A Prospective Study on the Safety, Tolerability, and Efficacy of PDR-001 Injection for Bilateral Stereotactic Subthalamic Nucleus (STN) Clearance of Alpha-Synuclein

July 6, 2025

NIH Clinical Protocol Template: PDR-001 Study

1. STUDY OVERVIEW

Full Protocol Title:

A Prospective Study on the Safety, Tolerability, and Efficacy of PDR-001 Injection for Bilateral Stereotactic Subthalamic Nucleus (STN) Clearance of Alpha-Synuclein

Protocol ID Number: NA

Version Number and Date: V1.0, July 6, 2025

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Study Period: May 2025 to December 2029

Study Phase: Phase I/II (Exploratory)

Study Sites: Single-site trial at Ruijin Hospital, Shanghai

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective (52-week Core Phase):

Evaluate the safety and tolerability of PDR-001 injected bilaterally into the STN of patients with early primary PD.

2.2 Secondary Objective:

Evaluate the clinical efficacy of PDR-001 within 52 weeks post-injection.

2.3 Long-term Objective:

Evaluate long-term safety and efficacy from week 52 up to 5 years.

2.4 Endpoints

Primary Endpoints:

- Incidence of adverse events (AEs) and serious adverse events (SAEs)

- Change in rAAV neutralizing and binding antibody titers

- Change in whole blood rAAV vector titers

Secondary Endpoints:

- Change in daily Levodopa dose or Levodopa Equivalent Dose (LED)

- Change from baseline in the following scales:

  - MDS-UPDRS I-IV

  - PGI-I, CGI-I

  - MMSE, HAMD, HAMA

  - PDSS-2, PDQ-39

  - MoCA, NMSQ, SCOPA-AUT, RBDSQ, SS-16, PSQI, Wexner, Berg, Tinetti, Webster, GFQ

Long-term Endpoints (52 weeks – 5 years):

- All primary and secondary endpoints continued over time

- [18F]F-dopa PET gene expression

- DaT-SPECT putaminal binding ratio changes

3. BACKGROUND AND RATIONALE

3.1 Disease Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by the death of dopaminergic neurons in the substantia nigra. Motor and non-motor symptoms impair

quality of life. In China, PD prevalence ranges from 16.7 to 440.3 per 100,000, affecting 1.7% of the elderly population.

3.2 Unmet Medical Need

Current treatments offer symptomatic relief but do not halt disease progression. Alpha-synuclein aggregation is a hallmark of PD pathology. There is a need for innovative therapies that directly target and degrade alpha-synuclein.

3.3 Study Agent (PDR-001)

PDR-001 is a novel gene therapy delivered via AAV9 vector encoding a tripeptide (Tat-βsyn-deg) designed to degrade α-synuclein.

3.4 Preclinical Data

- **Mice (A53T model):** Significant reduction in α-syn, increased dopaminergic neurons, improved behavior

- **Non-human primates:** Improved motor scores, PET signal in striatum, no systemic toxicity

3.5 Rationale for Study Design

First-in-human trial assessing safety and potential clinical benefit of PDR-001 in early-stage PD. Bilateral STN chosen for direct delivery.

3.6 Risk/Benefit Assessment

Risks: Neurosurgical injection, immune response to AAV, transient neuropsychiatric symptoms

Benefits: Potential disease-modifying effect by reducing toxic α-synuclein burden

Conclusion: Favorable risk-benefit ratio supports study initiation

4. STUDY DESIGN AND METHODS

4.1 Overall Design

Single-arm, open-label, single-center trial. Total enrollment of 12 participants. Dose-escalation (n=6 in 2 dose levels), followed by an expansion cohort (n=6).

4.2 Study Duration

- 52-week core study

- Up to 5-year long-term follow-up

4.3 Sample Size Justification

Exploratory study with 12 patients. No formal power calculation. Safety and biological signals will guide future studies.

4.4 Study Intervention

- **Drug:** PDR-001 injection (AAV9 vector expressing Tat-βsyn-deg)

- **Route:** Bilateral stereotactic injection into the STN

- **Method:** Stereotactic multi-point microinjection (4 targets total)

4.5 Study Population

12 patients with early-stage primary PD.

Inclusion Criteria (summary):

- Age 40–65, Hoehn-Yahr ≤ 2, disease duration ≤ 5 years

- Adequate cognitive and liver/renal function

- Negative for HIV, HBV, HCV

Exclusion Criteria (summary):

- Atypical or secondary Parkinsonism

- History of brain surgery, malignancy, or severe comorbidities

- Pregnancy or nursing

5. STUDY PROCEDURES AND ASSESSMENTS

Participants will undergo the following evaluations:

- **Preoperative screening:** Informed consent, demographics, physical exam, imaging, lab tests (hematology, biochemistry, serology, pregnancy test), ECG, PD assessments

- **Intervention:** Stereotactic bilateral STN injection of PDR-001 under general anesthesia

- **Follow-up:** At week 4, 12, 26, 39, and 52 post-injection, and every 26 weeks during long-term follow-up. Evaluations include lab tests, imaging (MRI, PET, DaT-SPECT), PD scales, safety assessments

6. SAFETY MONITORING AND ADVERSE EVENT REPORTING

- All AEs and SAEs will be recorded from consent through 52-week core study and throughout long-term follow-up if related to gene therapy.

- SAEs will be reported to the sponsor and Ethics Committee within 24 hours.

- Safety will be reviewed by an independent Safety Review Committee (SRC).

7. STATISTICAL ANALYSIS PLAN

- **Descriptive statistics** will summarize safety, tolerability, and efficacy outcomes.

- Categorical data: frequencies and percentages

- Continuous data: mean, median, standard deviation, range

- No formal hypothesis testing due to exploratory nature

8. ETHICAL CONSIDERATIONS

- The study will comply with the Declaration of Helsinki and GCP guidelines.

- Ethics Committee approval is required before initiation.

- Informed consent will be obtained from all participants.

9. DATA HANDLING AND RECORD RETENTION

- Electronic Data Capture (EDC) system will be used for data collection.

- All source documents and CRFs will be retained for a minimum of 5 years after study completion.

- Patient confidentiality will be protected through anonymization and restricted access.

10. REFERENCES

(Full reference list available upon request, based on Chinese and international preclinical and clinical gene therapy literature, supporting PDR-001 development.)