IACT16049-01

An investigator-initiated clinical trial of safety and efficacy of transplantation of human induced pluripotent stem cell-derived dopaminergic progenitors for Parkinson's disease (Phase I/II)

Protocol

Principal investigator: Jun Takahashi, Professor of Department of Clinical Application
Center for iPS Cell Research and Application, Kyoto University
Sponsor-investigator: Ryosuke Takahashi, Professor of Department of Neurology, Kyoto University Hospital

Version 3.2 8 September 2022

Revision history of the protocol

Version	Date of creation (revision)
Version 1.0	6 April 2018
Version 1.1	11 May 2018
Version 1.2	14 June 2018
Version 1.3	09 July 2018
Version 1.4	07 August 2018
Version 1.5	12 September 2018
Version 2.0	2 October 2018
Version 2.1	7 October 2019
Version 3.1	1 March 2021
Version 3.2	8 September 2022

Confidentiality

This document is a confidential communication and provided exclusively to those involved in the study, including study sites, investigators, subinvestigators, study collaborators, institutional review boards, data and safety monitoring board, and data center. This document should not be disclosed to a third party or used for any purpose other than for this study without written authorization from the principal investigator, except to explain the study to potential subjects.

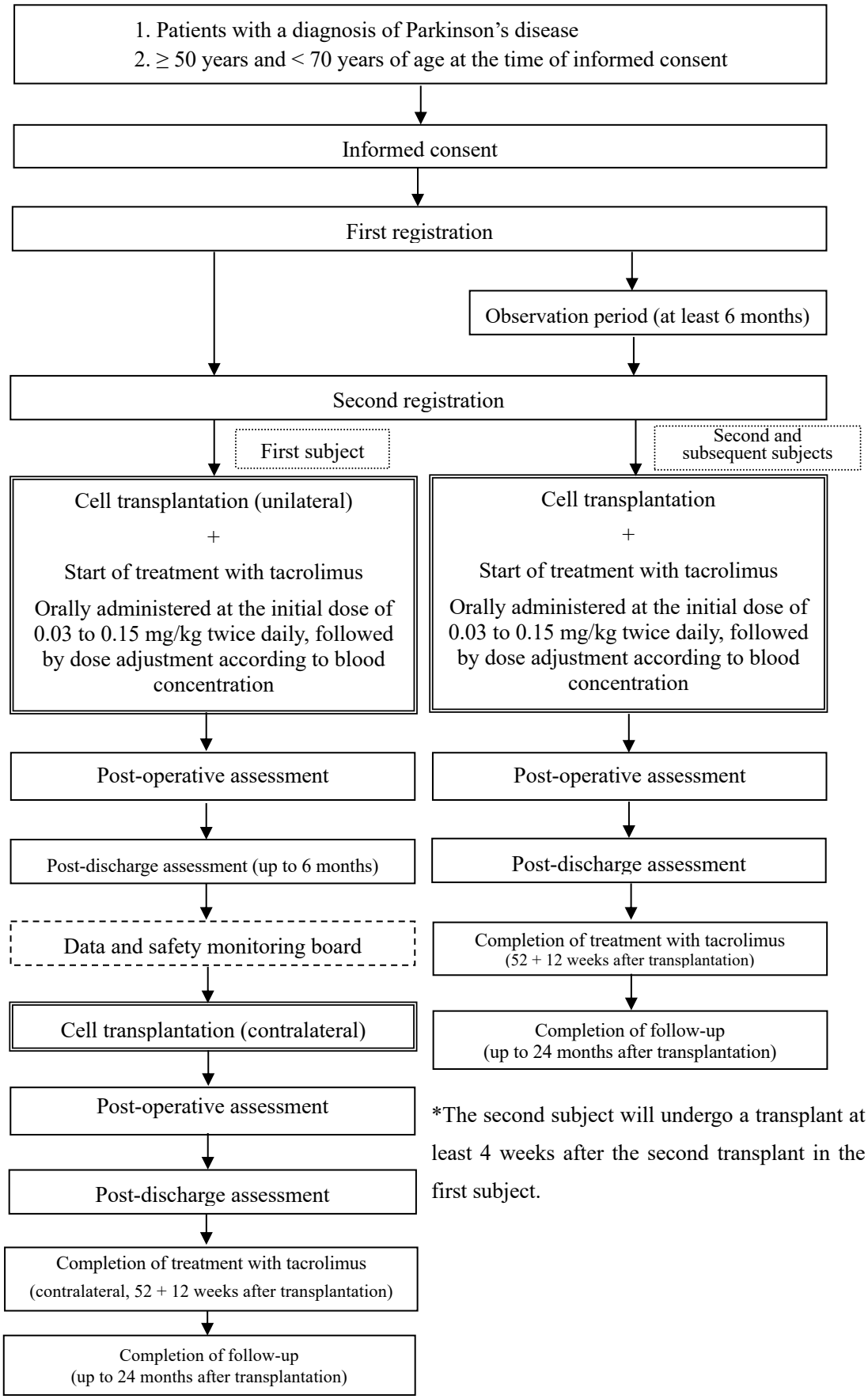
Table of Contents

Synopsis of the Study

Item	Contents
Title of the study	An investigator-initiated clinical trial of safety and efficacy of transplantation of human induced pluripotent stem cell-derived dopaminergic progenitors for Parkinson's disease (Phase I/II)
Objectives of the study	To evaluate the safety and efficacy of transplantation of human induced pluripotent stem cell-derived dopaminergic progenitors into the corpus striatum in patients with Parkinson's disease
Study design	Single-center, open-label, uncontrolled
Study product/ study drug	Study product: iPSC-derived dopaminergic progenitors Study drug: tacrolimus
Target sample size	7 patients
Target patients	Patients with Parkinson's disease (PD)
Eligibility criteria	[Main inclusion criteria] 1) The patient has PD. 2) The patient plans to undergo transplantation of human iPSC-derived dopaminergic progenitors. 3) The patient has a poor response to existing drug treatments. 4) The patient is ≥ 50 years and < 70 years of age at the time of informed consent. 5) The patient has had PD for at least 5 years. 6) The patient is in stage 3 or higher on the Hoehn and Yahr scale at OFF time. 7) The patient is in stage 3 or lower on the Hoehn and Yahr scale at ON time. 8) The patient has an L-dopa response of 30% or more. [Main exclusion criteria] 1) The patient has mental disease, dementia, or serious disease.
Endpoints	[Primary endpoints] <Safety endpoints> 1) Incidence and severity of adverse events 2) Presence or absence of graft expansion in the brain at 24 months after transplantation [Secondary endpoints] <Safety endpoints> 1) Uptake of [^{18}F]FLT 2) Uptake of [^{18}F]GE180 3) Dyskinesia score

	4) Graft size (MRI) <Efficacy endpoints> 1) MDS-UPDRS Part III total score (at ON and OFF times) 2) MDS-UPDRS Part II total score 3) MDS-UPDRS Part I total score 4) Sum score of MDS-UPDRS Part I, Part II, and Part III (at ON and OFF times) 5) Average daily ON duration (with or without dyskinesia) and OFF duration 6) Bradykinesia subscale 7) Uptake of [^{18}F]FDOPA 8) Uptake on DAT scan 9) Parkinson's Disease Questionnaire (PDQ-39) 10) Hoehn and Yahr severity 11) L-dopa equivalent dose 12) Euro-QOL 5 Dimensions-5 Levels (EQ-5D-5L) 13) Work Productivity and Activity Impairment Questionnaire (WPAI) 14) Nursing care category
Study site	Kyoto University Hospital
Planned study period	1 August 2018 to 31 March 2024

0. Schema



*The second subject will undergo a transplant at least 4 weeks after the second transplant in the first subject.

1. Objectives

Transplantation of dopaminergic progenitors induced to differentiate from human induced pluripotent stem cells into the patient's corpus striatum is expected to improve the symptoms of Parkinson's disease. The primary objective of this study is to determine the incidence and severity of adverse events, especially graft expansion, after transplantation of human iPSC-derived dopaminergic progenitors into the corpus striatum in patients with Parkinson's disease.

Primary endpoints:

1) Incidence and severity of adverse events
2) Presence or absence of graft expansion (> 3 cm^3) in the brain at 24 months after transplantation (MRI)

Secondary endpoints:

Safety evaluation

1) Uptake of [^{18}F]FLT
2) Uptake of [^{18}F]GE180
3) Dyskinesia score
4) Graft size (MRI)

Efficacy evaluation

1) MDS-UPDRS Part III total score (at ON and OFF times)
2) MDS-UPDRS Part II total score
3) MDS-UPDRS Part I total score
4) Sum score of MDS-UPDRS Part I, Part II, and Part III (at ON and OFF times)
5) Average daily ON duration (with or without dyskinesia) and OFF duration
6) Bradykinesia subscale
7) Uptake of [^{18}F]FDOPA
8) Uptake on DAT scan
9) PDQ-39
10) Hoehn and Yahr severity
11) L-dopa equivalent dose
12) EQ-5D-5L
13) WPAI
14) Nursing care category

2. Background and Rationale

2.1 Target Disease and Current Treatments

2.1.1 Target Disease

Parkinson's disease (PD) is a chronic progressive neurologic degenerative disease with motor symptoms that may result from imbalanced action of the neural circuit of the basal ganglia, which controls the brain motor function, due to a marked decrease in dopamine content in the corpus striatum associated with degeneration/loss of dopaminergic neurons in the brain.

