Title Page

Brief Title:

Intranasal MSC-Derived Exosomes for Parkinson's Disease

Official Title:

A Single-Center, Open-Label, Dose-Escalation Study to Evaluate the Safety and Efficacy of Intranasal Umbilical Cord Mesenchymal Stromal Cell-Derived Exosomes in Patients With Parkinson's Disease

Protocol Version:

V1, dated 20 August 2024

Protocol Number:

[Not provided in the source protocol; insert before submission]

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Sponsor:

Ruijin Hospital, Shanghai Jiao Tong University School of Medicine

Responsible Party:

Principal Investigator

Collaborators:

None stated in the protocol

Funding Source:

Not stated in the protocol

Study Location:

Department of Neurology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

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1. Study Overview

Study Type:

Interventional

Recruitment Status:

To be confirmed by the sponsor

[Protocol planned start: October 2024]

Estimated Enrollment:

3 to 18 participants

Study Start Date:

October 2024

Study Completion Date:

September 2027

Conditions:

Parkinson's Disease

Intervention:

Biological: Umbilical cord mesenchymal stromal cell-derived exosomes (UCMSC-Exo), administered intranasally by spray

Study Design:

Single-center, open-label, dose-escalation, 3+3 cohort design

Allocation:

Sequential cohort assignment per 3+3 dose escalation

[3+3 sequential dose-escalation design without blinding]

Intervention Model:

Sequential Assignment

Masking:

None (Open Label)

Primary Purpose:

Treatment

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2. Brief Summary

This is a single-center, open-label, dose-escalation clinical study to evaluate the safety and efficacy of intranasal umbilical cord mesenchymal stromal cell-derived exosomes (UCMSC-Exo) in patients with early Parkinson's disease. Eligible participants will be 50 to 75 years of age, with idiopathic Parkinson's disease diagnosed according to the UK Brain Bank criteria, Hoehn and Yahr stage ≤2.5, dopaminergic treatment for at least 60 days, and hyposmia defined as SS-16 <9. Participants will receive intranasal UCMSC-Exo twice weekly for 12 weeks using a 3+3 dose-escalation design at low, medium, and high dose levels. Safety will be assessed through Week 48. Efficacy will be explored through motor and non-motor clinical scales, blood inflammatory cytokines, nasal mucosal α-synuclein expression, and DAT-PETMR/TSPO-PETMR imaging.

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3. Detailed Description

Parkinson's disease (PD) is a progressive neurodegenerative disorder and a major cause of disability in older adults. Current treatments, including dopaminergic drugs and surgery, mainly improve symptoms but do not stop disease progression or achieve a cure. Mesenchymal stromal cells (MSCs) can modulate inflammation, secrete neurotrophic factors, reduce oxidative stress, and support endogenous neural repair. MSC-derived exosomes are considered a promising cell-free therapeutic approach because they are easier to obtain

and administer than whole cells and may cross biological barriers more effectively. Preclinical studies suggest that intranasally administered MSC-derived exosomes can reach brain tissue, including midbrain dopaminergic neurons, through the olfactory route.

This study is designed as the first clinical evaluation of intranasal umbilical cord MSC-derived exosomes in patients with Parkinson's disease. The study will use a 3+3 dose-escalation design to assess safety and preliminary efficacy. Participants will receive low-dose, medium-dose, or high-dose UCMSC-Exo by nasal spray twice weekly for 12 weeks, with safety follow-up to Week 48 and efficacy assessments at scheduled visits. The results are expected to inform the design of future larger multicenter studies.

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4. Arms and Interventions

Arm 1: Low-Dose UCMSC-Exo

Type: Experimental

Intervention: Biological: UCMSC-Exo

Dose: 5×10^{8} particles/mL

Administration: Intranasal spray, 0.4 mL per administration total (approximately 200 µL per nostril)

Frequency: Twice weekly (Monday/Thursday)

Duration: 12 weeks (24 administrations)

Dose-escalation rule:

Three participants will receive low-dose UCMSC-Exo. If no participant experiences a protocol-defined dose-limiting toxicity (DLT), escalation to the medium-dose cohort will proceed. If one participant experiences DLT, an additional three participants will be enrolled at the same dose. If more than one participant experiences DLT, the study intervention will be terminated.

