1 PROTOCOL SYNOPSIS

Title of Study	A Phase 2, Multi-Arm, Multi-Cohort, Open-Label Study to Evaluate the Safety and Efficacy of Cretostimogene Grenadenorepvec in Participants with High-Risk Non-Muscle-Invasive Bladder Cancer (NMIBC)
Sponsor:	CG Oncology, Inc.
Investigational Products:	**Cretostimogene Grenadenorepvec:** Engineered human adenovirus serotype 5 with an E2 transcription factor (E2F) promoter and human granulocyte-macrophage colony stimulating factor (hGM-CSF) **n-dodecyl β-D-maltoside (DDM):** Non-ionic surfactant, comprised of maltose derived from a single 12-carbon chain, which acts as a mild detergent and solubilizing agent
INN Name:	Cretostimogene grenadenorepvec
Phase:	2
Study Objectives:	**Cohort A** **Primary Objective:** • Determine the complete response (CR) rate at any time following treatment with cretostimogene in participants with Bacillus Calmette-Guerin (BCG)-naïve carcinoma *in situ* (CIS) with or without concomitant high-grade (HG) Ta or T1 disease at baseline **Secondary Objectives:** • Compare cretostimogene genome and GM-CSF levels, treatment efficacy, and safety by 2 different methods of cretostimogene instillation • Assess duration of response (DoR) in participants with CIS with or without concomitant HG Ta/T1 disease at baseline • Determine all-cause event-free survival (EFS) • Assess HG and low-grade (LG) recurrence-free survival (RFS) • Determine cystectomy-free survival • Assess bladder cancer-specific survival • Assess safety of cretostimogene **Exploratory Objectives:** • Evaluate overall survival • Assess patient-reported outcomes (PROs) and health-related quality of life measures, via the European Organization for Research and Treatment of Cancer (EORTC) QLQ-NMIBC24 and EuroQol EQ-5D-5L questionnaires

	Cohort B **Primary Objectives:** • **Arm 1:** Determine the CR rate at any time following treatment with cretostimogene in participants with BCG-exposed CIS with or without concomitant HG Ta or T1 disease at baseline. • **Arm 2:** Determine the HG EFS following treatment with cretostimogene in participants with BCG-exposed HG Ta/T1 papillary disease without CIS at baseline **Secondary Objectives:** • **Arm 1 only:** Assess DoR in participants with CIS with or without concomitant HG Ta/T1 at baseline • Determine all-cause EFS • Assess LG RFS • Determine cystectomy-free survival • Assess bladder cancer-specific survival • Assess safety of cretostimogene **Exploratory Objectives:** • Evaluate overall survival • Assess PROs and health-related quality of life measures, via EORTC QLQ-NMIBC24 and EuroQol EQ-5D-5L questionnaires • Analyze the molecular profile of urothelial cancer genes in urine before and after cretostimogene treatment
Study Design Overview:	This is a Phase 2, multi-arm, multi-cohort, open-label trial to evaluate the safety and efficacy of cretostimogene in participants with high-risk NMIBC. **Cohort A** Cohort A will enroll up to 50 participants with pathologically confirmed, CIS-containing, high-risk NMIBC (i.e., CIS with or without concomitant Ta/T1) who are naïve to BCG treatment. BCG-naïve will be defined as the following: • No prior treatment with BCG OR • No treatment with BCG within the past 24 months prior to current pathological diagnosis OR • A maximum of 1 or 2 doses of BCG within the past 24 months prior to current pathological diagnosis.

	Randomization:
	
	Participants will be randomized 1:1 to receive DDM and cretostimogene as a 5-step instillation procedure (Arm 1) or a modified 2-step instillation procedure (Arm 2).
	
	Treatment Schedule:
	
	Treatment will be performed in a classic induction course followed by maintenance therapy:
	
	• **Induction course**:
	  ○ Cretostimogene will be administered as an induction course every week for 6 treatments on Weeks 1, 2, 3, 4, 5, and 6. If the participant has persistent CIS and/or HG Ta disease at Week 11, the participant may receive a re-induction cycle of 6 weekly treatments on Weeks 13, 14, 15, 16, 17, and 18. Participants who have persistent/progress with HG T1 disease at the Week 11 assessment should discontinue the treatment phase.
	
