Safety and feasibility of intranasal delivery of human dental follicle mesenchymal stem cel-derived exosomes for negative symptoms in treatment-resistant schizophrenia: A pilot study

Informed Consent Form

Zigong Mental Health Center

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Dear Volunteer:

We invite you to participate in a clinical drug study titled "Safety and Feasibility of Intranasal Delivery of Human Dental Follicle Mesenchymal Stem Cell-derived Exosomes for Negative Symptoms in Treatment-Resistant Schizophrenia: A Pilot Study," in order to provide evidence for the clinical use of this investigational product.

Before you decide whether to participate in this study, please read the following information carefully. It will help you understand the study, why it is being conducted, the procedures and duration of the study, and important information such as potential benefits, risks, and discomforts that may arise from participation. If you wish, you may also discuss it with your relatives or friends, or consult the principal investigator or other research staff at any time to assist you in making your decision. If you choose to participate in this clinical study, you will be required to sign this informed consent form. You will also receive a copy of the signed document for your records.

This study has been reviewed and approved by the Clinical Trial Ethics Committee of Zigong Mental Health Center (Ethics Approval No. 20260101). The study complies with relevant Chinese laws and regulations, adheres to the principles of the Declaration of Helsinki, and conforms to medical ethical standards.

I. Study Overview

Schizophrenia is a severe chronic mental illness with high disability rate, affecting approximately 1% of the global population and imposing a substantial disease burden on patients, families, and society. It is primarily characterized by positive symptoms (e.g., hallucinations, delusions, thought disorder, behavioral disturbances), negative symptoms (e.g., blunted affect, avolition, social withdrawal, alogia), and cognitive symptoms (e.g., memory impairment, executive dysfunction). Currently, schizophrenia treatment primarily relies on antipsychotics modulating dopamine and serotonin systems. However, approximately one-third of patients do not respond to conventional antipsychotic treatment, and even responsive patients require long-term medication while enduring unavoidable side effects. Furthermore, the

Treatment Response and Resistance in Psychosis (TRRIP) working group defines treatment-resistant schizophrenia (TRS) as persistent symptoms and functional impairment despite at least two adequate trials of antipsychotic medications, with approximately 25% of schizophrenia patients meeting TRS criteria. TRS severely impairs individual social function and quality of life, imposing heavy burdens on families and society.

Extensive preclinical studies have reported that exosomes derived from mesenchymal stem cells of various tissue sources exhibit antipsychotic effects. Human dental follicle mesenchymal stem cells (hDFSCs), originating from ectodermal neural crest cells, possess enhanced potential for neural lineage differentiation, promote neuronal axon elongation, exhibit low immunogenicity, and offer advantages in accessibility and reduced ethical concerns. Exosomes derived from dental follicle mesenchymal stem cells (hDFSCs-Exo) demonstrate similar anti-inflammatory and neurotrophic effects, lack immunogenicity, and possess favorable biosafety profiles. Therefore, hDFSCs-Exo may offer superior antipsychotic effects. Additionally, clinical studies have already investigated intranasal administration of adipose-derived mesenchymal stem cell exosomes for Alzheimer's disease, confirming good safety and certain clinical efficacy.

II. What is the Purpose of This Study?

This study will investigate intranasal delivery of human dental follicle mesenchymal stem cell-derived exosomes (hDFSCs-Exo) for treatment-resistant schizophrenia, aiming to evaluate the safety and feasibility of this therapy and preliminarily explore the clinical efficacy of hDFSCs-Exo in schizophrenia.

III. What is the Investigational Product?

1. Investigational Drug: Human Dental Follicle Mesenchymal Stem Cell-derived Exosomes (hDFSCs-Exo)
2. Route of Administration: Intranasal spray
3. Specification: 30 billion particles / 2 mL (particle concentration)
4. Storage Conditions: Store at -80°C
5. Manufacturer: Chengdu Shilian Kangjian Biotechnology Co., Ltd.