The peak age of onset is 50 to 65 years, and the incidence increases with increasing age. In Japan, there is estimated to be a total of 163,000 patients, with a prevalence of approximately 100 to 150 per 100,000 persons (150 to 200 in Europe and the United States) [References 1 and 2].

There are four chief motor symptoms characteristic to PD: tremor, muscle rigidity, bradykinesia, and postural reflex disorder. Among these motor symptoms, many patients initially suffer from tremor, followed by bradykinesia and muscle rigidity, which slowly extend from a unilateral upper or lower limb to the other limbs. As the disease further progresses, postural reflex disorder characterized by unstable posture occurs. In addition to the motor symptoms that slowly progress while spreading from four limbs to the trunk, non-motor symptoms, including autonomic symptoms, psychiatric symptoms, and sleep disorder, occur.

PD is broadly classified into familial PD (5% to 10%), which also affects other relatives, and sporadic PD (90% to 95%), which occurs without affecting other relatives.

2.1.2 Current Standard Treatments

At present, PD is treated with drug therapy or surgical therapy. In the 2011 Practical Guideline for Parkinson's Disease [Reference 3], the drug therapies described below are proposed for early PD.

Once the disease begins to interfere with daily life, treatment with a single levodopa preparation or single dopamine agonist is started.

Levodopa preparations, which are quickly taken up by the brain to release dopamine, act rapidly. However, long-term treatment with levodopa preparations induces motor complications, including wearing-off phenomenon, which occurs due to reduced duration of action of antiparkinsonian drugs, on-off phenomenon, which is diurnal variation in symptoms or rapid or sudden loss of effect in parallel with changes in drug concentration, and dyskinesia, which is a series of involuntary movements. On the other hand, dopamine agonists, which are associated with fewer motor complications than levodopa preparations, are initially used to treat non-elderly patients with neither psychiatric symptoms nor impaired cognitive function. If a single levodopa preparation or single dopamine agonist cannot improve symptoms sufficiently, it is replaced with a combination of two drugs.

In the 2011 Practical Guideline for Parkinson's Disease [Reference 3], the treatments described below are proposed for wearing-off. The regimen of a levodopa preparation or a dopamine agonist is readjusted to optimize the treatment; if a good response is not obtained, treatment with a new drug is

started. In the absence of dyskinesia, additional concomitant use of entacapone [catechol-O-methyl transferase (COMT) inhibitor], selegiline [monoamine oxidase B (MAO-B) inhibitor), or zonisamide is considered. In the presence of dyskinesia, on the other hand, additional concomitant use of entacapone or zonisamide with a dose reduction of the levodopa preparation is considered. If these multiple drug therapies fail to control wearing-off adequately, frequent dosing of the levodopa preparation (5 to 8 times daily) and dose increase/alternation of the dopamine agonist are attempted with or without dyskinesia. Other drugs for PD, including anticholinergics, amantadine, and droxidopa, are used as an auxiliary according to the patient's condition. If further disease progression occurs, highlighting the limitations of drug treatment, surgical therapy is considered.

Surgical therapy is deep brain stimulation (DBS) involving the implantation of an electrode into the deep brain (thalamus, globus pallidus, and subthalamic nucleus). DBS is high-frequency stimulation by a stimulator implanted into the anterior chest connected to an electrode implanted stereotactically in the deep brain. High-frequency stimulation suppresses the neuronal hyperexcitability to correct the imbalance in the neural circuit due to dopamine deficiency, resulting in improvement of motor symptoms.

2.2 Position of Study Treatment/Study Product

Both drug and surgical therapies for PD are palliative and cannot improve the fundamental pathological condition, loss of dopaminergic neurons in the nigrostriatal pathway, or reverse its progression. In treatment with levodopa, the effect is attenuated as the disease progresses, inducing the aforementioned complications such as wearing-off and on-off phenomena as well as dyskinesia. Moreover, since synthesis of dopamine from L-dopa is carried out by dopaminergic neurons, advanced-stage patients, who have lost most of their dopaminergic neurons to below a certain number, are not capable of synthesizing enough dopamine. In brief, the current problem is that there is no therapy for patients whose condition cannot be controlled by drug treatment. On the other hand, dopamine agonists, which are systemically administered, affect the dopaminergic neuron system outside the nigrostriatal pathway as well and thus cause nausea, anorexia, sudden onset of sleep, and even hallucination and delusion. Heart valve disease has also been reported as an adverse drug reaction to a certain dopamine agonist. These adverse drug reactions not infrequently make it difficult to administer or continue to administer dopamine agonists.

Given these pathological conditions, it is clear that resolution of lost dopaminergic neurons by cell transplantation is required as a more definitive treatment. Dopaminergic neurons transplanted and engrafted into the corpus striatum can release dopamine locally within the corpus striatum where dopamine is needed as well as also regulate the amount of dopamine through dopamine granules in the cell body and dopamine transporters on nerve terminals. In addition, since transplanted dopaminergic neurons are capable of synthesizing dopamine from L-dopa, the effect of levodopa is likely to be boosted.

In expectation of such benefits, clinical trials of transplantation therapy using midbrain nigral cells from aborted human fetuses have been conducted mainly in Europe and the United States since the late 1980s. To date, approximately 400 patients have undergone transplantation, and some had a dramatic response: the transplanted cells survived and the clinical effect was sustained for more than 10 years after transplantation [References 4-6]. However, the transplantation therapy has not been established as a standard treatment because of problems including the ethical issues surrounding the use of aborted fetuses as donor, the demand for a lot of aborted fetuses in order to obtain a good therapeutic response, and dyskinesia developed in several recipients. In Japan, moreover, there is no guideline for clinical application of tissues from aborted fetuses, making it practically difficult to implement this therapy.

On the other hand, dopaminergic progenitors induced to differentiate from induced pluripotent stem cells established from the patient's own blood (human iPSC-derived dopaminergic progenitors), when transplanted into the corpus striatum in rat and monkey models of PD, improved behaviors without symptomatic expansion or cancerization of the transplants. In a 12-month tumorigenicity study in immunocompromised rats, no symptomatic expansion or cancerization of the transplants was observed. These results indicate that transplantation of human iPSC-derived dopaminergic progenitors, which is expected to increase the dopamine content in the corpus striatum and boost the effect of levodopa by replenishing lost dopaminergic neurons, may provide a more definitive treatment for advanced PD that is difficult to control with drug therapy alone.

2.3 Rationale for Study Population and Selection of Study Treatment/Study Product

2.3.1 Study Population and its Rationale

In this study, the study population is patients with PD. As concerns the disease stage, it is important that symptoms cannot be controlled by drug treatment alone, but the response to levodopa has not been completely lost; therefore, patients must satisfy both conditions. The early stage of the disease can be well managed with drug treatment alone, requiring no cell transplantation. In contrast, advanced disease with no response to levodopa or dopamine agonists involves impairment of secondary neurons that receive dopamine. Study treatment, which is intended to replenish dopamine, is not expected to work in patients who have an impaired ability to receive dopamine. Since clinical studies of cell transplantation using the human fetal midbrain tissue in Europe and the United States and non-clinical studies of stem cells in monkeys at Kyoto University indicated that cell transplantation into the brain may cause immunoreaction, it is desirable to use immunosuppressants in cell transplantation recipients.

2.3.2 Rationales for Selecting Study Treatment/Study Product and Study Drug

Both drug and surgical therapies for PD are symptomatic and cannot resolve the fundamental condition, progressive loss of dopaminergic neurons, ending in eventual loss of efficacy. Cell transplantation is a more definitive treatment as it replenishes the lost dopaminergic neurons, and is

thus expected to have novel effects that existing treatments do not. More specifically, dopaminergic neurons transplanted and engrafted into the corpus striatum can release dopamine locally within the corpus striatum where dopamine is needed and also regulate the amount of dopamine through dopamine granules in the cell body and dopamine transporters on nerve terminals. In addition, since transplanted dopaminergic neurons are capable of synthesizing dopamine from L-dopa and thus likely to boost the effect of levodopa, cell transplantation, when combined with drug therapy, is expected to enhance the efficacy of drug therapy.

While iPSC therapy for PD has not been reported, the efficacy of cell transplantation has been demonstrated by transplantation of human fetal ventral midbrain cells [References 4-6].

On the other hand, previous non-clinical studies [References 7-10] indicate that transplantation of PSC-derived dopaminergic progenitors may be effective for PD. ES cells and iPS cells can be used to supply dopaminergic progenitors.

In addition, immunosuppressants such as cyclosporine, a calcineurin (CNI) inhibitor, were used in transplantation of human fetal ventral midbrain cells in the 1980s and 1990s, and were shown to be effective in improving the engraftment rate of transplanted cells. In clinical practice of organ transplantation, on the other hand, tacrolimus, another CNI inhibitor, has been increasingly used in recent years due to better adverse drug reaction profile and potency. Non-clinical studies in monkeys at Kyoto University also demonstrated the immunosuppressive activity of tacrolimus after cell transplantation into the brain.

2.4 Rationales for Study Design and Endpoints

2.4.1 Study Design and its Rationale

This study will be conducted as a single-center, open-label, uncontrolled study to evaluate the safety of transplantation of human iPSC-derived dopaminergic progenitors as the primary objective, and also to evaluate the efficacy. Seven patients with PD will be followed up for 24 months after transplantation of approximately 2.4×10^6 dopaminergic progenitors per side into the bilateral putamen.

