

LEGEND, A PHASE 1/2 STUDY OF DETALIMOGENE VORAPLASMID (EG-70) INTRAVESICAL MONOTHERAPY, DEMONSTRATED CLINICAL RESPONSES IN BCG-UNRESPONSIVE NON-MUSCLE-INVASIVE BLADDER CANCER PATIENTS WITH CARCINOMA IN SITU

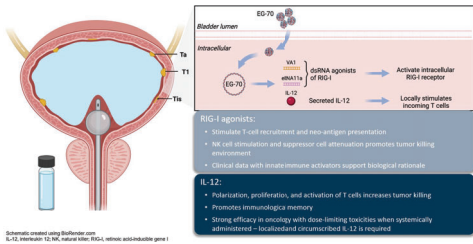
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Background

- An estimated 75% of bladder cancers are non-muscle invasive.¹ High-risk non-muscle-invasive bladder cancer (NMIBC), which includes high-grade Ta, T1, and carcinoma *in situ* (CIS) NMIBC, is treated with adjuvant intravesical Bacille Calmette-Guérin (BCG), which reduces the risk of disease recurrence.² However, approximately 50% of BCG-treated patients experience recurrence and/or progression after BCG treatment and are considered BCG unresponsive.²
- enGene has developed a non-viral gene therapy platform for delivery of nucleic acids to the epithelia of mucosal tissues.³ EG-70 (detaimogene voraplasmid) is an investigational drug product that includes a plasmid drug substance and a delivery vehicle. The plasmid simultaneously expresses a recombinant single-chain human interleukin-12 (IL-12) and two double-stranded RNA activators of the intracellular innate immunity regulator retinoic acid-inducible gene-1 (RIG-I).
- EG-70 was specifically engineered for intravesical administration to elicit local stimulation of anti-tumor immune responses and drive durable efficacy in patients with BCG-unresponsive NMIBC (Figure 1), while mitigating the risk of systemic toxicities from immune stimulation. The nanoparticle formulation can be handled without onerous administration and decontamination procedures for clinicians or patients.
- LEGEND (NCT04752722) is an ongoing phase 1/2 study of EG-70 in patients with high-risk BCG-unresponsive NMIBC with CIS. We previously reported preliminary efficacy and safety findings from the phase 1 portion of the study.⁴ Enrollment into the phase 1 part of the study is now complete, the RP2D has been determined and the updated findings reported here. The phase 2 part of the study is currently enrolling.

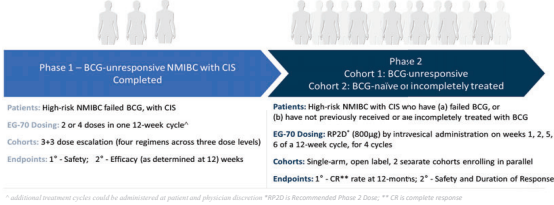
Figure 1. EG-70 is an easy-to-use lyophilized drug product reconstituted in urology clinics at point of administration



Methods

- Study design**
- LEGEND is an ongoing phase 1/2 study. Phase 1 is a dose-escalation study to establish the safety of EG-70 at 12 weeks and determine the recommended phase 2 dose (RP2D); phase 2 will evaluate efficacy and safety (Figure 2) after 4 cycles of treatment at the RP2D.
- Inclusion criteria**
- Age ≥18 years; Eastern Cooperative Oncology Group performance status 0-2; BCG-unresponsive NMIBC with CIS, with or without resected coexisting papillary tumors (Ta/T1 tumors), who are ineligible for, or have elected not to undergo, cystectomy. Prior checkpoint inhibitor treatment is allowed if completed within 30 days before study entry.
 - Satisfactory bladder function with ability to retain study drug for ≥60 minutes.
 - In Phase 2, an additional cohort of patients will be enrolled who are BCG-naïve or have been incompletely or inadequately treated with BCG.
- Treatment**
- EG-70 is reconstituted to 50 ml in sterile water and instilled intravesically for 60 minutes retention time.
 - Three escalating doses of EG-70 were administered to patients enrolled into the phase 1 part of the study by one of two schedules: at study Weeks 1 and 2, and for Dose Level 2, on Weeks 1, 2, 5 and 6 in 12-week cycles.
 - At the Week 12 assessment, patients with stable disease (SD) or a complete response (CR), as assessed by urine cytology, cystoscopy, and bladder biopsy, were allowed electively to remain on EG-70 for up to three additional 12-week cycles.
- Objectives**
- The primary objective of the Phase 1 part of the study was to assess the safety and tolerability of EG-70 at 12 weeks. Efficacy was a secondary objective; complete response was defined as negative cystoscopy and negative (including atypical) urine cytology, or positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative cytology.
- Ethics**
- The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and with the principles of the Declaration of Helsinki. All patients provided written informed consent.

Figure 2. LEGEND Phase 1/2 combined registration study design



Results

- At the time of data cut, escalating doses of EG-70 had been administered intravesically to 24 patients for one to four cycles.
- Treatment**
- Three patients received EG-70 at the lowest dose (0.25 mg/ml), 15 patients received 0.8 mg/ml, (five with two instillations and 10 with four instillations), and three patients received the highest dose (2.5 mg/ml).