	• **Maintenance therapy**:
	  ○ If there is no HG disease present at Week 11 (i.e., the participant has a CR), the participant will receive a cycle of 3 weekly maintenance treatments on Weeks 13, 14, and 15.
	  ○ Three weekly cretostimogene maintenance will continue every 3 months in Year 1 and every 6 months in Year 2 until Month 25 (Weeks 105, 106, and 107).
	  ○ At the discretion of the Investigator, participants may continue treatment every 6 months in Year 3 until Month 36 (Weeks 157, 158, and 159) or until disease recurrence, initiation of new anti-cancer therapy, documented withdrawal of consent by the participant, participant is lost to follow-up, or the study is terminated.
	
	Efficacy Assessments
	
	• For the first 2 years after treatment initiation, participants will be assessed for disease status every 3 months by urine cytology, complete bladder visualization utilizing consistent light source (e.g., 'white', 'blue', narrow-band imaging) throughout the study, with directed trans urethral resection of bladder tumor (TURBT)/biopsy (if indicated). Computerized tomography (CT) urogram or magnetic resonance urography (MRU) will be performed every 6 months.
	  ○ At Week 51, in addition to the above assessments, participants will undergo mandatory bladder mapping (random biopsies of the trigone, bladder dome, right, left and posterior bladder walls [all must be included] and a prostatic urethra biopsy in males with prior documented involvement).
	
	• Thereafter, efficacy assessments will be performed at 6-month intervals for up to an additional 2 years (i.e., up to 4 years from Week 1 Day 1 of treatment) or until disease recurrence, initiation of new anti-cancer therapy, documented withdrawal of consent by the participant, participant is lost to follow-up, or the study is terminated.

- During the treatment phase, efficacy assessment procedures should be performed 2 weeks (±1 week) prior to the first dose of the next treatment cycle.
- Participants with recurrent disease will be discontinued from study treatment and followed for survival every 6 months from the date of recurrence until 4 years from Week 1 Day 1 of treatment or until documented withdrawal of consent by the participants, participant is lost to follow-up, or the study is terminated. Any new cancer therapy (including radical cystectomy/radiotherapy) and stage of disease at time of new therapy will also be documented.

Cohort B

Cohort B will enroll up to 150 participants with pathologically confirmed high-risk NMIBC (i.e., CIS with or without concomitant HG Ta or T1 disease **OR** HG Ta/T1 disease without CIS) who have previously been exposed to BCG treatment.

BCG-exposed will be defined as the following:

- BCG-resistant NMIBC: Persistent or recurrent HG Ta or CIS at the 3-month evaluation that follows at least 5 of 6 doses of induction BCG

  OR

- Delayed relapse after adequate BCG: HG recurrence outside of the BCG--unresponsive window (>6 months for Ta/T1 and >12 months for CIS) but within 24 months after the last dose of adequate BCG.
  - Adequate BCG is defined as at least 5 of 6 doses of induction BCG and at least 2 doses of 1 course of either re-induction or maintenance BCG

  OR

- Delayed relapse after inadequate BCG: HG recurrence after 6 months but within 24 months after the final dose of inadequate BCG
  - Inadequate BCG is defined as 3–6 doses.

Treatment Allocation:

- Participants with CIS-containing pathology at baseline will be recruited into Arm 1 (~75 participants). Participants with papillary-only pathology at baseline will be recruited into Arm 2 (~75 participants).
- All participants will receive DDM and cretostimogene as a modified 2-step instillation procedure.

Treatment Schedule:

Treatment will be performed in a classic induction course followed by maintenance therapy:

- **Induction course**:
  - Cretostimogene will be administered as an induction course every week for 6 treatments on Weeks 1, 2, 3, 4, 5, and 6. If the participant has persistent CIS and/or HG Ta at Week 11, the participant may receive a re-induction cycle of 6 weekly treatments on Weeks 13, 14, 15, 16, 17, and 18.

