and percentage of patients with a dose interruption as well as the reasons for dose interruption will be tabulated.

In addition, the average amount of INSTILADRIN instilled (mL) per dose and the average dwell time (minutes) per dose will be calculated for each patient and summarized using descriptive statistics. The percentage of protocol defined instilled dose (i.e., average instilled dose (mL)/75 mL) and the percentage of protocol defined dwell time (i.e., average dwell time (mins)/60 mins) will be calculated and summarized descriptively.

Study drug administration data will be listed by patient.

6.7 Protocol Deviations

Protocol deviations will be categorised as 'major' or 'minor' at a data review meeting convened by the sponsor. All major deviations and selected minor deviations (including but not limited to violation of entry criteria) will be listed.

6.8 Efficacy Analyses

All efficacy analyses will be performed based on the Efficacy Analysis Set. Additionally, supportive analyses will be performed based on the Per Protocol Analysis Set for selected efficacy endpoints.

6.8.1 Analysis of Primary Efficacy Variable

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 after the first administration of INSTILADRIN. 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. All efficacy assessment data will be listed by patient.

Determination of Complete Response (CIS)

A patient with CIS +/- papillary disease will be judged to have achieved a complete response where:

- Urine cytology is reported as normal, atypical, degenerative, reactive, inflammatory or non-specific, **and**
- Cystoscopy is reported as normal or with findings that do not include evidence of low grade or high grade recurrence
- Bladder biopsy/ ies, if performed (not mandatory), demonstrate absence of low grade or high grade recurrence

A patient with CIS +/- papillary disease will be judged to have achieved a complete response where:

- Urine cytology is reported as normal, atypical, degenerative, reactive, inflammatory, non-specific, suspicious, malignant cells or not done, **and**
- Bladder biopsy/ ies have been performed and demonstrate absence of low grade or high grade recurrence

A patient with CIS +/- papillary disease will be judged to have **not** achieved a complete response where:

- Urine cytology is reported as suspicious, malignant cells or not done, **and**
- Bladder biopsy/ ies have not been performed
- There is high grade recurrence, confirmed by bladder biopsy/ ies, observed at the next scheduled visit

Once a complete response has been achieved, treatment failure is defined as recurrence of high grade disease confirmed by bladder biopsy/ ies (see definition of high-grade disease in Section 3.5.2 and also below durability of complete response).

6.8.2 Analysis of the Key Secondary Efficacy Variable

Durability of complete response (CIS)

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, whichever occurs earlier.

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 along with the two-sided 95% confidence intervals for the median 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. Plots of Kaplan-Meier curves will be presented.

Sensitivity analysis for durability of complete response may be performed based on the Efficacy Analysis Set using the following definition:
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, discontinuation of study treatment, or death, whichever occurs earlier.

6.8.3 Analyses of Other Secondary Efficacy Variables

Incidence of High-Grade Recurrence Free Survival at 3, 6, 9, and 12 Months

The rate of HGRF survival at 3, 6, 9 and 12 months will be estimated based on the crude proportion of patients who are alive and without documented recurrence of high grade disease at each time point. The proportion of patients with high-grade Ta or T1 papillary disease (without concomitant CIS) achieving high-grade-recurrence-free survival at 3, 6, 9, and 12 months will be reported together with a two-sided 95% Clopper-Pearson CI for the proportion.

Additionally, the proportion of patients achieving high-grade-recurrence-free survival at 3, 6, 9 and 12 months together with a two-sided 95% Clopper-Pearson CI will also be presented for patients with CIS (with or without concomitant high grade Ta or T1) and for both cohorts combined.

High-Grade-Recurrence-Free Survival

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 along with the two-sided 95% confidence intervals for the median and of the probability of duration at 3 monthly intervals. Plots of Kaplan-Meier curves will be presented.

Incidence of Cystectomy

The proportion of patients undergoing cystectomy within 12 months, within 2 years and within 4 years will be reported together with an exact 95% CI for the proportion 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.