Arm 2: Medium-Dose UCMSC-Exo

Type: Experimental

Intervention: Biological: UCMSC-Exo

Dose: 1×10^{9} particles/mL

Administration: Intranasal spray, 0.4 mL per administration total

Frequency: Twice weekly (Monday/Thursday)

Duration: 12 weeks (24 administrations)

Dose-escalation rule:

Three participants will receive medium-dose UCMSC-Exo if the low-dose cohort meets escalation criteria. If no participant experiences DLT, escalation to the high-dose cohort will proceed. If one participant experiences DLT, an additional three participants will be enrolled at the same dose. If more than one participant experiences DLT, the study intervention will be terminated.

Arm 3: High-Dose UCMSC-Exo

Type: Experimental

Intervention: Biological: UCMSC-Exo

Dose: 2×10^{9} particles/mL

Administration: Intranasal spray, 0.4 mL per administration total

Frequency: Twice weekly (Monday/Thursday)

Duration: 12 weeks (24 administrations)

Dose-escalation rule:

Three participants will receive high-dose UCMSC-Exo if the medium-dose cohort meets escalation criteria. If one participant experiences DLT, an additional three participants will be enrolled at the same dose. If more than one participant experiences DLT, the study intervention will be terminated.

DLT definition in the protocol:

DLT is defined by the protocol as abnormal liver or kidney function indicators or the occurrence of adverse events (AE) or serious adverse events (SAE) that meet protocol-defined stopping criteria. The protocol does not provide a fully detailed DLT grading table; confirm the final DLT definition with the PI/IRB before registration.

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5. Intervention Description

Product name: UCMSC-Exo

Composition: Umbilical cord mesenchymal stromal cell-derived exosomes in

normal saline for injection

Appearance: Clear liquid

Route of administration: Intranasal spray

Storage: Long-term storage at −80°C; shelf life stated as 6 months in the protocol

Preparation: Thaw at room temperature approximately 20 minutes before administration; use immediately after thawing. If not used immediately, thaw/store at 4°C or on ice for short periods. Inspect the container; do not use if damaged or if the contents are turbid.

Administration procedure: Draw 0.4 mL of the preparation with a sterile syringe, attach the nasal spray nozzle, ask the participant to sit upright with the head slightly tilted back, and spray approximately 100 μL into one nostril per spray. Each nostril receives two sprays, for a total of approximately 200 μL per nostril and 0.4 mL per administration. The participant should gently press the nasal ala after spraying. Allow at least 1 minute of absorption before the next procedure.

Concomitant treatment: Participants will continue their usual dopaminergic medication regimen during the study.

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6. Eligibility

Sex: All

Age: 50 to 75 years

Accepts Healthy Volunteers: No

Inclusion Criteria

Participants must meet all of the following:

1. Diagnosis of sporadic primary Parkinson's disease according to the UK Brain Bank clinical diagnostic criteria.
2. Dopaminergic treatment initiated for at least 60 days.
3. Hyposmia, defined as SS-16 score <9.
4. Hoehn and Yahr stage ≤2.5.
5. Age 50 to 75 years.
6. MMSE ≥25.
7. Generally good health with no significant abnormalities on laboratory tests.
8. No contraindications to MRI.
9. No autoimmune suppressive disease and no current use of immunosuppressive drugs.
10. No other neurological diseases, including but not limited to stroke, traumatic brain injury, or brain surgery.
11. Able to provide independent, voluntary, dated written informed consent.

12. Willing to comply with study procedures and able to complete the full study follow-up.
13. The protocol states in Section 6.3 that all participants will be Han Chinese. Confirm with the IRB whether this is a formal inclusion criterion for the registration record.

Exclusion Criteria

Participants meeting any of the following will be excluded:

1. Severe allergic constitution.
2. Previous treatment with allogeneic mesenchymal stromal cells or their exosomes.
3. Severe or poorly controlled comorbidities, including but not limited to cardiovascular, cerebrovascular, hepatic, renal, endocrine, hematologic, dermatologic, or other systemic diseases.
4. Severe depression.
5. Other neurological diseases, including but not limited to stroke, traumatic brain injury, Parkinsonism, or cognitive impairment.
6. Severe psychiatric symptoms or hallucinations.
7. History of malignant tumor or markedly abnormal tumor markers.
8. Severe systemic infection within the past 3 months.

9. MRI contraindications, including but not limited to cardiac pacemaker or claustrophobia, or metallic implants.
10. Positive infectious disease markers: HIV, HBV, HCV, or TP.
11. History of drug abuse or addiction within the past 10 years.
12. Participation in another clinical trial within the past 6 months.
13. Pregnancy or breastfeeding within the past 6 months.
14. Any condition that, in the investigator's judgment, makes the participant unsuitable for enrollment.