	Participants who have recurrent/progress with HG T1 disease at the Week 11 assessment should discontinue the treatment phase. • **Maintenance therapy**: o If there is no HG disease present at Week 11 (i.e., the participant has a CR [Arm 1] or is HG recurrence-free [Arm 2]), the participant will receive a cycle of 3 weekly maintenance treatments on Weeks 13, 14, and 15. o Three weekly cretostimogene maintenance will continue every 3 months in Year 1 and every 6 months in Year 2 until Month 25 (Weeks 105, 106, and 107). o At the discretion of the Investigator, participants may continue treatment every 6 months in Year 3 until Month 36 (Weeks 157, 158, and 159) or until disease recurrence, initiation of new anti-cancer therapy, documented withdrawal of consent by the participant, participant is lost to follow-up, or the study is terminated. **Efficacy Assessments** • For the first 2 years after treatment initiation, participants will be assessed for disease status every 3 months by urine cytology, complete bladder visualization utilizing consistent light source (e.g., 'white', 'blue', narrow-band imaging) throughout the study, with directed TURBT/biopsy (if indicated). CT urogram or MRU will be performed every 6 months. o **Arm 1**: At Week 51, in addition to the above assessments, participants with CIS-containing disease at baseline will undergo mandatory bladder mapping (random biopsies of the trigone, bladder dome, right, left and posterior bladder walls [all must be included] and a prostatic urethra biopsy in males with prior documented involvement). o **Arm 2**: At Week 51, in addition to the above assessments, participants with papillary-only disease at baseline will undergo mandatory bladder biopsies directed at prior tumor location(s). • Thereafter, efficacy assessments will be performed at 6-month intervals for up to an additional 2 years (i.e., up to 4 years from Week 1 Day 1 of treatment) or until disease recurrence, initiation of new anti-cancer therapy, documented withdrawal of consent by the participant, participant is lost to follow-up, or the study is terminated. • During the treatment phase, efficacy assessment procedures should be performed 2 weeks (±1 week) prior to the first dose of the next treatment cycle. • Participants with recurrent disease will be discontinued from study treatment and followed for survival every 6 months from the date of recurrence until 4 years from Week 1 Day 1 of treatment or until documented withdrawal of consent by the participant, participant is lost to follow-up, or the study is terminated. Any new cancer therapy (including radical cystectomy/radiotherapy) and stage of disease at time of new therapy will also be documented. ***NOTE***: Additional cohorts may be added in a future protocol amendment to evaluate other treatment groups.

Study Population:	**<u>Cohort A</u>** To be eligible for participation in this trial, participants must meet all the following entry criteria. The participant must: 1. Be ≥18 years of age (or legal age of majority in the jurisdiction) on day of signing informed consent 2. Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. 3. Have pathologically confirmed (World Health Organization [WHO] grading system employed for tumor grading) *(Compérat 2019)* BCG-naïve, CIS-containing (i.e., CIS with or without concomitant HG Ta/T1) high-risk NMIBC within 90 days of randomization. Participants with BCG-naïve NMIBC should have either: • No prior treatment with BCG OR • No treatment with BCG within the past 24 months prior to current pathological diagnosis OR • A maximum of 1 or 2 doses of BCG within the past 24 months prior to current pathological diagnosis. ***NOTE:*** ○ Tumor risk stratification is determined by 2024 American Urological Association (AUA) guidelines (*Holzbeierlein 2024*). ○ All pathology specimens must be predominantly urothelial (transitional cell) and have less than 50% histologic subtype/variant histology (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid, squamous, or glandular differentiation). ○ Any prior combination BCG treatment will be considered as additional BCG therapy. 4. Have all Ta and/or T1 disease resected, and all CIS resected or fulgurated, as feasible within 90 days prior to randomization. ***NOTE:*** ○ Participants with T1 NMIBC at screening should have a repeat biopsy evaluation of the prior resection site at least 2 weeks prior to randomization to adequately rule out muscle invasion or T2 disease. ○ If there is a concern for incomplete resection/regrowth, a repeat cystoscopy is recommended to ensure absence of disease prior to randomization. ○ Starting at screening and throughout the treatment phase, study treatment will be administered at least 14 days following the most recent transurethral resection (TUR) or biopsy. In addition, during the treatment phase, cretostimogene treatment will begin no later than

28 days after the most recent TUR or biopsy. CG Oncology approval is required for cretostimogene treatment cycle to begin less than 14 days after the most recent TUR or biopsy.