Cystectomy-free Survival

Cystectomy-free survival will be summarized by Kaplan-Meier methods 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. The Kaplan-Meier estimate of the median time to cystectomy or death from any cause along with the two-sided 95% confidence intervals for the median 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 will be analyzed using the Kaplan-Meier methods 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. The Kaplan-Meier estimates of the median, Q1, Q3, and the two-sided 95% confidence intervals for the median overall survival will be presented. The estimated probability of overall survival at 3 monthly intervals will also be presented. Plots of Kaplan-Meier curves will be presented.

6.8.4 Subgroup Efficacy Analyses

The primary efficacy variable rate of complete response in the CIS patients based on the Efficacy Analysis Set will be analyzed for the following subgroups:

- Gender (male or female)
- Race (white vs. non-white)
- Age group (< 65 or ≥ 65 years)
- Time from initial diagnosis of bladder cancer (categories to be determined prior to database lock)
- Tumor type at study entry (CIS only, CIS with Ta/T1)
- Presence of anti-adenoviral antibodies at post-baseline (yes or no)

Additional subgroup analyses may be performed if deemed necessary.

6.8.5 Exploratory Efficacy Analyses

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

The exploratory analyses may include, but are not limited to,

- Evaluation of all treated patients on the efficacy endpoints
- Evaluation of the effect of selected baseline demographics and disease characteristics on the efficacy endpoints HGRF survival at 12 months and identification of predictive tissue and urine biomarkers for HGRF survival at 12 months if data warrant.

All exploratory analyses will be described as such in the CSR.

6.9 Safety Analyses

Safety assessments include treatment emergent adverse events, clinical laboratory assessments, vital signs, physical examinations, urinary symptoms, resting 12-lead electrocardiogram (ECG), and levels of anti-adenoviral antibodies.

All safety analyses will be performed by cohort and overall based on the Safety Analysis Set.

6.9.1 Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any adverse event that occurs or worsens at or after the first dose of study drug.

An overview of adverse events will be provided which summarizes patient incidence of all TEAEs, drug-related TEAEs, grade 3/4/5 TEAEs, drug-related grade 3/4/5 TEAEs, treatment-emergent SAEs, drug-related treatment-emergent SAEs, and TEAEs leading to discontinuation of study drug and/or deaths.

The number and percentage of subjects with TEAEs will be tabulated by SOC and preferred term. Drug-related TEAEs, grade 3/4/5 TEAEs, drug-related grade 3/4/5 TEAEs, treatment emergent SAEs, drug-related treatment-emergent SAEs, TEAEs leading to discontinuation of study drug, and drug-related TEAEs leading to discontinuation of study drug will be summarized in the same manner. For these summaries, patients with multiple adverse events will be counted only once per SOC and preferred term.

The incidence of TEAEs and drug-related TEAEs will also be summarized by SOC, preferred term, and by study period (i.e., overall, months 1-3, months 4-6, months 7-10, etc). For these summaries, patients with multiple adverse events with onset date during a specific period of time will be counted only once per SOC and preferred term. In addition, summaries will be provided by the worst NCI-CTCAE grade, system organ class and preferred term for the number and percentage of patients with TEAEs and drug-related TEAEs. For these summaries, patients with multiple adverse events will be counted only once by the worst NCI-CTCAE grade within an SOC and preferred term.

Listings will be provided for SAEs, grade 3/4/5 AEs, AEs leading to discontinuation of study drug, and AEs leading to deaths. A by-patient AE (including treatment-emergent) data listing including, but not limited to, verbatim term, preferred term, system organ class, NCI-CTCAE grade, and relationship to study drug will be provided.

6.9.2 Clinical Laboratory Assessments

Descriptive statistics will be provided for selected clinical laboratory test results (hematology and blood chemistry) and changes from baseline by scheduled time of evaluation, maximum post-treatment value, and minimum post-treatment value. Both scheduled and unscheduled post-treatment values will be considered for the summaries of the maximum and minimum post-treatment values.

