CLINICAL STUDY PROTOCOL

A BIOMARKER STUDY IN MEN WITH LOCALIZED, INTERMEDIATE-RISK PROSTATE CANCER TREATED WITH AGLATIMAGENE BESADENOVEC

Protocol number: PrTK05

Phase: 2a

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Version: 2

IND: 08437

Sponsor: Candel Therapeutics, Inc.
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Sponsor Representative: W. Garrett Nichols, M.D.
Chief Medical Officer

Sponsor Representative Signature: See last page for approval.

CONFIDENTIALITY STATEMENT

1. SYNOPSIS

Name of Sponsor/company: Candel Therapeutics, Inc.	
Name of investigational product: aglatimagene besadenovec (also known as CAN-2409, AdV-tk, HSV-tk, ProstAtak®, and GMCI™)	
Name of active ingredient: aglatimagene besadenovec: a genetically modified replication-defective adenoviral vector expressing the herpes simplex virus (HSV) thymidine kinase (tk) gene.	
Title of study: A Biomarker Study in Men with Localized, Intermediate-risk Prostate Cancer Treated with aglatimagene besadenovec	
Study center(s): multi-center study, USA	
Principal Investigator: Dr. Glen Gejerman	
Study period (years): Estimated date first patient enrolled: 30 November 2025 Estimated date last patient completed: 30 June 2026	**Phase of development:** Phase 2a

Primary Objective:

- To evaluate the potential for vector biodistribution outside the site of aglatimagene besadenovec delivery and the duration of vector shedding associated with the use of aglatimagene besadenovec in patients with localized, intermediate-risk, prostate cancer.

Primary Endpoint:

- Proportion of patients with detectable shedding of aglatimagene besadenovec viral genomes in urine, blood, and semen samples over time.

Secondary Objectives:

- To evaluate changes in biomarkers after administration of aglatimagene besadenovec.
- To further confirm the safety and tolerability of aglatimagene besadenovec in patients with localized, intermediate-risk prostate cancer.

Secondary Endpoints:

- Change from baseline for biomarker levels at each scheduled timepoint over time in both treatment and concurrently enrolled control groups.
- Frequency, duration, and severity of treatment-emergent adverse events (TEAEs) and changes in clinical laboratory values.

Methodology:

This is an open-label study in which up to 45 patients diagnosed with localized intermediate-risk prostate cancer, with planned external beam radiation therapy (EBRT) treatment will be enrolled.

Treatment Group:

Approximately 30 patients will be recruited to receive 3 injections of aglatimagene besadenovec each, followed by 14-day courses of valacyclovir. Patients will have aglatimagene besadenovec administered either transrectally or transperineally into the prostate gland.

The biospecimens to be collected are blood and urine for all patients, with semen samples as an additional biospecimen to be collected when obtainable. Samples will be collected before and after injections of aglatimagene besadenovec. Biosampling will occur during study visits or at home (in the case of semen samples). See Figure 1.

Viral genomes will be quantified in samples using a validated quantitative PCR (qPCR) method specific for aglatimagene besadenovec. Samples will be collected at the timepoints described in Figure 1 and in the Schedule of Assessments (Table 1 and Table 2).

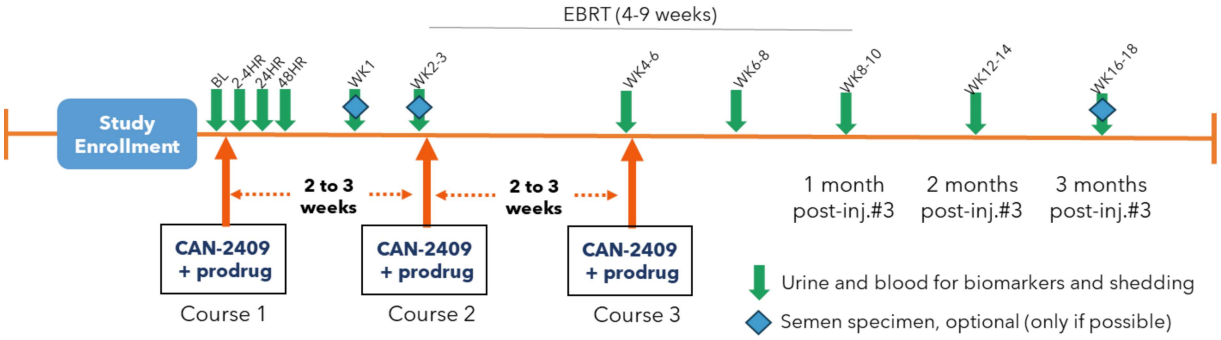
Patients will be followed for 3 months after their 3rd injection of aglatimagene besadenovec for biosampling. Patients who do not complete all planned courses will be followed up to 3 months after their last injection, prior to discontinuation.