5. Refuse radical cystectomy.
6. Demonstrate adequate organ function, defined as:
   - Aspartate transaminase (AST), alanine aminotransferase (ALT) ≤2.5×upper limit of normal (ULN)
   - Total serum bilirubin ≤1.5×ULN (OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5×ULN)
   - Absolute neutrophil count (ANC) ≥1,000 cells/mm^3
   - Hemoglobin ≥8 g/dL or ≥4.96 mmol/L
   - Platelet count ≥75,000 platelets/mm^3
   - Serum creatinine ≤1.5×ULN or glomerular filtration rate (GFR) ≥30 mL/min/1.73 m^2 for participants with creatinine levels >1.5 institutional ULN according to the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Modification of Diet in Renal Disease (MDRD) or Cockroft-Gault equations.
   - Serum chemistries: sodium, potassium, and calcium within normal limits (WNL) or Grade 1.

     NOTE: Participants with chronic, asymptomatic Grade 2 hyponatremia will be permitted.
   - International normalized ratio (INR) or prothrombin time (PT) ≤1.5×ULN unless receiving anticoagulation therapy and INR or PT is within the therapeutic range of intended use of anticoagulants.

     NOTE: Participants must be able to suspend, based on local practice, anticoagulant and antiplatelet therapy for study specific biopsies and procedures.
7. Be willing to use barrier contraception during sexual activity, starting at least 14 days prior to Day 1 for women and starting at Day 1 for men, through 6 weeks after the last dose of cretostimogene.
8. Be willing to comply with all study-mandated cystoscopies, urine cytologies, biopsies, imaging, and other procedures (including TURBT or other resection for all Ta/T1 disease) for the duration of the study. Participants who withdraw consent for these procedures will be withdrawn from the trial.

Cohort B

Inclusion Criteria

To be eligible for participation in this trial, participants must meet all the following entry criteria. The participant must:

1. Be ≥18 years of age (or legal age of majority in the jurisdiction) on day of signing informed consent.
2. Have ECOG performance status of 0 to 2.

	3. Have pathologically confirmed (WHO grading system employed for tumor grading) *(Compérat 2019)* BCG-exposed high-risk NMIBC (i.e., HG Ta/T1 disease with or without CIS) within 90 days of treatment allocation.
	
	Participants with BCG-exposed NMIBC should have either:
	
	• BCG-resistant NMIBC:
	  ○ Persistent or recurrent HG Ta or CIS at the 3-month evaluation that follows at least 5 of 6 doses of induction BCG.
	
	OR
	
	• Delayed relapse after adequate BCG:
	  ○ HG recurrence outside of the BCG-unresponsive window (>6 months for Ta/T1 and >12 months for CIS) but within 24 months after the last dose of adequate BCG.
	  ▪ Adequate BCG is defined as at least 5 of 6 doses of induction BCG and at least 2 doses of one course of either re-induction or maintenance BCG.
	
	NOTE: The 5+2 minimum BCG treatment must be completed within 12 months of the initial qualifying BCG induction dose.
	
	OR
	
	• Delayed relapse after inadequate BCG:
	  ○ HG recurrence after 6 months but within 24 months after the final dose of inadequate BCG.
	  ▪ Inadequate BCG is defined as 3–6 doses.
	
	NOTE:
	
	  ○ Tumor risk stratification is determined by 2024 AUA guidelines (*Holzbeierlein 2024*).
	
	  ○ All pathology specimens must be predominantly urothelial (transitional cell) and have less than 50% histologic subtype/variant histology (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid, squamous, or glandular differentiation).
	
	  ○ Any prior combination BCG treatment will be considered as additional BCG therapy.
	
	4. Have all Ta and/or T1 disease resected, and all CIS resected or fulgurated, as feasible, within 90 days prior to treatment allocation.
	
	NOTE:
	
	• Participants with T1 NMIBC at Screening should have a repeat biopsy evaluation of the prior resection site at least 2 weeks prior to treatment allocation to adequately rule out muscle invasion or T2 disease.
	
	• If there is concern for incomplete resection/regrowth, a repeat cystoscopy is recommended to ensure absence of disease prior to study entry.
	
	• Starting at Screening and throughout the Treatment Phase, study treatment will be administered at least 14 days following the most recent TUR or biopsy. In addition, during the Treatment Phase, cretostimogene treatment

will begin no later than 28 days after the most recent TUR or biopsy. CG Oncology approval is required for cretostimogene treatment cycle to begin less than 14 days after the most recent TUR or biopsy.

