Clinical Research Informed Consent Form

Protocol Title: *Lactobacillus plantarum* PS128 may improve OFF duration in Parkinson's disease: a pilot study

Institution/ Department:

Study Sponsor: Professor Lu Neurological Clinic

Principle Investigator: CHIN-SONG LU Title: Professor Tel: +886-3-396-0388

Co-Investigator: NA

Emergency contact study Personnel: YI-SHAN KUO Tel: +886-921-878-024

Subject's Name:
Gender: Date of Birth (DD-MMM-YYYY):
Medical Chart No.:
Address:
Tel:
Name of Legally Representative:
Relationship with the subject:
Gender: Date of Birth (DD-MMM-YYYY):
ID No.:
Address:
Tel:

1. Introduction of the Marketing Status of the Study Drug

The probiotics used in this proposal are selected to be more related to mental conditions. The PS128, which belongs to Lactobacillus plantarum subsp. plantarum. Administration of probiotics for 4 weeks in animal experiments showed significant improvements in depression and anxiety behaviors, and increased mobility in mice (Liu et al., 2016). The concentration of dopamine in the prefrontal cortex, which was reduced due to depression, was also restored by feeding PS128 (Liu et al., 2016). The strains used in this study are food usable bacteria listed on the front of the Food and Drug Administration in Taiwan. The products have been sold in Taiwan in 2015 and there have been no serious adverse reactions. Relevant clinical studies have been reviewed by Institutional Review Boards in multiple hospitals (Including the National Taiwan University Children's Hospital, Kaohsiung KaiSyuan Psychiatric Hospital, Wanfang Hospital, Antai Hospital, and National Yangming University). These probiotics and placebo will be provided by the Yifu Biomedical Company Ltd. The probiotic powder contains no lactose and can be eaten by people with lactose intolerance.

About The Study Drugs

Lactobacillus plantarum PS128 was isolated, and deposited under DSMZ Accession No. DSM 28632. In the present study, the PS128 product was provided by Bened Biomedical Co., Ltd. in the final form of capsules containing creamy white powders. The probiotic capsules weighed 300 ± 25 mg and contained 3 × 1010 CFU/capsule of PS128 with microcrystalline cellulose as the carrier and all capsules were stored at a refrigerated temperature (4–8 °C).

2. Study Objective

About This Study

The purpose of this study is to investigate the short term effects (12 Weeks) of *Lactobacillus plantarum* PS128 (PS128) on Parkinson's disease (PD) symptoms.

This study is designed to examine the extent to which *L. plantarum* PS128 can improve symptoms in PD patients. *L. plantarum* PS128 is a psychobiotic that regulates the level of

dopamine in specific brain regions. Patients with PD will receive PS128 treatment for 12 weeks. Symptoms of PD will be clinically evaluated before and after the treatment, and the results will be compared.

3. Main Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patients diagnosed with idiopathic Parkinson's Disease.
- According to the record of ON / OFF diary for 3 consecutive days, the patient's daily off periods must be more than 3 hours a day.
- Between ages of 40-80 years old.

Exclusion Criteria:

- Patients on antibiotics within the preceding one month.
- Patients using of other probiotic products (sachet, capsule or tablet) within the preceding two weeks.
- Have undergone surgery of liver, bladder, or gastrointestinal tract.
- Have current or history of inflammatory bowel disease.
- Have history of cancer.
- Known allergy to probiotics.
- Patients with comorbid dementia (Mini-Mental State Examination score ≤ 26) or major depression (The Beck Depression Inventory-II score ≥ 29).
- Have received deep brain stimulation.
- Patients receiving artificial enteral or intravenous nutrition.

4. Study Method, Procedure, and Related Examinations

This is an open label study and the recruitment will be started after the IRB approval and ended up on 2021/12/31. All the participants have to complete the On-Off diary to confirm the eligibility for acceptance. All the participants will complete the baseline assessment and administered with probiotics 2 capsules daily for 12 weeks.

What will happen during the study visits?