Safety

- There were 132 adverse events in total (Figure 3). The most common treatment-related adverse events (AEs) were hematuria (8%), dysuria (6%), arthralgia (4%), and constipation (4%).
- There were four grade 3 adverse events and no grade 4 or 5 events. Acute renal failure in a patient with pre-existing upper renal tract pathology and hydronephrosis was considered treatment-related. The event resolved and treatment discontinued. The other grade 3 events were not considered treatment-related.

Figure 3. Adverse events

	Grade 1 AEs (mild)	Grade 2 AEs (moderate)	Grade 3 AEs (severe)	Grade 4 AEs (life-threatening)	Grade 5 AEs (result in death)
Aggregate data (N, all dose-levels)	99	29	4	0	0
Most commonly reported AEs (%)	- Hematuria (8%) - Dysuria (6%) - Arthralgia (4%) - Constipation (4%) - Flank pain (3%) - Micturition urgency (3%) - Pain (3%) - Fatigue (3%)	- Urinary tract infection (17%) - Urinary tract infection-enterococcal (3%) - Micturition urgency (7%)	- Renal failure* - Pneumonia* - Pneumonia* - Meningitis injury*	-	-

*Patient had a history of renal failure – enrollment criteria for phase 2 have been amended to exclude history of renal failure; [†]Deemed not related to study drug.

- Reported AEs to date are largely consistent with instrumentation/intravesical administration.
- No correlation between dose and grade or number of adverse events.

Efficacy

- EG-70 resulted in strong positive findings in patients with BCG-unresponsive NMIBC with CIS based on cytology, cystoscopy, and biopsy at all doses tested (Figure 4).
- The transgene IL-12 protein was detected in a dose-responsive manner in the urine of every patient, demonstrating transfection, and was still induced through four instillations (Figure 5).
- No clinically significant IL-12 was detected in plasma; urine IL-12 levels at dose level 2 were an order of magnitude higher than dose level 1 and no further increases in IL-12 production were observed at dose level 3.

References and acknowledgments

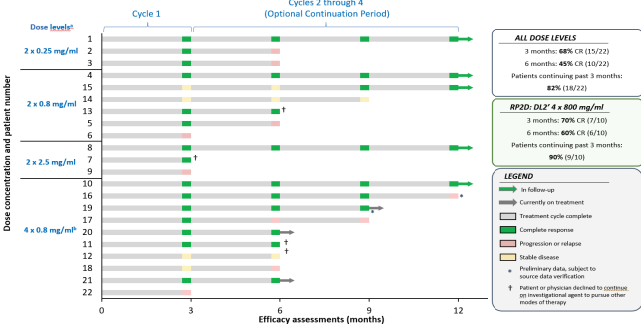
References

- Kamat AM, et al. Lancet 2016;388:2796-810.
- Balbjuk M, et al. Eur Urol 2022;81:75-94.
- Cheung A. Controlled Release Society Annual Meeting July 24-28, 2023.
- Steinberg GD, et al. J Clin Oncol 2023;41(6 suppl):512v.

Acknowledgments

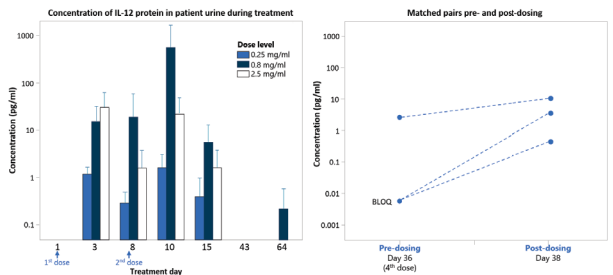
- The authors would like to thank the patients and their families for participating in the study, all research staff and others involved in the trial, and Miller Medical Communications for their editorial/layout support for this poster (funded by enGene).

Figure 4. Treatment duration and efficacy



Data cutoff: 8.22.2023. Includes preliminary data that may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data. *Dosing during each 12-week cycle, on either the 2 instillations or 4 instillations schedule as shown.

Figure 5. IL-12 protein concentrations in patients treated with EG-70



Conclusions and future directions

- EG-70 is a non-viral gene therapy administered intravesically for the treatment of BCG unresponsive NMIBC with CIS and in a separate cohort in phase 2 in patients who are BCG naïve or inadequately treated with BCG.
- No special handling requirements such as BSL2 practices and equipment are necessary, no premedication is required and there is no need for urine or toilet decontamination after treatment.
- The phase 1 part of the study is complete and the phase 2 part is currently enrolling using the RP2D of 0.8 mg/ml administered at weeks 1, 2, 5, and 6 of 12-week cycles for 1 year.
- Reported AEs to date are largely consistent with instrumentation/intravesical administration: the most commonly reported treatment-related AEs in phase 1 were hematuria, micturition urgency, and dysuria. Grade 3 and serious AEs were uncommon and were not considered related to treatment.
- Results from the phase 1 study are encouraging: the CR rate at 3 months across all efficacy-evaluable patients was 68%, and 45% at 6 months. The CR rate at 6 months in the 10 patients dosed at the RP2D was 60%.