Concurrently enrolled control group:

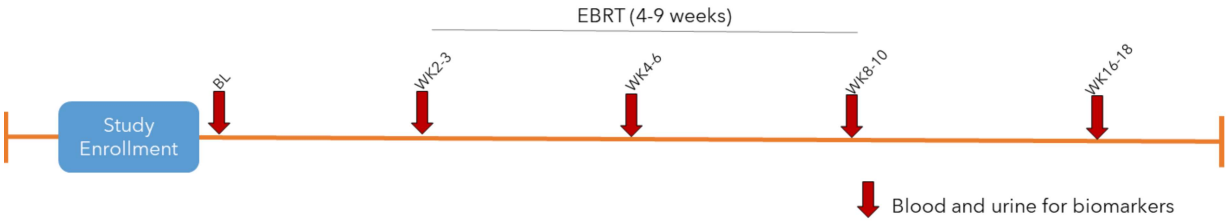
Approximately 15 patients undergoing standard of care radiation therapy treatment will be recruited to provide control blood and urine samples for biomarker analysis. Patients will be followed until their last biospecimen collection 16-18 weeks after enrollment.

Figure 1: Study Design and Biosampling

Treatment group



Concurrent control group



Abbreviations: BL, baseline; CAN-2409, aglatimagene besadenovec; EBRT, external beam radiation therapy; hr, hour; inj, injection; WK, week.
Note: prodrug = valacyclovir for 14 days following each injection
Note: biospecimens include blood, urine, and semen (if possible).

Number of patients (planned):

We plan to recruit approximately 45 patients diagnosed with localized, intermediate-risk prostate cancer, in order to include at least 20 patients with a complete set of longitudinal blood and urine samples in the treatment group and at least 10-15 in the concurrent control group.

Diagnosis and main criteria for inclusion:

Inclusion criteria 5 and 8 are not applicable to concurrent control group
Exclusion criteria 10 is not applicable to concurrent control group

Inclusion criteria

1. Patients must give study specific informed consent prior to enrollment
2. Histologically confirmed adenocarcinoma of the prostate
3. Patients meeting National Comprehensive Cancer Network (NCCN) intermediate-risk criteria:
    - Has one or more intermediate risk factors (IRFs):
        - cT2b–cT2c
        - Grade Group 2 or 3 (Gleason score of 7 (3+4 or 4+3))
        - PSA 10–20 ng/mL
    - No high-risk group features
    - No very-high-risk group features
4. Patients must be planning and medically able to undergo standard or moderate hypofractionated prostate-only EBRT
5. Patients must be able to tolerate multiple transrectal or transperineal ultrasound guided injections (treatment group only)
6. 18 years of age or older
7. Performance status must be Eastern Cooperative Oncology Group 0-2
8. The following laboratory criteria must be met (treatment group only):
    a. Aspartate aminotransferase (AST) < 3 x upper limit of normal
    b. Serum creatinine < 2 mg/dL
    c. Calculated creatinine clearance > 30 mL/min
    d. White blood cells > 3000/mm^3
    e. Platelets >100,000/mm^3

Exclusion criteria

1. Active liver disease, including known cirrhosis or active hepatitis
2. Patients on systemic corticosteroids (>10 mg prednisone per day) or other immunosuppressive drugs
3. Known HIV+ patients
4. Known regional lymph node involvement or distant metastases
5. Patients planning to receive whole pelvic irradiation
6. Other current malignancy (except squamous or basal cell skin cancers)
7. Other serious co-morbid illness or compromised organ function that, in the opinion of the Investigator, would interfere with treatment or follow up. For example, patients with diseases that

preclude radiation therapy to the prostate, such as severe prostatitis and inflammatory bowel disease.

8. Prior treatment for prostate cancer except transurethral resection of the prostate (TURP). If prior TURP, patients must be deemed able to receive multiple intra-prostatic injections by the Investigator.
9. Patients who had or plan to have orchiectomy as the form of hormonal ablation
10. Known sensitivity or allergic reactions to acyclovir or valacyclovir (treatment group only)

Investigational product, dosage and mode of administration:

Aglatimagene besadenovec: total 5 x 10^{11} vector particles (vp) x 3 injections, transrectally or transperineally, via ultrasound guided injection into the prostate gland.

Each injection is followed by a 14-day course of valacyclovir 2 grams orally, three times per day.

Duration of study:

Treatment group: Patients will be followed for 3 months from the 3rd injection of aglatimagene besadenovec (or 3 months after the last injection, in case of early discontinuation) for biosampling.

Concurrent control group: Patients will be followed until their last biospecimen collection 16-18 weeks after enrollment.

Reference therapy, dosage and mode of administration:

NA

Criteria for evaluation:

Safety:

Safety will be monitored in patients in the treatment group based on adverse events (AEs), and changes in laboratory values. AEs will be assessed and graded via National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

For the concurrent control group patients, only SAEs related to biomarker collection procedure (e.g., blood draw) will be recorded.

Biodistribution and viral shedding:

Biodistribution and shedding will be evaluated on blood, urine and semen of patients dosed with aglatimagene besadenovec to assess presence of viral genome. Aglatimagene besadenovec viral genome will be quantified in collected samples using a quantitative polymerase chain reaction (qPCR).

Biomarkers:

Biomarker analyses will be performed on blood and urine samples of both patients treated with aglatimagene besadenovec and concurrently enrolled controls to assess immune activation pre- and post-treatment with aglatimagene besadenovec. Biomarker assays will include, but are not limited to, evaluation of PSA dynamics, frequency and functional activity of peripheral immune cells, antigen-specific T cell profiling, circulating and urine cytokines and protein levels, and assessment of clinical immunological features such as immunoglobulins and antibodies over time. Changes in biomarkers will be compared to the concurrent control patients.