However, since human iPSC-derived dopaminergic progenitors have never been transplanted into the human putamen and there is limited information on the safety and efficacy, safety will be evaluated and efficacy will be estimated at two dose levels of human iPSC-derived dopaminergic progenitors in this study. Therefore, no control group is included to assess the efficacy. In anticipation of any unexpected adverse event, the first subject will receive unilateral administration initially and then contralateral administration only if no significant risk is detected in the safety evaluation, and then second and subsequent subjects will receive bilateral simultaneous administration. The study schedule differs between the first subject, who will be treated unilaterally twice, and second and subsequent subjects, who will be treated bilaterally at once. Therefore, the first subject will be evaluated primarily for safety, and efficacy will be evaluated in the second and subsequent subjects.

When the graft size on MRI was followed up for 12 to 24 months after transplantation of 2.4×10^6 cells per side into the bilateral putamen in a cynomolgus monkey model of PD, the mean graft size estimated in the mixed effects model peaked at 18 months, and no animal had a 95% confidence upper limit of > 110 mm^3 at 24 months. According to simulation using the relevant data of 1000 random samples with replacement from 6 animals, no graft expansion of > 110 mm^3 was predicted. Based on these results, 2.4×10^6 cells per side will be administered in the first to third subjects and $4.2–5.4 \times 10^6$ cells per side will be administered in the fourth or later subjects. Total 7 subjects will be observed for 24 months in the present study.

To assess the efficacy of cell transplantation, information on progression and change in symptoms along the natural course of PD may be important. While one study reported that the Unified Parkinson's Disease Rating Scale (UPDRS) score at OFF time increased by approximately 20 over 2 years, another study reported no major change over 2 years [References 4 and 5]. In the present study, therefore, post-transplantation change will be assessed based on pre-transplantation data at 2 time points in the same patient. It is proposed that a change of approximately 5 in UPDRS score may be clinically significant [Reference 11]. Based on the assumption that the UPDRS score increases by approximately 20 over 2 years, the observation period will be at least 6 months, during which the UPDRS score is expected to change by approximately 5.

2.4.2Endpoints and their Rationales

In this study, the primary endpoint is incidence and severity of adverse events. Among adverse events, subjects will be checked for graft expansion, with expansion defined as graft size of > 3 cm^3 on MRI at 24 months. One secondary endpoint is change in MDS-UPDRS score, that is, improvement of PD symptoms.

To provide transplantation of human iPSC-derived dopaminergic progenitors as an effective treatment for PD, the safety and efficacy must be evaluated. Development of new neurological symptoms due to graft expansion must be investigated to demonstrate safety, and engraftment of transplanted cells in the human brain and improvement of PD symptoms must be confirmed to demonstrate efficacy. However, since human iPSC-derived dopaminergic progenitors have never been transplanted into the human putamen, it is unknown whether cells transplanted into the human putamen will be engrafted or not, or whether the graft will expand or not. In this study, therefore, the graft size on MRI will be measured over time.

Since there are motor fibers located adjacent to the putamen, where cells will be transplanted, the mass effect due to graft expansion may cause neurological symptoms such as movement disorder; therefore, graft expansion is the greatest concern. According to the guidelines of the Japan Neurological Society, surgery is indicated for putamen hemorrhage with a hematoma volume of ≥ 31 cm^3. While hematoma, which occurs suddenly, causes more damage to the brain than a slowly expanding graft, a graft size of > 31 cm^3 at 20 years is specified as a strict hazard criterion. In previous

cell transplantation experiments, cells transplanted into the brain did not remain undifferentiated, but differentiated; therefore, graft expansion declines over time. Should the graft expand linearly without decline, the critical point at 2 years is 3.1 cm^3. Accordingly, expansion is defined as graft size of > 3 cm^3 on MRI at 24 months in this protocol, and the safety will be declared when the graft size does not exceed 3 cm^3

Since study treatment is intended to improve neurological symptoms of PD, the MDS-UPDRS, a global standard for assessing PD symptoms, will be employed in this study. The MDS-UPDRS score will be measured over time to assess the change as a secondary endpoint. Given the progressive nature of PD, the criterion for efficacy assessment is defined in terms of MDS-UPDRS Part III at OFF time at 2 years after cell transplantation, with the score change from registration to each time point of assessment as the change.

The criteria for efficacy assessment were specified in reference to the results of studies described below. In a study by Olanow et al., the UPDRS score at OFF time increased by approximately 20, on average, over 2 years in relatively mild PD with a UPDRS score of ≤ 49. On the other hand, no major change was observed in relatively severe PD with a UPDRS score of ≥ 50 in the placebo group [Reference 5]. In a study by Freed et al., no major change was observed over 1 year in subjects with a UPDRS score at OFF time of approximately 60 in the placebo group [Reference 4]. In a study by Williams et al., no major change was observed over 1 year in subjects with a UPDRS score at OFF time of approximately 50 in the drug therapy group [Reference 12]. Given these results, good response and excellent response are defined as a decrease of 0 to 4 and a decrease of ≥ 5 in MDS-UPDRS Part III at OFF time over 2 years after cell transplantation, respectively, in the present study.

In this study, other endpoints include average daily ON duration, which is widely used as a measure of PD progression, bradykinesia subscale, uptake of [^{18}F]FDOPA, uptake of [^{18}F]GE180, PDQ-39, Hoehn and Yahr severity, and L-dopa equivalent dose. In addition, EQ-5D-5L, WPAI, and nursing care category are selected as endpoints from a medical economic perspective.

2.5 Potential Benefits and Risks/Disadvantages of Participating in the Study

2.5.1 Potential Benefits

In previous non-clinical studies, behaviors improved in model animals after single transplantation of human iPSC-derived dopaminergic progenitors into the corpus striatum [References 6 and 10]. Therefore, motor symptoms of PD might improve in participants in the present study.

2.5.2 Potential Risks/Disadvantages

As safety concerns, transplantation of human iPSC-derived dopaminergic progenitors into the corpus striatum might induce involuntary movement (dyskinesia), which was observed after transplantation of human fetal ventral midbrain cells [Reference 5], or new neurological symptoms due to expansion of an iPSC-derived graft.

During stereotactic brain surgery for cell transplantation, anesthetic-related adverse events or surgical procedure-related adverse events or complications might occur. To date, adverse events and/or complications, including intracerebral hemorrhage, cerebral infarction, infection, vagal reflex, hypotension, and convulsion, have been reported in relation to stereotactic brain surgery. In addition, adverse events and adverse drug reactions listed in Section 8.3, "Expected Adverse Events" may occur.

3. Information of Study Product, etc.

In this study, the study product, etc. described below will be used in study treatment.

3.1 Study Product

3.1.1 Human iPSC-derived Dopaminergic Progenitors

Human iPSC-derived dopaminergic progenitors, the study product, are induced to differentiate from iPSCs established using blood of an HLA-homozygous healthy volunteer. iPSCs will be established and induced to differentiate at the cell processing center (CPC).

Human iPSC-derived dopaminergic progenitors improved behaviors in model animals in an experiment of transplantation into the corpus striatum and stimulated the uptake of [^{18}F]FDOPA at the graft site in a PET study.

- Overview

This product is manufactured from iPSCs established by introducing multiple plasmids into human peripheral blood mononuclear cells of an HLA-homozygous healthy volunteer and then culturing these cells in laminin 511-E8 fragment-coated dishes. The iPSCs are induced to differentiate in laminin 511-E8 fragment-coated dishes and then sorted using anti-CORIN antibody. Obtained CORIN-positive cells are further induced to differentiate by floating culture, evolving into a cell population consisting mainly of dopaminergic progenitors. These cells, when transplanted and engrafted into the brain, differentiate into dopaminergic neurons that are capable of synthesizing and secreting dopamine.

- Identification code

CT1-DAP001

- Description and structure

A cell mass of cell population consisting mainly of dopaminergic progenitors

- Appearance

A macroscopically white, spherical cell mass with a long-axis diameter ≤ 1 mm

3.2 Study Drug

3.2.1 Tacrolimus

Tacrolimus is an immunosuppressant that has been commercially available since 1993 (capsule formulation) in Japan.

Towa Pharmaceutical Co., Ltd. released the generic form in December 2013.

- Overview

Tacrolimus strongly suppresses immunity primarily by selectively inhibiting T-cell activation, probably through binding to tacrolimus binding protein (FKBP) in the cells.

1) Study component code

TW-247

2) Name of the study drug

TW-247 0.5 mg tablet (tacrolimus 0.5 mg tablet)

TW-247 1 mg tablet (tacrolimus 1 mg tablet)

TW-247 3mg tablet (tacrolimus 3mg tablet)

3) Ingredient/content

- Tacrolimus 0.5 mg tablet

Containing 0.51 mg of JP tacrolimus hydrate (0.5 mg of tacrolimus) per tablet

- Tacrolimus 1 mg tablet

Containing 1.02 mg of JP tacrolimus hydrate (1 mg of tacrolimus) per tablet

- Tacrolimus 3 mg tablet

Containing 3.06 mg of JP tacrolimus hydrate (3 mg of tacrolimus) per tablet

3.3 Drugs Used in the Clinical Trial Other than the Investigational Product (Concomitant Drugs)

3.3.1PET Agents

All PET agents will be purchased from Nihon Medi-Physics Co., Ltd. and administered to subjects in accordance with the brochure of PET agents. The brochure of PET agents contains the manufacturing method, specifications, quality testing, clinical usage, and safety and efficacy information for individual PET agents. Three unapproved PET modalities will be performed using PET agents described below. The overview of each PET agent, including the characteristics, is presented below.

