CORE-008

Phase 2, Multi-Cohort, Open-Label Study of Cretostimogene Grenadenorepvec in High-Risk NMIBC

High-Risk NMIBC	Cretostimogene grenadenorepvec Cohort A (n=50), Cohort B (n=150)	CR (CIS) or HG-EFS Rate (Papillary)

Population / Key Entry Criteria	Study Design / Regimen	Additional Endpoints

• AUA definition HR NMIBC
  • CIS, HG T1, HG Ta (>3cm, multifocal)
  • Other HR features
• BCG-naïve* (Cohort A)
• BCG-exposed** (Cohort B)
• Complete resection at baseline
• Adequate organ function
• ECOG 0-2
	• Cohort A = Randomization to instillation method (5-step vs 2-step)
	• Cohort B = Assigned to CIS or Papillary-only treatment arms
	• IVE Treatment Schedule
	  • Induction course = Weekly x 6
	  • Maintenance courses = Weekly x 3
	• Disease assessment
	  • Every 3 months cystoscopy and urine cytology for 2 years; then every 6 months in Years 3-4
		• DoR
		• EFS and RFS
		• Cystectomy-free survival
		• Safety
		• Exploratory endpoints include Biomarkers, PRO and HRQoL, OS

* BCG-naïve includes no prior treatment with BCG, no BCG within past 24 mo prior to current diagnosis, or maximum 1-2 doses of BCG within past 24 mo prior to current diagnosis
** BCG exposed includes BCG resistant and delayed relapse after adequate and inadequate BCG
AUA- American Urologic Association, BCG-Bacillus Calmette-Guerin, CR- Complete Response, DoR- Duration of Response, EFS- Event-free survival, HR- High risk, HRQoL, Health-Related Quality of Life, IVE- intravesical, LG- Low grade, OS- Overall Survival, PFS-Progression Free Survival, PRO- Patient Reported Outcomes, RFS-Recurrence Free Survival
NCT06567743

Protocol Design

- N = 50 (Cohort A) and 150 (Cohort B)
- Target Population: **High-Risk NMIBC** as defined by 2024 AUA guidelines
  - **Cohort A are BCG-naïve** and **must contain CIS**
    - At most 2 doses in last 24 months
  - **Cohort B are BCG-exposed** and may have **CIS or papillary only** disease
    - Persistent or recurrent disease after inadequate BCG; delayed relapse
- Enrollment projected over 12-18 months
- Patient participation is 48 months
- After confirmation of HR-NMIBC and TURBT,
  - **Cohort A are randomized 1:1 to cretostimogene instillation methods (5 vs 2-step)**
  - **Cohort B are allocated to arms for CIS-containing or papillary only disease**

Inc/Exc Criteria

Key Eligibility Criteria

Inclusion Criteria
• HR NMIBC, AUA definition
• BCG-naïve (Cohort A)
• BCG-exposed (Cohort B)
• Complete TURBT within 90 days
• Adult, ECOG 0-2
• Willing to use contraception, comply with procedures
• Adequate organ function

Exclusion Criteria
• MIBC, Nodal or Metastatic UC
• UC in upper tract or urethra within 24 months
• Any history of T2 or higher in upper tract
• Prior systemic treatment, radiation, or surgery (beyond TURBT) for bladder cancer
• Intravesical therapy within 90 days
• Antiplatelet/anticoagulation, antiviral or immunosuppressive meds that can't be held
• Transplant, AIDS, active Hep B/C, malignancy, active infection
• Live vaccine, within 30 days
• Not recovered from AE's, condition that contraindicates study, pregnant/breastfeeding (or planning to), can't tolerate study procedures

Inc/Exc Criteria

Inclusion Criteria

1. ≥18 years of age (or legal age of majority) on day sign informed consent
2. ECOG performance status 0 to 2
3. [See **Cohort A** or **Cohort B** specific slide]

Inc/Exc Criteria

Inclusion Criteria – Cohort B only

3. Pathologically confirmed BCG-exposed, high-risk NMIBC within 90 days of allocation. This can be 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

   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 with < 50% histologic subtype/variant histology
Any prior combination BCG treatment will be considered as additional BCG therapy

Inc/Exc Criteria

Inclusion Criteria (cont.)

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 concern for incomplete resection/regrowth, a repeat cystoscopy is recommended to ensure absence of disease prior to randomization
   - From screening through treatment, study treatment will be administered at least **14 days** following the most recent transurethral resection (TUR) or biopsy. 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

Inclusion Criteria (cont.)

6. Demonstrate adequate organ function, defined as:

- AST, ALT ≤ 2.5 ǔ ULN
- TBil ≤ 1.5 ǔ ULN (or Dbil ≤ ULN if Tbil > 1.5 ǔ ULN)
- ANC ≥ 1,000 cells/mm^3
- Hgb ≥ 8 g/dL or ≥ 4.96 mmol/L
- Plt ≥ 75,000 platelets/mm^3
- SCr ≤ 1.5 ǔ ULN (or GFR ≥ 30 mL/min/1.73m^2 if SCr > 1.5 x institutional ULN)
- Serum chemistries: Na, K, Ca^{++} within normal limits or Grade 1

  NOTE: Participants with chronic, asymptomatic Grade 2 hyponatremia will be permitted
- INR or PT ≤ 1.5 ǔ ULN (unless receiving anticoagulation therapy and INR or PT is within intended therapeutic range)

  NOTE: Participants must be able to suspend, based on local practice, anticoagulant and antiplatelet therapy for study specific biopsies and procedures

Inclusion Criteria (cont.)

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

Inc/Exc Criteria

Exclusion Criteria

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

Exclusion Criteria (cont.)

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) 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

Inc/Exc Criteria

Exclusion Criteria (cont.)

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: Participant 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

Exclusion Criteria (cont.)

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: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, intradermal BCG, and typhoid vaccine. Seasonal influenza vaccines (injection) are generally killed virus vaccines (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

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

Inc/Exc Criteria

Exclusion Criteria (cont.)

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

Exclusion Criteria (cont.)

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

    NOTE: Participants with Grade ≤2 neuropathy or participants having any alopecia 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 prior to randomization or treatment allocation

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, IVE administration, or 1-hour bladder hold of cretostimogene