5. Refuse radical cystectomy.
6. Demonstrate adequate organ function, defined as:
   - AST, ALT ≤2.5×ULN
   - Total serum bilirubin ≤1.5×ULN (OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5×ULN)
   - ANC ≥1,000 cells/mm^3
   - Hemoglobin ≥8 g/dL or ≥4.96 mmol/L
   - Platelet count ≥75,000 platelets/mm^3
   - Serum creatinine ≤1.5×ULN or GFR ≥30 mL/min/1.73 m^2 for participants with creatinine levels >1.5 institutional ULN according to the 2021 CKD-EPI, MDRD, or Cockcroft-Gault equations.
   - Serum chemistries: sodium, potassium, and calcium WNL or Grade 1.

     NOTE: Participants with chronic, asymptomatic Grade 2 hyponatremia will be permitted.
   - INR or PT ≤1.5×ULN unless receiving anticoagulation therapy and INR or PT is within the therapeutic range of intended use of anticoagulants.

     NOTE: Participants must be able to suspend, based on local practice, anticoagulant and antiplatelet therapy for study specific biopsies and procedures
7. Be willing to use barrier contraception during sexual activity, starting at least 14 days prior to Day 1 for women and starting at Day 1 for men through 6 weeks after the last dose of cretostimogene.
8. Be willing to comply with all study-mandated cystoscopies, urine cytologies, biopsies, imaging and other procedures (including TURBT or other resection for all Ta/T1 disease) for the duration of the study. Participants who withdraw consent for these procedures will be withdrawn from the trial.

Exclusion Criteria (Cohort A and B):

NOTE: There are no differences in the Exclusion Criteria between Cohort A and Cohort B.

The participant must be excluded from participating in the trial if the participant:

1. Has a current or past history of muscle invasive (T2 or higher stage), locally advanced (T3/T4, any N) or metastatic bladder cancer.
2. Any HG, non-muscle-invasive urothelial carcinoma (T1, HG Ta, or CIS) in the upper genitourinary tract or prostatic urethra (including CIS of the urethra) within 24 months prior to randomization or treatment allocation OR any history of T2 or higher stage urothelial carcinoma in the upper genitourinary tract (kidneys, renal collecting systems, ureters).

	3. Has had any prior systemic treatment (except for checkpoint inhibitor therapy), radiation therapy, or surgery (except for TURBT/biopsy/fulguration) for bladder cancer. Previous intravesical therapies are allowed if they do not contravene any other exclusion criteria. 4. Has received intravesical therapy within 90 days prior to randomization or treatment allocation except for cytotoxic agents (e.g., mitomycin C, gemcitabine, doxorubicin, and epirubicin) when administered as a single instillation immediately following a TURBT. 5. Has had any of the following within the 6 months prior to randomization or treatment allocation: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, cerebrovascular accident, pulmonary embolus, uncontrolled hypertension, or uncontrolled congestive heart failure. 6. Requires use of antiplatelet or anticoagulant therapy that cannot be safely suspended for per protocol biopsies and other standard of care procedures. 7. Has used excluded anti-viral medication (e.g., interferon/peg-interferon, ribavirin, etc.) within 14 days prior to randomization or treatment allocation and which cannot be suspended for at least 14 days prior to and after each treatment with cretostimogene. 8. Has significant immunodeficiency due to underlying illness (e.g., known HIV/AIDS). ***NOTE***: HIV testing is not mandatory unless required by local health authorities. HIV without viral load or stable infection may be considered in consultation with Medical Monitor. 9. Has received (or will receive during the study) systemic immunosuppressive medication including high-dose corticosteroids (e.g., systemic corticosteroids >10 mg prednisone or equivalent), within 4 weeks prior to randomization or treatment allocation. ***NOTE***: Participants with contrast dye allergies may be given 1–3 dose(s) of a systemic steroid to complete a contrast-enhanced CT urogram) for trial purposes. A steroid dose may also be administered as part of general anesthesia premedication, if required. A 14-day minimum separation of the steroid dose and cretostimogene dose must occur. 10. Has had active autoimmune or inflammatory disease requiring systemic treatment within 4 weeks of randomization or treatment allocation (i.e., with use of disease modifying agents, corticosteroids, or immune-modulating drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered an excluded form of systemic treatment and is allowed. 11. Has had prior organ or allogenic stem cell transplant. 12. Has received a live, replication competent vaccine within 30 days prior to randomization or treatment allocation. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, intradermal BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally

killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live, attenuated vaccines and are not allowed.