For more details, see the brochure of PET agents.

1) 6-[^{18}F]-fluoro-L-dopa ([^{18}F]FDOPA) (imaging of dopaminergic neurons)

- Overview

[^{18}F]FDOPA has been used in PET for patients with PD or related disease since the 1980s. It has been reported that the specific uptake of [^{18}F]FDOPA in the corpus striatum measured by PET is correlated with the pathological progression and duration of PD as well as the functional status. [^{18}F]FDOPA was also used to assess the function of transplanted cells after transplantation of human fetal ventral midbrain cells in patients with PD.

In this study, [^{18}F]FDOPA PET will be performed for screening assessment before transplantation, as well as to confirm the engraftment and functioning of dopaminergic neurons and for follow-up after transplantation.

- Safety

The exposure dose during [^{18}F]FDOPA PET is approximately 26 μSv/MBq as the effective dose and 5.4 mSv as the standard dose, and the dose attributed to CT during brain PET/CT is at most 0.5 mSv, giving a total exposure of approximately 6 mSv during one [^{18}F]FDOPA examination, which is acceptable.

After mass administration (approximately 43 times the maximum dose in humans) of [^{18}F]FDOPA synthesized in the same conditions as that for humans, mice were observed for 2 weeks and necropsied, revealing no obvious toxicity. In addition, no adverse drug reaction to [^{18}F]FDOPA, which is clinically used in many patients in Japan and overseas, has been reported.

2) 3'-[^{18}F]fluoro-3'-deoxy-L-thymidine ([^{18}F]FLT) (imaging of cell growth)

- Overview

[^{18}F]FLT is a radioactive drug created by labelling a derivative of thymidine, a component and material of DNA, with fluorine-18 (^{18}F) and developed as a PET agent to visualize the cell proliferation ability and nucleic acid synthetic ability. [^{18}F]FLT has been widely used in studies in non-small cell lung cancer and various other cancers. Since more [^{18}F]FLT accumulates in tumor cells, which generally have a higher proliferation ability than normal cells, [^{18}F]FLT is expected to be useful in tumor diagnosis and therapeutic response assessment. In the present study, [^{18}F]FLT PET will be performed to check for cancerization of dopaminergic progenitors after transplantation, keeping in mind that transplanted cells might become cancerous if containing iPSCs.

- Safety

The exposure dose during [^{18}F]FLT PET is 28±12 μSv/MBq in males and 33±12 μSv/MBq in females as the effective dose, and 4.5 mSv and 5.3 mSv as the standard dose, respectively, and the dose attributed to CT during brain PET/CT is at most 0.5 mSv, giving a total exposure of approximately 5 to 6 mSv during one [^{18}F]FLT examination, which is acceptable.

3) [^{18}F]GE180 (imaging of nerve inflammation)

- Overview

[^{18}F]GE180 is an antagonist for translocator protein (TSPO, formerly known as peripheral benzodiazepine receptor), which may be expressed in activated microglia, and developed as a PET agent to visualize neural inflammatory response. [^{18}F]GE180 has been used to assess nerve inflammation in multiple sclerosis, etc. In this study, [^{18}F]GE180 PET will be performed to check for neural inflammatory response to transplanted cells and, if there is a response, the severity.

- Safety

The exposure dose during [^{18}F]GE180 PET is 26.1 μSv/MBq as the effective dose and

approximately 5.4 mSv as the standard dose, and the dose attributed to CT during brain PET/CT is at most 0.5 mSv, giving a total exposure of approximately 6 mSv during one [^{18}F]GE180 examination, which is acceptable.

3.3.2Carbidopa (DOPA Decarboxylase Inhibitor)

Since [^{18}F]FDOPA is rapidly converted to dopamine by dopa decarboxylase outside the brain after administration, only a fraction of the dose reaches the central nervous system as the unchanged drug. After coadministration of [^{18}F]FDOPA and carbidopa, more levodopa is carried to the brain. Carbidopa is used in standard [^{18}F]FDOPA PET to increase the delivery of [^{18}F]FDOPA into the brain and enhance the image contrast. In Japan, carbidopa, which is commercially available in the form of combination with levodopa, is commonly used in the treatment of PD, but is not approved as monotherapy. Therefore, carbidopa used for premedication is imported from the United States. The premedication dose of 150 mg is higher than the usual clinical oral dose per dosing, but is commonly used in [^{18}F]FDOPA PET in Japan and overseas. Additional details can be found in the package insert (see https://www.bauschhealth.com/Portals/25/Pdf/PI/Lodosyn - PI.pdf).

1) Manufacturer/distributor

Bausch Health Companies Inc. (former Valeant Pharmaceuticals)

2) Product name

LODOSYN 25MG TAB

3) Ingredient/content

25 mg of carbidopa per tablet

4) Pharmacokinetics

Since levodopa is rapidly converted to dopamine outside the brain after oral administration, only a fraction of the dose reaches the central nervous system as the unchanged drug. As a result, a high dose of levodopa is required to obtain a therapeutic response, and dopamine formed outside the brain may cause nausea and other adverse drug reactions. Carbidopa inhibits the peripheral metabolism of levodopa, but does not substantially change its pharmacokinetics at usual doses. In addition, carbidopa, which does not readily penetrate the blood-brain barrier, has no effect on the central metabolism of levodopa up to the maximum dose, which inhibits the peripheral metabolism of levodopa. After coadministration of levodopa and carbidopa, which acts exclusively outside the brain, more levodopa is carried to the brain, but absorption of carbidopa, which competes with amino acids that penetrate the intestine, is delayed in patients on high-protein diets.

5) Pharmacology

Carbidopa decreases the required dose of levodopa to 75%, and when coadministered with levodopa, increases blood concentration and blood half-life of levodopa, and decreases dopamine and homovanillic acid in urine. Clinically, when coadministered with levodopa, carbidopa increases urinary excretion of levodopa and secretion of dopamine.

3.4 Instruments Used in the Clinical Trial (Concomitant Instruments)

3.4.1 Cell Injector

Device for infusion of iPSCs (provisional name)

3.4.2 Intended Use

The instrument will be used to administer dopaminergic progenitors into the putamen. After aspirating cells, the instrument will be attached to a Leksell stereotactic frame to administer the cells into the brain.

3.4.3 Manufacturer

TOP Corporation

3.4.4 Specifications

See the brochure.

4. Diagnostic Criteria and Staging/Classification

4.1 Diagnostic Criteria for Parkinson's Disease

PD is as specified in the Movement Disorder Society (MDS) Clinical Diagnostic Criteria for Parkinson's Disease (2015) [Reference 13]. PD will be diagnosed in accordance with the diagnostic criteria listed in 1) to 2) below.

1) MDS Clinical Diagnostic Criteria for Parkinson's Disease

A. Diagnosis of clinically established PD requires:

i) Absence of absolute exclusion criteria

ii) At least two supportive criteria

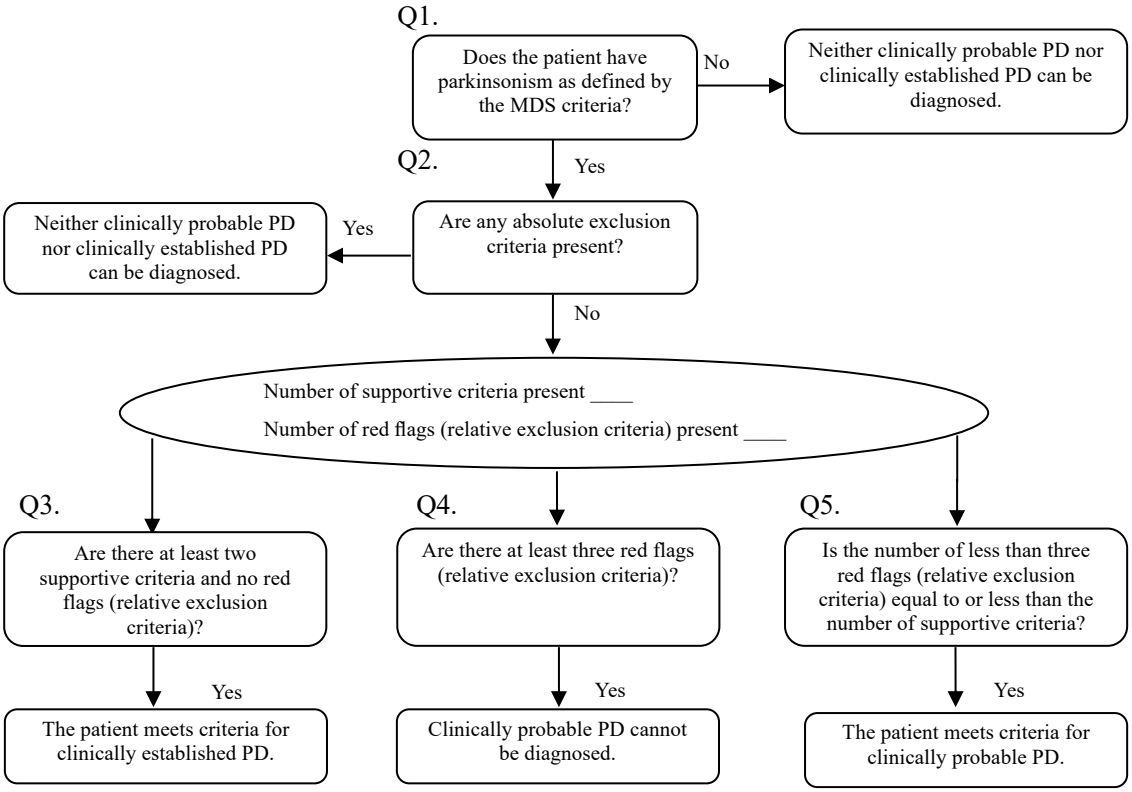
iii) No red flags (relative exclusion criteria)

B. Diagnosis of clinically probable PD requires:

i) Absence of absolute exclusion criteria

ii) Presence of less than three red flags (relative exclusion criteria) counterbalanced by supportive criteria

Red flags (relative exclusion criteria)	Supportive criteria
If one flag is present	At least one criterion must be met.
If two flags are present	At least two criteria must be met.
If three flags are present	Clinically probable PD cannot be diagnosed.