IV. Who is Eligible to Participate in This Study?

1. Diagnosed with schizophrenia according to ICD-10 criteria;

2. Aged between 18 and 60 years;
3. Long-term inpatients with a disease duration of more than 5 years;
4. No acute exacerbation in the past 6 months, and no change in medication regimen in the past 2 months;
5. Poor response to adequate dose and duration of treatment with at least two different antipsychotics, including clozapine;
6. Positive and Negative Syndrome Scale – Factor Score for Negative Symptoms (PANSS-FSNS) ≥ 24;
7. At least two of the three core negative symptom items on the PANSS (N1, N4, and N6) scored ≥ 4;
8. Clinical Global Impression – Severity of Illness (CGI-S) score ≥ 4.

V. Who is Not Suitable to Participate in This Study?

1. History of severe allergic reactions;
2. Definite organic brain lesions;
3. Comorbid severe physical diseases (e.g., unstable coronary heart disease, malignant arrhythmia, hepatic or renal insufficiency, bronchial asthma, acute exacerbation of chronic obstructive pulmonary disease, autoimmune diseases, etc.);
4. Current diagnosis of other mental disorders according to ICD-10 criteria (e.g., schizoaffective disorder, schizophreniform disorder, bipolar I disorder, bipolar II disorder, pervasive developmental disorder, mental retardation, delirium, dementia, amnestic disorder, or other cognitive disorders);
5. Unstable condition requiring adjustment of medication regimen;
6. Non-compliance with treatment;
7. Severe rhinitis or nasal allergies;
8. History of modified electroconvulsive therapy (MECT) within the past 3 months;
9. Individuals at risk of suicide;
10. Pregnant or lactating women;
11. Other conditions deemed unsuitable for enrollment.

VI. What Will You Need to Do If You Decide to Participate?

1. If you decide to participate in this study, you will need to provide accurate information to the researcher, comply with study requirements, and attend scheduled visits on time. If you fail to adhere to these study requirements, the researcher may withdraw you from the study at any time based on the study

circumstances.

2. Regularly participate in interviews with research staff;
3. Complete the examinations required in the study protocol, including electrocardiogram (ECG), electroencephalography (EEG), functional near-infrared spectroscopy (fNIRS), magnetic resonance imaging (MRI), blood collection, etc. All above examinations are provided free of charge and will not adversely affect your health or condition;
4. Receive hDFSCs-Exo intranasal spray treatment according to the study requirements, twice weekly for eight weeks;
5. After the intervention, continue to participate in follow-up assessments until the study concludes at six months.

VII. Can You Participate Voluntarily or Withdraw from the Study?

Participation in this study is entirely voluntary. You may refuse to participate or have the right to withdraw from the study at any stage without any discrimination or retaliation, and your medical treatment and rights will not be affected.

In your best interest, if circumstances arise during the trial that make continued participation inadvisable, the researcher has the right to decide on your withdrawal from the study. Such circumstances include:

① Occurrence of allergic reactions or serious adverse events;

② Development of certain complications, concurrent conditions, or special physiological changes affecting the assessment of efficacy and safety;

③ Poor compliance, with treatment medication below 80% or exceeding 120% of the prescribed amount during the treatment period.

If you withdraw from the study for any reason, you may be asked about your use of the medication. If the physician deems it necessary, you may also be required to undergo relevant laboratory tests and physical examinations.

VIII. What Are the Potential Risks and Benefits of Participating in This Study?

1) Potential Risks and Countermeasures

Although previous studies have demonstrated favorable safety profiles for this product, individual responses to any product and its potential side effects may vary. Some individuals using this or any other product may experience rare or previously unseen side effects. Possible adverse reactions to this product may include nasal dryness, headache, dizziness, head discomfort, bloating, diarrhea, constipation, nausea,

abdominal pain, or other rare symptoms.

Physicians will make every effort to prevent and treat any harm that may result from this study. During the study, please cooperate closely with your study physician. If you experience any discomfort, new changes in your condition, or any unexpected situations, regardless of whether they are related to the study medication, please inform your study physician immediately. They will assess the situation and provide appropriate management based on your condition.

2) Potential Benefits of Participation

The hDFSCs-Exo used in this study may have therapeutic effects on treatment-resistant schizophrenia. Your condition may improve, or your symptoms may be alleviated. However, this requires further validation. It is also possible that the investigational drug may not improve your condition or symptoms, or that any improvement may be minimal or temporary.

IX. Are There Alternative Treatments Besides Participating in This Study?

This study represents adjunctive treatment. In principle, your current treatment regimen will not be modified during the study. However, it is also recommended that subjects do not modify their previous treatment regimens or participate in any other form of new treatment during the study period. If your condition requires a new treatment regimen, you may consider withdrawing from this study.