NOTE: COVID-19 vaccination is permitted at least 7 days after cretostimogene treatment. Please contact CG Oncology if the participant has received, or plans to receive, live, replication competent COVID-19 vaccination and document the date and type of COVID-19 vaccine received.

13. Has known active Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

- Participants with active acute or active chronic Hepatitis B or C, who take medications with anti-Hepatitis B or C activity are ineligible. Participants who have evidence of hepatic decompensation or cirrhosis on physical exam, laboratory, pathologic or radiographic testing also are ineligible.
- Participants with inactive chronic Hepatitis B infection (asymptomatic healthy carriers) who meet the trial-defined laboratory parameters are eligible for trial entry.

NOTE: No testing for Hepatitis B and Hepatitis C is required unless mandated by a local health authority.

14. Has a history of another malignancy within 3 years except the following:

- Prostate cancer that was localized, stage ≤T2b, Gleason score ≤4 + 3 = 7 treated with curative intent and without prostate-specific antigen recurrence.
- Prostate cancer that is localized, treatment-naïve, stage T1/T2a, Gleason score ≤3 + 4 = 7, prostate specific antigen ≤10 ng/mL, and undergoing active surveillance.
- Cancers with negligible risk of metastasis or death (e.g., risk of death or metastasis <5% at 5 years) that have been treated with curative intent and no evidence of recurrence or metastasis (e.g., adequately treated CIS of the cervix, basal or squamous cell skin cancer, or ductal CIS of the breast).

15. Has received systemic anti-cancer therapy, including investigational agents, within 90 days of randomization or treatment allocation.

16. Has had pelvic (including the bladder) external beam radiotherapy within 4 weeks of randomization or treatment allocation.

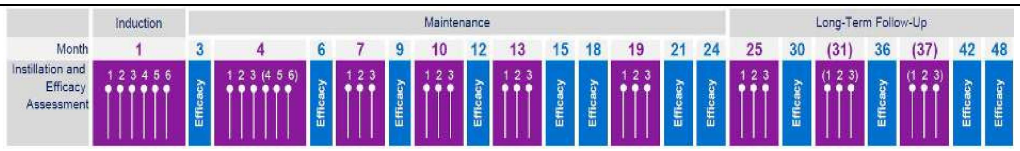
NOTE:

- Participants receiving prior radiation must have recovered (<Grade 1) from any acute toxicity.

17. Has not recovered (i.e., to Grade ≤1 or to Baseline status) from adverse events (AEs) due to a previously administered agent or therapy.

NOTE:

- Participants with Grade ≤2 neuropathy or participants having any alopecia are an exception to this criterion and may qualify for the study.

	• If the participant received major surgery, they must be at least 4 weeks from surgery and have recovered adequately from the toxicity and/or complications from the surgery prior to randomization or treatment allocation. TURBT or biopsy is not considered major surgery. • Participants with irreversible but not clinically significant toxicity are eligible. 18. Has an active infection requiring systemic therapy (e.g., active infection that requires long-term intravenous or oral antibiotics). 19. Has an illness, metabolic dysfunction, physical examination finding, or clinical laboratory finding that gives reasonable suspicion of a disease or condition that would contraindicate study treatment or that would limit compliance with study requirements. 20. Is pregnant, currently breastfeeding or intending to breastfeed, within the projected duration of the trial beginning at Screening through 6 weeks after the last study treatment. 21. Cannot tolerate study related biopsies, intravesical (IVE) administration, or 1-hour bladder hold of cretostimogene.
Study Schema:	 *Optional treatment year 3 in parentheses
Procedures:	**Cretostimogene Administration** In both cohorts, cretostimogene will be administered at a dose of 1×10^{12} vp intravesically following instillation of 0.1% DDM. A summary of the instillation procedure for each cohort is provided: **<u>Cohort A</u>** • **Cohort A, Arm 1:** o Initial bladder wash with 100 mL normal saline then drain o Second bladder wash with 75 mL 0.1% DDM then drain o Instillation of 100 mL 0.1% DDM with 15 minutes dwell time (±5 minutes) then drain o Third bladder wash with 100 mL of normal saline then drain o Instillation of cretostimogene in up to 100 mL normal saline with 60 minutes dwell time (±5 minutes) then drain. • **Cohort A, Arm 2:** o Instillation of 100 mL 0.1% DDM with 15 minutes dwell time (±5 minutes) then drain. o Instillation of cretostimogene in up to 100 mL normal saline with 60 minutes dwell time (±5 minutes) then drain.