2) Exclusion criteria and supportive criteria specified in the MDS Clinical Diagnostic Criteria for Parkinson's Disease

- Absolute exclusion criteria:

The presence of any of these features rules out PD.

i) Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities
ii) Downward vertical supranuclear gaze palsy or selective slowing of downward vertical saccades
iii) Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to the MDS criteria (consensus criteria), within the first 5 years of disease
iv) Parkinsonian features restricted to the lower limbs for more than 3 years
v) Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
vi) Absence of observable response to high-dose levodopa despite at least moderate severity of disease
vii) Unequivocal cortical sensory loss (i.e. graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
viii) Normal functional neuroimaging of the presynaptic dopaminergic system
ix) Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or the expert evaluating physician, based on the full diagnostic assessment, feels that an alternative syndrome is more likely than PD

- Supportive criteria:

i) Clear and dramatic beneficial response to dopaminergic therapy
(A dramatic response is defined as marked improvement with dose increases or marked worsening with dose decreases, or unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.)
ii) Presence of levodopa-induced dyskinesia
iii) Rest tremor of a limb, documented on clinical examination (in the past or on current examination)
iv) Olfactory loss or ^{123}I-MIBG myocardial scintigraphy clearly documenting cardiac sympathetic denervation

- Red flags (relative exclusion criteria):

i) Rapid progression of gait impairment requiring regular use of wheelchair within 5 years of onset

ii) A complete absence of progression of motor symptoms or signs over 5 or more years unless stability is related to treatment

iii) Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 years

iv) Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs

v) Severe autonomic failure in the first 5 years of disease. This can include:

a) Orthostatic hypotension: orthostatic decrease of blood pressure within 3 minutes of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or

b) Severe urinary retention or urinary incontinence in the first 5 years of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction.

vi) Recurrent (> 1/year) falls because of impaired balance within 3 years of onset

vii) Disproportionate anterocollis (dystonic) or contractures of hands or feet within the first 10 years

viii) Absence of any of the common non-motor features of disease despite 5-year disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, or symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations).

ix) Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)

x) Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination.

4.2 Severity Classification of Parkinson's Disease

4.2.1 Hoehn and Yahr Scale for Grading Severity

The severity of PD will be classified using the Hoehn and Yahr scale for grading severity [Reference 14] described below.

Table 1. Hoehn and Yahr scale for grading severity

Stage	Features

Stage 1	Unilateral involvement only usually with minimal or no functional disability
Stage 2	Bilateral involvement without impairment of balance; physically and socially competent despite minimal impairment
Stage 3	Mild to moderate disability with impaired postural reflexes; physically independent; decreased social competence, but employable depending on job
Stage 4	Severely disabled; physically dependent; still able to walk or stand unassisted
Stage 5	Unable to stand; confined to bed or wheelchair unless aided

4.3 Global Assessment Scale for Parkinson's Disease

In this study, the Unified Parkinson's Disease Rating Scale (UPDRS) revised by the MDS, which is known as the MDS-UPDRS, will be used.

The MDS-UPDRS consists of the following four parts, and the same clinical grading scale (0 = normal, 1 = slight, 2 = mild, 3 = moderate, 4 = severe) is applied to all questions:

- Part I: non-motor aspects of experiences of daily living: 13 questions
  Part 1A focuses on complex behaviors and is completed by the person interviewing the patient and/or the caregiver (six questions).
  Part 1B is the self-administered Patient Questionnaire (seven questions), which is completed by the patient and/or the caregiver.
- Part II: motor aspects of experiences of daily living (M-EDL): 13 questions
  This portion is completed by the patient and/or the caregiver.
- Part III: motor examination: 18 questions
  This portion assesses the symptoms of PD (e.g., speech, facial expression, rigidity, finger tapping, hand movements, pronation-supination movements of hands) objectively and is completed by the examiner in an objective manner. Since some questions have multiple items (e.g. right and left of the body), there are a total of 33 items.
- Part IV: motor complications: 6 questions
  In this portion, the person interviewing the patient and/or the caregiver uses historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia.

In this study, assessment will be performed by physicians who have completed the MDS-specified training program, using the Japanese version of the MDS-UPDRS.

4.4 Mini-Mental State Examination (MMSE)

In this study, the Mini Mental State Examination (MMSE) will be used as the intelligence test (Appendix 1).

4.5 Other Motor Scores

In this study, scales listed below will be used as motor scores.

The PDQ-39 will be administered by a physician or an individual with experience in psychological testing.

- Unified Dyskinesia Rating Scale (MDS-UDysRS) (assessment of dyskinesia) (Appendix 2)
- Parkinson's Disease Questionnaire-39 (PDQ-39) (assessment of QOL) (Appendix 3)

4.6 Acute Dopaminergic Challenge Test

In this study, the response to L-dopa without influence of antiparkinsonian drugs will be assessed in accordance with the criteria used by our hospital in clinical practice (see Appendix 4, "Acute dopaminergic challenge test").

After confirming the medication that the patient is receiving, all antiparkinsonian drugs will be interrupted as specified below so that the test is performed in a fasted state in the early morning. In this study, the method (A) described below will be employed.

Interruption method (A)

- Levodopa (+ carbidopa): 12 hours
- Dopamine agonists
  Sustained-release: 48 hours
  Patch: removed no later than 20:00 on the day before testing
  Cabergoline: 72 hours
  Other: 24 hours
- MAOB inhibitors: 72 hours
- Other antiparkinsonian drugs: 24 hours

Interruption method (B)

- Levodopa (+ carbidopa): 12 hours
- Other than levodopa: 24 hours
  (Patch: removed no later than 20:00 on the day before testing)

4.7 Japanese Version of the Euro-QOL 5 Dimensions-5 Levels (EQ-5D-5L)

In this study, the EQ-5D-5L (Appendix 5) will be used to calculate the utility index (QOL value) from the following five scores [Reference 15]:

- Mobility
- Self-care
- Usual activities
- Pain/discomfort
- Anxiety/depression

4.8 Work Productivity and Activity Impairment Questionnaire (WPAI)

In this study, WPAI: General Health V2.2 (WPAI-GH) (Appendix 6) will be used to assess the work productivity and activity impairment [Reference 16].

5. Eligibility Criteria

Patients who meet all of the inclusion criteria and none of the exclusion criteria are eligible to participate in this study.

5.1 Inclusion Criteria

1) The patient has a diagnosis of PD (clinically established or clinically probable) in accordance with the MDS Clinical Diagnostic Criteria for Parkinson's Disease (2015) [Reference 13].
2) The patient plans to undergo transplantation of human iPSC-derived dopaminergic progenitors.
3) The patient has a poor response to existing drug treatments.
4) The patient is ≥ 50 years and < 70 years of age at the time of informed consent.
5) The patient has had PD for at least 5 years.
6) The patient has both ON and OFF (as demonstrated by the MDS-UPDRS Part III and a symptom diary).
7) The patient is in stage 3 or higher on the Hoehn and Yahr scale at OFF time.
8) The patient is in stage 3 or lower on the Hoehn and Yahr scale at ON time.
9) The patient has an L-dopa response of 30% or more without influence of antiparkinsonian drugs.
10) The patient has a decrease pattern characteristic to PD in the basal ganglia region on DAT scan.
11) The patient has the following organ functions as determined by laboratory tests within 7 days before registration:
   i) Neutrophil count ≥ 2,000/μL
   ii) Platelet count ≥ 5.0×10^4/μL
   iii) AST, ALT ≤ 3.0 × upper limit of normal at the study site
   iv) Total bilirubin ≤ 1.5 × upper limit of normal at the study site
   v) eGFR ≥ 60 mL/min/1.73 m^2
   vi) eGFR (mL/min/1.73 m^2) = $194 \times Cr^{-1.094} \times age^{-0.287}$ (× 0.739 for females)
12) The patient provides written informed consent to participate in the study.
   A patient who cannot write due to the disease may be enrolled if he or she provides verbal consent and a witness signs the informed consent form.

Rationale for the inclusion criteria

The inclusion criteria, for which the rationale is summarized in Section 2.3.1, "Study Population and its Rationale" in this document, were specified in reference to the indication for previous transplantation of human fetal ventral midbrain cells as well as the indication for deep brain stimulation (DBS), an established surgical treatment for advanced PD [Reference 17]. The rationale for each inclusion criterion is described below.

1) This is influential in the efficacy evaluation (allogeneic transplantation is applicable to both sporadic and familial PD).