Abnormal laboratory results will be graded according to NCI-CTCAE Version 4.03, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. Both scheduled and unscheduled post-treatment values during the treatment period will be considered.

The number and percentage of subjects with treatment-emergent laboratory abnormalities (any grade and grade ≥ 3) will be presented for hematology and serum chemistry laboratory parameters if applicable. Treatment-emergent laboratory abnormalities are defined as post baseline laboratory abnormalities with worsening CTCAE grade from baseline. Post-baseline laboratory abnormality with unknown baseline grade will be considered as treatment-emergent.

All clinical laboratory data will be listed, and values deemed clinically significance will be flagged.

6.9.3 Vital Signs

Descriptive statistics will be provided for the vital signs measurements (systolic blood pressure, diastolic blood pressure, heart rate, body temperature, respiratory rate, and body weight) and changes from baseline by scheduled time of evaluation, including the maximum and minimum post-treatment values. Both scheduled and unscheduled post-treatment values will be considered for summaries of the maximum and minimum post-treatment values.

All vital sign data will be listed by subject.

6.9.4 12-Lead Electrocardiogram (ECG)

Electrocardiogram parameters (PR, RR, QRS, QT, QTcB, and QTcF) will be summarized using descriptive statistics for actual values and for changes from baseline by scheduled time of evaluation, including the maximum post-treatment value. Both scheduled and unscheduled post-treatment values will be considered for summaries of the maximum post-treatment values. The corrected QT intervals using Bazett's and Fridericia's formula will be calculated as follows: $QTcB = QT/(RR)^{1/2}$ and $QTcF = QT/(RR)^{1/3}$.

The incidence of notable ECG changes in maximum absolute QT, QTcF, and QTcB intervals (> 450, > 480, and > 500 ms) over all post-treatment evaluations, as well as in QT, QTcF, and QTcB maximum changes from baseline (> 30 and > 60 ms) over all post-treatment evaluations will be summarized.

A listing of ECG data will be provided.

6.9.5 Physical Examination

Physical examination result will be tabulated by body system for each scheduled visit.

All physical examination data will be listed by patient.

6.9.6 Urinary Symptoms

Urinary symptoms data will be tabulated at each scheduled visit and listed by patient.

6.9.7 Anti-Adenoviral Antibody Assessment

Anti-adenoviral antibody status will be tabulated at each scheduled visit and overall at post-baseline.

All data for anti-adenoviral antibody assessment will be listed by patient.

6.10 Analyses of Pharmacodynamic Parameters and Exploratory Biomarkers

Pharmacodynamics data will be listed and summarized by scheduled time point. Exploratory biomarkers will be summarized descriptively and presented in data listings if data are available.

6.11 Timing of Analyses

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.

The final analysis of the study will be performed after all patients have completed their M12 assessment or have withdrawn before then.

A follow-up analysis will be performed after the last patient has completed the long term follow up.

No formal interim analyses are planned for this study.

6.12 Data Review Meeting

A data review meeting will be convened by the Sponsor at the following timepoints

- before any administrative analyses
- before the final analysis of 12 month data
- before the follow-up analyses.

  Each data review meeting will take place after the data have been cleaned but prior to the database being locked for analysis.

The terms of reference of the Data Review Meeting before the final analysis at 12 months shall include but not be limited to:

- the determination of whether protocol violations are 'major' or 'minor', or not a protocol violation at all
- the allocation of subjects to analysis sets
- a review of missing data and of outliers
- a decision on whether centres need to be combined
- a review of the distribution of the efficacy variables, considering any implications for the proposed method of statistical analysis
- a review of whether additional covariates need to be included in the analyses
- the finalization of the SAP

The Data Review Report will be an Appendix to the CSR.

6.13 Changes from Analyses Specified in the Protocol

No changes have been issued or planned.