NOTE (Both Arms):

- The optimal instillation volume of DDM and cretostimogene is 85-100 mL. For participants with known limited bladder capacity, 55 mL (±10%) is the minimum target volume of cretostimogene allowed. Provided the entire volume of diluted cretostimogene is instilled, a reduction in normal saline flush volume will not be considered a protocol deviation.
- Instillation of the complete volume of DDM and cretostimogene must be completed within 30 minutes +5 minutes) of the first bladder wash/instillation. Dwell times begin following instillation completion. Deviation from these infusion times must be documented in the source documents and case report form.

Cohort B (Arm 1 and Arm 2)

- Instillation of 100 mL 0.1% DDM with 15 minutes dwell time (±5 minutes) then drain.
- Instillation of cretostimogene in up to 100 mL normal saline with 60 minutes dwell time (±5 minutes) then drain.

NOTE:

- The optimal instillation volume of DDM and cretostimogene is 85-100 mL. For participants with known limited bladder capacity, 55 mL (±10%) is the minimum target volume of cretostimogene allowed. Provided the entire volume of diluted cretostimogene is instilled, a reduction in normal saline flush volume will not be considered a protocol deviation.
- Instillation of the complete volume of DDM and cretostimogene must be completed within 30 minutes (+5 minutes) of the first bladder instillation. Dwell times begin following instillation completion. Deviation from these infusion times must be documented in the source documents and case report form.

Details on dose preparation, storage conditions, and/or administration can be found in the CORE-008 *Pharmacy Manual, Cretostimogene Instillation Manual,* and *Cretostimogene Intravesical Injection Preparation Worksheet*.

Safety Assessment

Safety assessments will include the following:

- Physical examination
- Vital signs
- Assessment of treatment emergent AEs
- Safety laboratory assessments

The procedures will be performed as described in the Schedule of Events beginning from Screening and continuing through 30 days after the last treatment with cretostimogene. An End of Treatment/Safety Follow-up visit should be scheduled approximately 30–60 days from the last study treatment or from the date it is determined

that the participant will discontinue, whichever is later. Additional assessments may be performed as deemed appropriate by the Investigator.

Treatment-emergent AEs and serious adverse events (SAEs) will be captured from Treatment Day 1 through 30 days after the last treatment with cretostimogene; in addition, SAEs that occur during screening procedures will be captured. Any other toxicities noted at Screening, including clinically relevant physical examination or laboratory findings, will be recorded as medical history.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Efficacy Assessments (Treatment Phase and Long-Term Efficacy Follow-up Phase):

Cohort A

Efficacy Assessments during the Treatment phase and the Long-Term Response Follow-up phase will include the following:

Procedures	**Frequency**
Complete bladder visualization (e.g., cystoscopy)	• Every 3 months in Year 1 and Year 2 • Every 6 months in Year 3 and Year 4
Directed TURBT/biopsy, as indicated, based on complete bladder visualization	• Every 3-months in Year 1 and Year 2 • Every 6-months in Year 3
Urine cytology	• Every 3 months in Year 1 and Year 2 • Every 6 months in Year 3 and Year 4
CT urogram/ MR Urogram	• Every 6 months in all participants • As part of additional workup of an isolated positive urine cytology
Scheduled bladder mapping (to include all: trigone, bladder dome, right, left, and posterior bladder walls) and prostatic urethra biopsy (prostatic urethra biopsy required *only* in males with prior documented involvement)	• At Week 51 efficacy assessment
For-cause bladder mapping (trigone, bladder dome, right, left, and posterior bladder walls) and prostatic urethra biopsy (in all males *regardless* of prior documented involvement)	• As part of additional workup of an isolated positive urine cytology
Bilateral direct upper tract additional evaluation. • At a minimum, bilateral ureteric washings with additional/alternative workup at the discretion of the site's Primary Investigator.	• As part of additional workup of an isolated positive urine cytology