2) This is influential in the efficacy evaluation.
3) This is influential in the efficacy evaluation (advanced PD is targeted).
4) This is influential in the efficacy evaluation (≥ 50 years of age specified to select patients with a definite diagnosis, < 70 years of age specified to eliminate the effect of dementia on motor function).
5) This is influential in the efficacy evaluation (to select patients with a definite diagnosis).
6) This is influential in the efficacy evaluation (advanced PD is targeted).
7) This is influential in the efficacy evaluation (advanced PD is targeted).
8) This is influential in the efficacy evaluation (cell transplantation may work only in the presence of drug response).
9) This is influential in the efficacy evaluation (cell transplantation may work only in the presence of drug response).
10) This is influential in the efficacy evaluation (to make a reliable diagnosis).
11) A patient who would be at risk if treated with tacrolimus must be excluded for safety considerations.
12) This is essential to select an appropriate subject.

5.2 Exclusion Criteria

1) The patient has a symptomatic organic lesion as detected by head MRI.
2) The patient has abnormal immune function.
3) The patient is demented or deemed at high risk of dementia.
4) The patient has bleeding tendency or abnormal coagulation function.
5) The patient is HBs antigen-positive, or HBs antibody- or HBc antibody-positive with evidence of HBV-DNA.
6) The patient is anti-HIV antibody-positive.
7) The patient is anti-HTLV-1 antibody-positive.
8) The patient has active infection such as hepatitis C or syphilis (STS/TPHA).
9) The study drug (tacrolimus), concomitant drugs (e.g., levodopa, carbidopa, MRI contrast) are contraindicated in the patient.
10) The patient has hypersensitivity to the study drug (tacrolimus), concomitant drugs (e.g., levodopa, carbidopa, MRI contrast), and/or their components.
11) The patient has a serious allergy to a component (e.g., gentacin, component of bovine origin, or component of porcine origin) used in the preparation of the study product.
12) The patient has undergone transplantation of human iPSC-derived dopaminergic progenitors.
13) The patient has any of the following diseases concurrently:
    - Malignant neoplasm
    - Epilepsy

- Mental disease (e.g., depression, bipolar disorder, schizophrenia)
- Other serious concurrent diseases (e.g., cerebrovascular disorder, heart disease, chronic respiratory disease, inadequately controlled hypertension, diabetes mellitus)

14) The patient has a history of any of the following:
    - Malignant neoplasm
    - Epilepsy
    - Cerebral hemorrhage
    - Mental disease (e.g., depression, bipolar disorder, schizophrenia)
    - Pallidotomy, thalamotomy, or deep brain stimulation
15) The patient is pregnant or lactating, or does not agree to avoid pregnancy throughout the study.
16) The patient, in the opinion of the investigator or subinvestigator, is not appropriate to conduct the study safely.

Rationale for the exclusion criteria

1) This is influential in the efficacy evaluation.
2) This is influential in the efficacy evaluation.
3) This is influential in the efficacy evaluation.
4) A patient who would be at risk if treated with surgery must be excluded for safety considerations.
5) A patient who would be at risk if treated with surgery must be excluded for safety considerations.
6) This is influential in the efficacy and safety evaluation.
7) This is influential in the efficacy and safety evaluation.
8) This is influential in the efficacy and safety evaluation.
9) Such a patient is not an appropriate subject.
10) Such a patient is not an appropriate subject.
11) Such a patient is not an appropriate subject.
12) Such a patient is not an appropriate subject.
13) Such a patient is not an appropriate subject.
14) Such a patient is not an appropriate subject.
15) Such a patient is not an appropriate subject.
16) Such a patient is not an appropriate subject.

6. Registration

6.1 Informed Consent from Subjects

6.1.1 Informed Consent from Subjects

Prior to patient registration, the investigator or subinvestigator shall provide a full explanation to each potential subject using the written information and informed consent form approved by the head of the study site and the institutional review board (IRB) to obtain his or her voluntary written consent for participation in the study. A patient who is able to consent, but cannot date or sign the informed consent form due to disability may consent in the presence of a witness. In this case, the witness shall sign (or write name and seal) and date the informed consent form to certify that the patient voluntarily consents after receiving a full explanation (see Section 16.3, “Explanation and Informed Consent”).

The examinations performed in general practice before informed consent may be substituted for those required to determine the patient’s eligibility for the study.

6.1.2 Subjects Being Treated at another Department or Hospital

For any subject being treated at another department or hospital (including a new visit to another department or hospital during participation in the study), the investigator, subinvestigator, or study collaborator shall inform the relevant physician of the subject’s participation in the study.

6.1.3 Screening

After obtaining informed consent from each subject, the investigator or subinvestigator shall investigate and confirm the baseline characteristics of the subject and his or her eligibility for the study as specified in Section 9.2, “Examination/Observation/Investigation Items before First Registration.” Results of any examination performed before informed consent may be employed only with the agreement of the relevant subject.

6.2 Procedure for Patient Registration

In this study, patients will be centrally registered through the Web system.

6.2.1 Receipt of Information of the Study Site and Information for User Account Registration

After the conduct of the study is approved by the IRB, the investigator or subinvestigator shall provide information of the study site, investigator, subinvestigator, and study collaborator to the monitor.

The data center shall receive information of the study site through the monitor, go through the procedure for starting to use Web registration, and inform the investigator that patient registration is ready. The procedure for starting to use Web registration shall be in accordance with a patient registration plan specified separately. The registration manual shall specify the procedures for starting to use the EDC system (user registration), including Web registration, up to patient registration. After being registered as users, unique ID codes and passwords shall be provided to the investigator,

subinvestigator, and study collaborator at the study site. The investigator, subinvestigator, and study collaborator shall store the assigned ID codes and passwords appropriately, and register each patient.

6.2.2Patient Registration

1) The investigator or subinvestigator shall obtain written informed consent from each potential subject and confirm his or her eligibility for the study.
2) The investigator or subinvestigator shall access the Web registration system for the study via the Internet to enter information necessary for patient registration (available 24 hours a day, every day of the year, including weekends and holidays).
3) If the candidate is determined to be eligible in the Web registration system, a unique registration number will be displayed with registration results. The investigator or subinvestigator shall confirm the registration results and start the study-specified study treatment. The registration results will also be communicated to the investigator or subinvestigator, etc. via e-mail or other means.
4) If the candidate is determined to be ineligible in the Web registration system, the investigator or subinvestigator shall inform the candidate that he or she cannot be enrolled in the study.

Once the investigator or subinvestigator completes the patient registration form and confirms the eligibility, the study collaborator may assist in the tasks described in 2) to 3) in accordance with the completed patient registration form, and the investigator or subinvestigator shall confirm the registration results. The completed patient registration form shall be appropriately retained after registration.

The investigator or subinvestigator should not start cell transplantation before the subject is enrolled in the study.

Registration destination (data center)
Department of Clinical Trial Science, Institute for Advancement of Clinical and Translational Science, Kyoto University Hospital

Available for registration: 9:00 to 17:00 on Monday through Friday
(excluding official holidays, anniversary of Kyoto University (6/18), summer holidays, and year-end and New Year holidays)

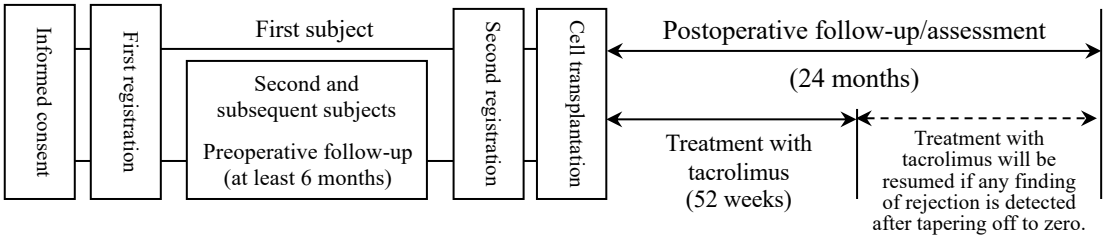
7. Investigational Plan

7.1 Study Treatment

In this study, study treatment will start with cell transplantation and end with the completion of treatment with tacrolimus.

Cell transplantation will be performed within 28 days after the second registration.

For each subject, the observation period will start with the first registration and end at 24 months after transplantation.



The study product in this study, that is, human iPSC-derived dopaminergic progenitors will be transplanted into the bilateral putamen of each subject under general anesthesia using a stereotactic brain surgery system. The dose levels are approximately 2.4×10^6 cells per side in the first to third subjects and $4.2–5.4 \times 10^6$ cells per side in the fourth and subsequent subjects. The first subject will undergo unilateral transplantation initially and then contralateral administration after the safety evaluation at a meeting of the data and safety monitoring board following 6 months of observation. Second and subsequent subjects will receive bilateral administration. Due to the higher dose in the fourth and subsequent subjects, however, after the one-month observation period following bilateral transplantation in the fourth subject, the safety will be evaluated and confirmed at a meeting of the data and safety monitoring board and then the fifth and subsequent subjects will experience transplantation.

Immunosuppressant treatment will be started in the morning on the day of transplantation, continued until 52 weeks after transplantation, and then tapered off to zero over 12 weeks. For the first subject, treatment will be started in the morning on the day of unilateral transplantation, continued until 52 weeks after contralateral transplantation, and then tapered off to zero over 12 weeks. Treatment with tacrolimus may be resumed if any finding of rejection is detected after the end of treatment.

Tacrolimus will be orally administered at the initial dose of 0.03 to 0.15 mg/kg twice daily, which will then be titrated to achieve the target trough blood concentration of 5 to 10 ng/mL. If rejection occurs at 12 weeks or 6 months, the trough concentration will be adjusted to between 10-20 ng/mL.