Procedure	**Screen visit (S0)**	**Baseline/ Enrollment visit (V0)**		**Telephone contact (TC1-10)**	**Telephone contact (TC11)**	**Telephone contact (TC12)**	**Efficacy evaluation visit (V1)**	
Visit	1	2		TC1-10	TC11	TC12	3	
Week	-4	0		1-10	11	12	12	
±window (day)	± 7	± 7		± 7	± 7	± 7	± 7	
PD medication (ON/OFF)		**OFF**	**ON**				**OFF**	**ON**
Written informed consent	V							
Medical history	V							
Concomitant medication	V							V
Safety measurements								
Physical exam			V					V

and vital signs								
Adverse events				V	V	V		V
Questionnaire assessment								
ON-OFF diary	V				V	V		
MMSE	V							
UPDRS(I-IV)			V					V
UPDRS(III)		V					V	
Hoehn & Yahr		V	V				V	V
NMS			V					V
PAC-SYM			V					V
BDI-II	V							V
PDQ-39			V					V
PGIC								V
Sample collection								
Blood			V					V
Urine			V					V
Investigational product (IP)								
PS128 dispensing			V					
PS128 return Accountability								V

5. The frequency and handling of possible side effects:

What side effects could the study drugs cause?

The PS128 probiotic capsules tested in this study contain only PS128 probiotics and excipients. The all excipients are food additives approved by the Food and Drug Administration, and the strain of PS128 is also listed as one of the edible fungi, and many studies have proved the probiotic effect of this strain, so this capsule will not cause seriously potential risks and side effects. Some people consuming dairy products may be prone to bloating, diarrhea and other adverse gastrointestinal reactions. If you belong to this type of physique, it is recommended not to participate in this study. Discomfort symptoms such as exhausted, involuntary tremor, and muscle rigidity may occur when the medication is stopped. There are very few people have Parkinson's disease drugs that do not work best when you take probiotics. In addition, if you have a history of migraine, you may induce migraine attacks after taking probiotics.

6. The Introduction of Alternatives treatment for the indication of this study:

What are my options if I am not in the study?
There is no restriction on Parkinson's disease or other medications during your participation in the study. There is no need to adjust the dose of the medications or change the medicine for observe the effects of probiotics on Parkinson's disease. However, the medications taken during the study must be recorded in detail.

7. Potential Benefits of the Study:

What benefit could there be from taking part in the study?

Participation in this study, you may not benefit, but the results of the study may be helpful to the trial investigator, and may benefit other patients with the same disease in the future. It may be possible to improve the symptoms of motor or non-motor disorders in Parkinson's disease subject by supplementing with probiotics. Due to depending on individual conditions, the improvement is unknown.

8. Your obligation and what you would be prohibited and refrained during the study:

What will I be asked to do?

The PS128 probiotic test capsules provided by this study must be protected from light and refrigerated in the refrigerator. Do not take other probiotic-related products (including powders, lozenges and capsules ... etc.) two weeks before the whole test and during the test period, excluding yogurt, yogurt, Yakult and other related foods. If you take antibiotics, please contact us, thank you.

This study requires a complete evaluation in twice. The medication needs to be stop taken for 12-24 hours before the evaluation. The research nurse will remind you by phone the day before the evaluation, and to ensure your safety and rights during the trial, research nurses will confirm by phone every week whether you have taken the PS128 probiotic on time, whether there are any adverse event, and remind you to record the diary of fluctuations in drug efficacy. When you have an adverse event, the host and the research nurse will perform emergency treatment or consultation according to your symptoms.

Discomfort symptoms such as exhausted, involuntary tremor, and muscle rigidity may occur when you stop take the medicine. You and your family should pay attention to the safety when you stop take the medicine to avoid falls.

9. Confidentiality:

How will my privacy be protected?

If you decide to be in this study, the study doctor and research team will use health data about you to conduct this study. This may include your name, address, phone number, medical history, and information from your study visits. This health data may come from your family doctor or other health care workers.

For this study, the research team will share health data about you with government agencies and ethics committees that oversee the research. It will also be shared with the Sponsor and those working for the Sponsor. People who work for the Sponsor to make sure the study rules are followed will be able to see all health data about you at the study site.

When possible, the health data that is sent to the Sponsor and those working for the Sponsor will not identify you by name. Instead, it may include your initials, date of birth, and study visit dates. If you think that you were harmed from being in the study, the research team may also share health data about you with the Sponsor’s insurer to resolve your claim.

The Sponsor and those working for the Sponsor may use the health data sent to them:

- to see if the study drug works and is safe;
- to compare the study drug to other drugs;
- for other activities (such as development and regulatory) related to the study drug.

For these uses, the Sponsor may share this with others involved in these activities, as long as they agree to only use the health data as described here. The Sponsor and those working for the Sponsor may transfer health data about you from your country to other countries where the privacy laws are not as strict.