Cohort B

Efficacy Assessments during the Treatment phase and the Long-Term Follow-up phase will include the following:

Procedures	Frequency
Complete bladder visualization (e.g., cystoscopy)	• Every 3 months in Year 1 and Year 2 • Every 6 months in Year 3 and Year 4
Directed TURBT/biopsy, as indicated, based on complete bladder visualization	• Every 3 months in Year 1 and Year 2 • Every 6 months in Year 3 and Year 4
Urine cytology	• Every 3 months in Year 1 and Year 2 • Every 6 months in Year 3 and Year 4
CT urogram/ MR urogram	• Every 6 months in all participants • As part of additional workup of an isolated positive urine cytology
Arm 1 (CIS-containing disease): **Scheduled** bladder mapping (to include all: trigone, bladder dome, right, left, and posterior bladder walls) and prostatic urethra biopsy (prostatic urethra biopsy required *only* in males with prior documented involvement)	• At Week 51 efficacy assessment
Arm 2 (Papillary-only disease): **Scheduled** bladder biopsies directed at prior tumor locations	• At Week 51 efficacy assessment
For-cause bladder mapping (trigone, bladder dome, right, left, and posterior bladder walls) and prostatic urethra biopsy (in all males *regardless* of prior documented involvement)	• As part of additional workup of an isolated positive urine cytology
Bilateral direct upper tract additional evaluation • At a minimum, bilateral ureteric washings with additional/alternative workup at the discretion of the site's Primary Investigator.	• As part of additional workup of an isolated positive urine cytology

Number of Participants

- **Cohort A** will enroll up to 50 participants with BCG-naïve, CIS-containing high-risk NMIBC (i.e., CIS with or without Ta/T1 disease).
- **Cohort B** will enroll up to 150 participants with BCG-exposed, high-risk NMIBC (i.e., CIS with or without Ta/T1 disease [Arm 1] or HG Ta/T1 papillary disease without CIS [Arm 2]).

Additional cohorts may be added in a future protocol amendment to evaluate other treatment groups.

Study Duration	Study accrual is expected to occur over a maximum of approximately 12-18 months. Participant participation will be up to 48 months.
Survival Follow-up	**Cohort A and Cohort B:** When a participant is no longer considered in CR (Cohort A and Cohort B, Arm 1) or HG Recurrence-Free (Cohort B, Arm 2), participants will be followed for survival and new anti-cancer therapies (e.g., by telephone, email, clinic visit record) every 6 months for up to 4 years from Week 1 Day 1.
Statistical Design:	**Cohort A** will randomize up to 50 participants with BCG-Naïve, CIS-containing high-risk NMIBC. Analysis for this cohort will utilize descriptive statistics (such as mean, median, standard deviation, ranges for continuous data, and percentages for categorial data). These statistics will be used to summarize participant characteristics, treatment administration/compliance, efficacy, safety, and laboratory or exploratory parameters. For time-to-event variables (RFS, EFS, overall survival, etc.) survival analysis methods including Kaplan-Meier analyses will be used. Data will be displayed graphically, where appropriate. For the primary endpoint, (CR at any time) the percentage of participants with CR at any time will be presented by randomized treatment arm and overall, with 95% confidence interval estimates. Included within analysis of secondary endpoints will be a comparison of viral replication between Arm 1 and Arm 2. **Cohort B** will allocate treatment to up to 150 participants with BCG-exposed High-Risk NMIBC, ~75 participants with CIS-containing High-Risk NMIBC (Arm 1) and ~75 participants with papillary-only High-Risk NMIBC (Arm 2). Analysis for this cohort will utilize descriptive statistics (such as mean, median, standard deviation, ranges for continuous data, and percentages for categorial data). These statistics will be used to summarize participant characteristics, treatment administration/compliance, efficacy, safety, and laboratory or exploratory parameters. For time-to-event variables (RFS, EFS, overall survival, etc.) survival analysis methods including Kaplan-Meier analyses will be used. Data will be displayed graphically, where appropriate. For the primary endpoint in Arm 1, (CR at any time) the percentage of participants with CR at any time will be presented. For the Primary endpoint in Arm 2 (HG EFS), The proportion of participants who remain free from HG events (e.g., HG disease recurrence, progression or death) at 12 and 24 months will be presented.