<<Safety evaluation after unilateral transplantation in the first subject: whether to perform bilateral transplantation in the first subject>>

After verification of safety data collected up to 6 months after unilateral transplantation in the first subject through direct access to source documents and the case report form (CRF), contralateral administration shall be discussed by the data and safety monitoring board.

The data and safety monitoring board shall assess the following and make a recommendation to the sponsor-investigator:

- No serious adverse drug reaction has occurred.
- In addition, no concerns have been raised regarding subsequent contralateral administration.

The detailed procedure will be specified separately in written procedures for the data and safety monitoring board.

<<Safety evaluation after bilateral transplantation in the first subject: whether to perform transplantation in second and subsequent subjects>>

The safety will be evaluated 2 weeks after bilateral transplantation in the first subject to decide whether to administer the study product to second and subsequent subjects.

- No serious adverse drug reaction has occurred for 2 weeks after bilateral transplantation in the first subject.
  (It may take 2 weeks to determine that the short-term effect on the brain has disappeared.)
- In addition, no concerns have been raised regarding administration in the second subject.

<< Safety evaluation after bilateral transplantation in the fourth subject>>

After verification of safety data collected up to 1 month after bilateral transplantation in the fourth subject through direct access to source documents and the case report form (CRF), safety shall be evaluated by the data and safety monitoring board. The data and safety monitoring board shall make a recommendation to the sponsor-investigator on whether to perform transplantation in the fifth and subsequent subjects.

7.2 Cell Preparation

Cells will be prepared for the first to third subjects by Center for iPS Cell Research and Application (CiRA), Kyoto University and for fourth to seventh subjects by Sumitomo Pharma Co., Ltd. (former Sumitomo Dainippon Pharma Co., Ltd.) The period of cell preparation (human iPSC-derived dopaminergic progenitors will be induced to differentiate) will be approximately 2 months. The investigator, etc. shall prepare cells in time for cell transplantation.

Specifications for dopaminergic progenitor preparations are described in the table below.

Test item	Testing method	Specification
Morphology	Microscopic observation	Shape of cell mass
Viability	Flow cytometry	≥ 90%
Markers for dopaminergic progenitors	Expression of FOXA2 and TUJ1 Flow cytometry	FOXA2–TUJ1-copositive cells ≥ 80%

Markers for undifferentiated cells	Expression of OCT3/4/TRA-2-49/6E Flow cytometry	< 0.1%
Markers for early neurons	Expression of SOX1 and PAX6 Flow cytometry	SOX1–PAX6-copositive cells < 0.1%
Asepsis	JP membrane filter technique	Conform to JP requirement
Mycoplasma	JP C method (nucleic acid amplification test)	Negative
Endotoxin	JP turbidimetry	≤ 1 EU/mL
Residual plasmid*	qPCR	No introduction plasmid is detected.
Genome analysis*	a) CNV analysis b) SNV/Indel	1) No mutation is detected in comparison with iPSCs. 2) Any mutation detected should not be found on cancer- or disease-related databases. 3) Any mutation found on database shall be discussed to decide whether to use these cells.

* Reference test item

7.2.1Receipt of Cells (Kyoto University Hospital)

A cell preparation delivered shall be checked by the study product manager or the assistant at the Surgery Unit of Kyoto University Hospital, and then handed over to the operating surgeon at the Department of Neurosurgery. Prior to receipt, the items listed in Section 7.2.2 shall be confirmed.

7.2.2Confirmation Prior to Receipt (Kyoto University Hospital)

Prior to receipt of cells, the study product manager shall confirm that the following requirements are met to determine whether to use clinically, using a check sheet:

1) Confirmation of quality
   - The specifications for dopaminergic progenitor preparations are met.
   - Quality testing supports shipment.
2) Confirmation of management during delivery

- The secondary container has been securely sealed, with no damage or leakage detected.
- Temperature during delivery has been in a prespecified range.

Any abnormal issue such as unfulfilled requirement shall be promptly reported to Sumitomo Pharma Co., Ltd. (former Sumitomo Dainippon Pharma Co., Ltd.) so that a countermeasure can be planned. The determination of clinical usage shall be informed to Sumitomo Pharma Co., Ltd. (former Sumitomo Dainippon Pharma Co., Ltd.) with or without any abnormal issue.

7.3 Cell Transplantation (Kyoto University Hospital)

After the cells received are confirmed to be applicable for clinical usage, cell transplantation will be performed.

In anticipation of any unexpected adverse event, the first subject will receive unilateral administration initially and then contralateral administration only if the data and safety monitoring board detects no significant risk in the safety evaluation after 6 months of postoperative observation.

After completion of bilateral administration in the first subject, second and subsequent subjects will receive bilateral simultaneous administration. Transplantation in second and subsequent subjects is allowed only if no concerns are detected in the safety evaluation at 2 weeks after bilateral transplantation in the first subject, and shall be performed at least 4 weeks after contralateral transplantation in the first subject.

Due to the higher dose in the fourth subject, after the one-month observation period following bilateral transplantation in the fourth subject, the safety will be evaluated and confirmed at a meeting of the data and safety monitoring board and then the fifth and subsequent subjects will experience transplantation.

7.3.1 Preoperative Preparation

1) Preoperative interruption of antiparkinsonian drugs

No antiparkinsonian drug shall be interrupted; instead, antiparkinsonian drugs shall be orally administered with a small amount of water in the morning on the day of operation.

Other drugs may or may not be interrupted in accordance with the hospital guidelines for treatment interruption.

2) Preoperative procedure

Hair shall be shaved partially or completely according to the patient's request.

7.3.2 Transplantation of Human iPSC-derived Dopaminergic Progenitors

1) Determination of insertion site and tracts

Head MRI (contrast) will be performed preoperatively to determine an insertion point and targets. Targets will be identified by [^{18}F]FDOPA PET of the bilateral putamen as low uptake before the second registration. As in usual stereotactic brain surgery, head CT will be performed with a stereotactic brain surgery frame on the subject under general anesthesia to localize the targets

from composite images created with MRI using a navigation system. In addition, the non-dominant side and bilateral differences in symptoms will be taken into account in deciding which side to start an operation on.

2) Trephination

Trephination will be performed under general anesthesia in the operating room. After hair shaving, a 4 cm to 5 cm long skin incision will be made on the scalp, and an approximately 1 cm to 2 cm long hole will be created on the skull using a trephine. An incision will be made on the dura mater to reach the brain surface.

3) Cell transplantation

Dopaminergic progenitors in a cell preparation tube will be centrifuged at 150 × *g* (approximately 1,000 rpm) for 20 seconds at 15 to 25°C, and the supernatant will be removed into a 26-G tuberculin needle as much as possible. The dopaminergic progenitors in the tube will be aspirated into a dedicated cell injector. The guide needle microsyringe for cell injection will be attached and inserted into the stereotactic brain surgery frame in such a manner as to direct its tip toward the target, and the location of the cell injector will be identified by an intraoperative fluoroscope. The cell injector will be inserted into the guide needle, and after the needle is withdrawn 1 mm, approximately 1 μL cell mass (approximately 200,000 cells) will be manually infused per point over 10 seconds and allowed to stand for 1 minute. This procedure will be repeated multiple times in the same transplantation route. By this same procedure, cells will be implanted at 12 points (approximately 2,400,000 cells) per side in the pre-operatively planned transplantation routes (2 to 4 routes) in the first to third subjects. Cells will be transplanted in the same manner in the putamen on the other side (total of approximately 4,800,000 cells). For the fourth and subsequent subjects, cells will be implanted at 21–27 points (approximately 4,200,000–5,400,000 cells) per side in the pre-operatively planned transplantation routes (2 to 3 routes). Cells will be transplanted in the same manner in the putamen on the other side (total of approximately 8,400,000–10,800,000 cells).

4) Completion of operation

After confirming that there is no bleeding at the puncture site or elsewhere, the incision will be closed to complete the operation.

7.4 Immunosuppressant (Tacrolimus)

7.4.1Regimen

Tacrolimus will be orally administered at the initial dose of 0.03 to 0.15 mg/kg twice daily using tacrolimus 0.5 mg tablets, 1 mg tablets, and 3 mg tablets. The dose level will then be titrated according to blood drug concentrations.

[Standard regimen]
The standard regimen is oral administration of tacrolimus at a dose of 0.06 mg/kg twice daily starting in the morning on the day of transplantation.

<Rationale>

Non-clinical studies indicated that rejection may become more severe along with maturation of transplanted cells 2 to 3 months after transplantation than immediately after transplantation. While tacrolimus is less likely to be distributed to the brain than to other tissues, a possible increase in distribution to the brain due to breakdown of the blood-brain barrier has been suggested; therefore, oral administration of tacrolimus at the initial and maintenance dose of 0.03 to 0.15 mg/kg twice daily, which will then be titrated according to blood drug concentrations, was specified in reference to the initial dose for heart transplantation.

As the standard regimen, oral administration of tacrolimus at the initial dose of 0.06 mg/kg twice daily, which will then be titrated according to blood drug concentrations, was specified in reference to the maintenance dose for bone marrow transplantation and kidney transplantation, etc.