X. Will You Receive Compensation for Participating in This Study?

By participating in this study, you will receive:

1. Free medical examinations (e.g., EEG, MRI);
2. Medical monitoring and guidance from experienced healthcare professionals;
3. If any study-related adverse reactions are confirmed, you will receive prompt and free medical treatment;
4. Subjects will receive certain compensation for their participation. This study requires a total of 5 visits, with a compensation of 100 RMB per visit.

XI. Will Your Participation Be Kept Confidential?

If you agree to participate in this study, the hospital will retain information obtained during the study in accordance with international regulatory guiding principles and domestic regulations. In compliance with the Data Protection Law and domestic clinical trial GCP management requirements, the hospital, as the data controller, is responsible for data management. Your medical records (study records, laboratory reports, etc.) will be kept at the hospital where you receive treatment.

Physicians will record laboratory results in your medical records. During the collection of trial data, case report forms will not collect your identifying information; only a dedicated subject identification number (name abbreviation and subject number) will be used. Generally, only hospital staff and the sponsor's monitors will know that this information relates to you, and all such information will be kept confidential. The results of this study may be published, but your identity information will not be disclosed. Without violating confidentiality principles and relevant regulations, researchers, monitors, auditors, the Ethics Committee, and drug regulatory authority inspectors will be permitted to access subjects' original medical records to verify the clinical trial process and data.

XII. Emergency Contact Information

If you have any questions regarding this document that have not been addressed, the research staff will be happy to provide you with further information. During the study, if new issues arise or medical emergencies occur, you should also contact the research staff. You may contact the researchers, the clinical trial institution, and the Ethics Committee using the following contact information:

Drug Clinical Trial Institution, Zigong Mental Health Center: 0813-5532041

Clinical Trial Ethics Committee, Zigong Mental Health Center: 0813-8325667

Informed Consent Form · Signature Page

1. Subject's Statement of Consent

I have read the above introduction to the "Safety and Feasibility of Intranasal Delivery of Human Dental Follicle Mesenchymal Stem Cell-derived Exosomes for Treating Negative Symptoms of Treatment-Resistant Schizophrenia: A Pilot Study." I understand the purpose, significance, and specific methods of this study. I have discussed this study with the research physician and asked questions, and all my questions have been satisfactorily answered. I understand the potential risks and benefits of participating in this study. I am aware that participation in this trial is voluntary, and I confirm that I have had sufficient time to consider this decision. Furthermore, I understand that:

I may consult the physician for more information at any time.

My participation in this study is voluntary. I may refuse to participate or withdraw from the study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I am also aware that if I withdraw from the study midway, especially if withdrawal is due to medication-related reasons, I should inform the physician of any changes in my condition and complete the corresponding physical examinations and laboratory tests, which will be very beneficial to the overall study.

If my condition changes and I need to pursue any other treatment, I will seek the physician's advice beforehand or honestly inform the physician afterward.

My participation in this trial and all personal information collected during the trial will be kept confidential and protected in accordance with legal requirements. I agree that researchers, monitors, auditors, the Ethics Committee, and drug regulatory authority inspectors may review my research data.

If I experience any trial-related injury during the clinical trial, the physician will provide me with active medical treatment, and the sponsor will bear the relevant medical expenses and reasonable financial compensation arising therefrom.

I will receive a copy of this informed consent form signed by both the researcher and myself, dated.

Subject Signature:_____

Contact Number: _____

Date Signed:_____

If the subject is a person without capacity for civil conduct or with limited capacity for civil conduct, written informed consent shall be obtained from their legal guardian.

Guardian Signature:_____

Contact Number: _____

Relationship to Subject: _____

Date Signed:_____

If the subject or their legal guardian lacks reading ability, an impartial witness shall read the informed consent form and other written materials and witness the informed consent process.

Impartial Witness Signature:_____

Contact Number: _____

Date Signed: _____

2. Investigator's Statement

I confirm that I have fully explained the details of this trial to the subject (and/or their legal guardian, witness), including their rights and the potential benefits and risks, and have provided them with a signed copy of the informed consent form.

Investigator Signature: _____

Contact Number:_____

Date Signed: _____