You may take away your permission to use and share health data about you at any time by writing to the study doctor. If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after that date. However, health data about you that has already been gathered may still be used and given to others as described in this form.

When the study is over, you may write to the study doctor to ask to see health data about you that was collected during the study.

You will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. The compensation, medical costs and insurance for the study related injuries:

- When conducting the clinical trial according to the protocol, should any damage occurs due to adverse event, Professor Lu Neurological Clinic should bear the responsibility of making such compensation. No compensation will be given for those expected adverse event as described on ICF.
- When conducting the clinical trial according to the protocol, should any damage occurs due to adverse event, Professor Lu Neurological Clinic agreed to provide medical care and advice. You are not entitled to any medical payment should any adverse event or damage occurs.
- Except for the compensation and medical care and advice as mentioned in the above two terms, this study dose not provide compensation in any other form. Please do not participate in the trial if you are not willing to accept these potential risks.
- By signing this consent form, you do not lose any legal right entitled to you.
- This study has not insurance.

Will information about this trial be included in a Registry Databank?
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

11. The right for study subjects

A. You will be told in a timely manner about significant new information that might affect your decision to stay in the study.

B. If you have doubts about the nature of research work during the study period, or if you have any opinions on your rights as a patient, or if you suspect that you are injured due to participating in this study, please contact the hospital ethics committee for consultation. The phone number is +886-8-8329-966#5529.

C. In order to conduct this study, you will be taken care of by Dr. Lu. If you have any question or condition now, or during the study period, you can contact Dr. Lu in the Professor Lu Neurological Clinic. (24-hour contact number: +886-921-878-024; name of the contact person: YI-SHAN- KUO).

This informed consent form is a 2-counterpart document. The investigator has given you the copy of this consent form, and has explained to you the nature and purposes of this research

Information about the study will be posted to a registry database (clinicaltrials.gov). The information will not identify any patient individually.

12. Withdraw and Termination：

You may voluntarily decide whether to participate in this study. You may also withdraw your consent of participation and leave the study at any time during the study period. You do not need to provide any reason for your withdrawal. Your withdrawal will not result in any conflict, nor will it affect the medical care that the research doctor provides you. The research doctor or the sponsor may also terminate the study when necessary.

13. Signature

By signing below, I agree that:

- I have read this consent form.
- I have had the chance to ask questions and they have been answered.
- I understand that taking part in this study is voluntary.
- I may choose not to be in the study or to leave the study at any time by telling the study doctor. I will not be penalized or lose any benefits to which I am otherwise entitled.
- I may have to leave the study without my consent if I need other treatment, do not follow the study plan, have a study-related injury, or for any other reason.
- If I leave the study for any reason, the study doctor may ask me to have some end-of-study tests.

I will receive a signed copy of this consent form.

A. The principal investigator or the sub-investigator has explained the nature and purpose of the above study procedure, also the possible risk and benefits.
Principal Investigator/Co-Investigator signature：
Date：□□□□year□□month□□date

B. The subject has fully understood the above study methods and its possible risks and benefits. Questions regarding this study has been clearly explained and answered by the principal investigator. I voluntarily consent to take part in this study.

Subject signature：

Legal Representative of Subject：

Date：□□□□year□□month□□date

* If the subject is a person with no legal capacity (a minor more than 7 years old or limited legal capacity), this form should be signed and dated by the legal representative. The guardian will be the legal representative of interdiction subject.

＊If the subject limited in legal capacity (a minor more than 7 years old) shall act upon approval of subject's legal representative.

Power of Attorney：

Date：□□□□year□□month□□date

* If the subject is not a person with no legal capacity or a person with limited legal capacity, but if the subject is not conscious or suffers from mental disorder and cannot perform act on himself/herself, this form should be signed and dated by the person who is authorized to grant his/her consent (such authorized person being the spouse or lineal blood relatives).

C. Witness :

Name :

ID code : □□□□□□□□□□ Contact number : □□□□□□□□□□

Address :

Witness Signature : Date : □□□□year□□month□□date

* If the person who is authorized to sign for consent (could be the subject in person, the legal representative of the subject, or the spouse or co-habitant relative of the subject) cannot read the Informed Consent Form and relevant attachment, a witness must be present to witness the process of full explanation and the witness should sign and date in the witness signature column (personnel related to the trial can not serve as a witness).