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7. Outcome Measures

Primary Outcome Measure

Outcome Title:

Incidence and frequency of adverse events and serious adverse events

Description:

Safety will be assessed by the incidence, frequency, severity, and relationship to study intervention of AEs and SAEs. Assessments include local nasal reactions (pain, pruritus, sneezing, bleeding, allergy, hyposmia), systemic reactions (fever, rash/redness, inflammatory marker abnormalities, liver injury with ALT/AST >2×ULN, renal impairment with serum creatinine >ULN, anemia defined as hemoglobin <120 g/L in men or <110 g/L in women, tumor marker

abnormalities), and severe allergic reactions such as edema or asthma. Laboratory and physical examinations will be performed at scheduled visits.

Time Frame:

Baseline through Week 48; safety assessments at Weeks 4, 12, 16, and 48.

Secondary Outcome Measures

1、Change in motor and non-motor clinical scales

Scales include Hoehn and Yahr stage, MDS-UPDRS, NMS, HAMD-17, HAMA, PDQ-39, PDSS-2, MMSE, MoCA, SS-16, and SCOPA-AUT. Hoehn and Yahr stage and MDS-UPDRS Part III will be assessed in the OFF state (dopaminergic medication withdrawn for at least 12 hours).

Time Frame: Weeks 12, 16, 24, 36, and 48.

2、Change in blood inflammatory cytokines

IL-6, IL-1β, BDNF, and other protocol-specified cytokines measured by ELISA.

Time Frame: Weeks 12, 16, 24, 36, and 48.

3、Change in imaging biomarkers

DAT-PETMR and TSPO-PETMR assessed in the OFF state (dopaminergic medication withdrawn for at least 12 hours).

Time Frame: Week 36.

8. Participant Timeline

Screening/baseline: Informed consent, medical history, physical examination, laboratory tests, clinical scales, nasal mucosal sampling, blood cytokine testing, DAT-PETMR, and TSPO-PETMR.

Treatment period: 12 weeks; intranasal UCMSC-Exo twice weekly, 24 administrations total.

Safety follow-up: Weeks 4, 12, 16, and 48.

Efficacy follow-up: Weeks 12, 16, 24, 36, and 48.

Total follow-up: 48 weeks after treatment initiation, including the 12-week treatment period. The protocol summary also states that participant participation may require approximately 2 years from screening to final follow-up; confirm the final participant timeline in the registration record.

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9. Safety Assessments and Reporting

Safety assessments include:

1. Physical examination: temperature, blood pressure, pulse, respiration, body weight.
2. Laboratory tests: complete blood count/CRP, liver function tests, renal function tests, electrolytes, fasting glucose, IgE, EKG.
3. At Week 48: tumor markers, myocardial enzymes, DIC, and lipid panel.

AE/SAE questionnaire and follow-up.

All AEs will be recorded in the case report form, including description, onset time, investigator severity assessment, relationship to study product, and time to resolution or stabilization. AEs will be followed until resolution or stabilization. SAEs will be reported immediately to the sponsor, regardless of relationship to the study intervention.

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10. Statistical Analysis

Statistical analysis will be performed using SPSS or R. Continuous variables will be presented as mean ± standard deviation or median (interquartile range). Normally distributed continuous variables will be compared using the t-test; non-normally distributed or variance-heterogeneous data will be compared using the Mann-Whitney U test. Categorical variables will be presented as frequencies and proportions and compared using the chi-square test. A two-sided P value <0.05 will be considered statistically significant.

The primary analysis will describe the number and frequency of all AEs and laboratory abnormalities to assess safety. Secondary analyses will compare pre- and post-treatment clinical data, laboratory tests (including cytokines, α-synuclein, and PET-MR), and between-dose-group differences to explore efficacy. No interim analysis or subgroup analysis is planned according to the protocol.

11. Ethics, Privacy, and Data Handling

Written informed consent will be obtained from all participants. Participants are adults; pregnant women and children are excluded. The study will be conducted in a relatively private environment. Data will be stored securely, encrypted, and coded to reduce the risk of identifying individual participants. Biological samples will be stored in dedicated refrigerators and will not involve foreign-funded research institutions or companies. Study data will be retained until publication. The protocol states that no conflicts of interest exist.

If a participant experiences research-related injury, the participant may receive free treatment and/or compensation as specified by the protocol and applicable regulations.

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12. Contacts and Locations

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Study Location:

Ruijin Hospital, Shanghai Jiao Tong University School of Medicine

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13. IPD Sharing Statement

Not specified in the source protocol. Confirm the final IPD sharing plan with the sponsor/PI before submission.