7.4.2Measurement of Blood Drug Concentration

Blood drug concentration (whole blood) will be measured every day for 3 days after the start of oral treatment with tacrolimus.
Thereafter, blood drug concentration will be measured once or twice a week up to discharge, as a rule, but more or less frequently depending on the stability of blood concentrations.
The target trough blood concentration is 5 to 10 ng/mL.
Trough blood concentration will be measured at every outpatient visit to achieve the target concentration by titrating the dose level. If rejection occurs at 12 weeks or 6 months, the trough concentration will be adjusted to between 10-20 ng/mL.

<Rationale>
In an experiment of allogeneic transplantation in monkeys, immunoreaction was completely inhibited at blood concentrations of 10 to 20 ng/mL [Reference 18]. In the present study, trough concentrations of 10 ng/mL or lower are considered to be appropriate in view of the balance between the required efficacy and the risk of adverse drug reactions.

7.4.3Duration of Treatment

The duration of treatment, which will be started in the morning on the day of transplantation, is 52 weeks + 12 weeks.
For the first subject, treatment will be started in the morning on the day of unilateral transplantation, continued until 52 weeks after contralateral transplantation, and then tapered off to zero over 12 weeks. Treatment will be resumed and continued (up to 24 months after transplantation) if any finding of

rejection is detected at least 2 weeks after the end of treatment. The criteria for assessing rejection shall be in accordance with Table 9.25, “Criteria for assessing rejection treated with tacrolimus.” Any finding of rejection detected within 52 weeks after transplantation shall be treated in accordance with Appendix 7, “Flowchart of immunosuppressive therapy.”

<Rationale>

The brain is less immunoreactive after transplantation than many other organs and is therefore known as immunologically privileged site [Reference 19]. Nonetheless, the brain is not completely free of immunoreaction; transplantation of HLA-mismatched cells resulted in microglia activation, triggering a reaction to the graft due to lymphocytic infiltration and/or humoral immunity in a primate experiment [Reference 18] and a clinical study of cell transplantation using the human fetal midbrain [Reference 5]. In transplantation of human fetal ventral midbrain cells involving as many as 4 to 10 aborted fetuses, immunosuppressants may be expected to improve the engraftment rate and the graft function [Reference 20]. In actuality, a double-blind study in the United States suggested poor outcomes of transplantation of human fetal ventral midbrain cells with no or short-term use of immunosuppressants [References 4 and 5]. Taken together, a consensus that at least 12 months of immunosuppression is desirable has been reached among researchers in this field [References 20 and 21]. On the other hand, it has been reported that immunological tolerance induced over a certain period of time after transplantation allowed continuous engraftment without long-term use of immunosuppressants. In the present study, therefore, the immunosuppressant will be used for 52 weeks + 12 weeks after transplantation in consideration of efficacy, adverse drug reactions, patient burden, etc. After the end of the immunosuppressive treatment period, the absence of rejection shall be monitored through [^{18}F]GE180 PET, MRI, time course of parkinsonian symptoms, [^{18}F]FDOPA PET, and blood tests. In this study, a stock of one line of iPSCs derived from one human leukocyte antigen (HLA)-homozygous donor will be used. These donor cells may be less immunogenic than cells derived from multiple aborted fetuses previously used in transplantation. It should be noted that donor cells will not be matched to a recipient with regard to HLA type in this study. In future, donor-recipient HLA matching will be considered when cell stocks derived from donors with different HLA homozygous types become available.

In kidney transplantation and bone marrow transplantation, a basic combination of three immunosuppressants, that is, the calcineurin inhibitor tacrolimus, the metabolic inhibitor mycophenolate mofetil (MMF), and steroid, is often used. In transplantation of human fetal ventral midbrain cells, a combination of the previous generation of immunosuppressants, that is, cyclosporine A (CsA), azathioprine, and steroid, was used. Cell transplantation involving a single donor in the present study may be less immunogenic than transplantation of human fetal ventral midbrain cells (mixture of donors with different HLA types) or other organ transplantations. Meanwhile, adverse drug reactions to immunosuppressants include infection susceptibility and increased cancer risk. In

particular, tacrolimus-related abnormal glucose tolerance, renal disorder, and leukoencephalopathy require attention. When the risks of immunosuppressive therapy are compared with its benefits, the combination of three immunosuppressants may be more risky than beneficial in the current study.

In this study, therefore, tacrolimus alone will be used for immunosuppression, and common perioperative anti-inflammatory drugs (e.g., loxoprofen sodium, indomethacin) will be used concomitantly.

7.5 Postoperative Procedure

7.5.1 Postoperative Procedure (Neurosurgery Ward)

The wound will be monitored postoperatively, and wound sutures will be removed approximately 1 week later.

7.5.2 Rehabilitation

A regular postoperative rehabilitation program will be carried out for 2 weeks, and the dose level of the immunosuppressant will be adjusted.

Subjects will be discharged approximately 2 to 4 weeks postoperatively.

7.6 Storage of Samples

To clarify the cause of infection that any subject may develop in future, adequate samples, including parts of cells, will be cryopreserved in cell-cultivating and -processing facility for 10 years after the end of the study period.

7.7 Concomitant Drugs

Concomitant drugs shall be collected starting at the first registration.

7.7.1 Prohibited Concomitant Drugs and Prohibited Concomitant Therapies

1) Prohibited from the first registration to the completion of observation (to exclude any influence in the evaluation of study treatment)
   (Temporary use for postoperative management is allowed.)
   - Any investigational product other than tacrolimus
   - Stereotactic brain surgery such as deep brain stimulation
   - Levodopa/Carbidopa intestinal gel (LCIG)
   - Drugs that stimulate the release of monoamine: methylphenidate and methamphetamine
   - Central antihypertensive agents: reserpine, α-methyldopa, etc.
   - Psychoneurotic drugs: phenothiazines, butyrophenones, benzamides, serotonin/dopamine receptor antagonists, etc.
   - Digestive agents that antagonize the dopamine receptor: sulpiride preparations,

clebopride malate preparations, metoclopramide preparations, etc. (excluding domperidone)

- Tricyclic or tetracyclic antidepressants that strongly antagonize the dopamine receptor (D2 receptor): amoxapine, clomipramine, maprotiline, etc.

2) Prohibited from the second registration to the completion of treatment with tacrolimus (to avoid the concomitant use with tacrolimus)

- Live vaccines: lyophilized live attenuated measles vaccine, lyophilized live attenuated rubella vaccine, live oral poliovirus vaccine, etc.
- Cyclosporine
- Bosentan
- Potassium-conserving diuretics: spironolactone, potassium canrenoate, and triamterene

7.7.2 Concomitant Drugs Requiring Caution (from the Second Registration to the Completion of Treatment with Tacrolimus)

- Antibiotics
  Erythromycin, josamycin, and clarithromycin
  Rifampicin and rifabutin
- Azole antifungals
  Itraconazole, fluconazole, voriconazole, etc.
- Calcium antagonists
  Nifedipine, nilvadipine, nicardipine, diltiazem, etc.
- HIV protease inhibitors
  Ritonavir, saquinavir, and nelfinavir
- Antiepileptics
  Carbamazepine, phenobarbital, and phenytoin
- Nephrotoxic drugs
  Amphotericin B, aminoglycoside antibiotics, sulfamethoxazole/trimethoprim, non-steroidal anti-inflammatory drugs, etc.
- Inactivated vaccines
  Influenza HA vaccine, etc.
- Immunosuppressive drugs
  Immunosuppressants: adrenal corticosteroids, etc.
  Disease-modifying antirheumatic drugs (DMARDs): methotrexate, etc.
- Other drugs
  Bromocriptine, danazol, ethinyl estradiol, and omeprazole
  Lansoprazole, tofisopam, and amiodarone
  Telaprevir, grazoprevir, and letermovir

Ombitasvir/paritaprevir/ritonavir
Eplerenone

- Foods and beverages
  Grapefruit juice
  Foods containing St. John's Wort

7.7.3Drugs that may be Used Concomitantly and Recommended Supportive Care

1) Antiparkinsonian drugs may be used concomitantly from the first registration to the completion of observation, but with no change to the regimen, in principle. However, use or dose adjustment of antiparkinsonian drugs is allowed if necessary for symptom control.
2) Apart from the drugs described in 1) above, oral drugs that have been used for at least 28 days before cell transplantation (excluding prohibited concomitant drugs) may be continued. However, no change should be made to the regimen wherever possible.
3) The following drugs may be used to prevent post-transplantation complications:
   - Infection and fever: Antibiotics shall be administered as an intravenous infusion at the induction of anesthesia and 3 hours later. Antibiotics shall also be administered 6 hours postoperatively and twice on the following day. Prolonged antibiotic treatment shall be considered depending on the clinical course such as persistent postoperative fever.
   - Anti-inflammatory drugs shall be administered for 3 days starting immediately after operation.
   - Non-steroidal anti-inflammatory drugs (NSAIDs) and/or analgesics shall be administered if necessary.
4) The following expected surgery-related adverse event shall be appropriately treated:
   - Bleeding: Allogeneic transfusion shall be given.

7.7.4Treatment for Graft Expansion

Any graft expansion of > 3 cm^3 detected by head MRI postoperatively shall be treated with X-knife stereotactic radiotherapy.

7.8 Criteria for Discontinuing Starting Study Treatment

If one of the following conditions occurs, starting study treatment shall be discontinued, and the date and reason for discontinuation shall be described in the medical chart:

1) The subject is found to fail to meet all of the eligibility criteria after registration.
2) The subject makes a request to discontinue starting study treatment.
3) The subject dies.
4) The subject withdraws his or her consent.
5) The study cannot be started due to transfer to another hospital.
6) The investigator or subinvestigator concludes that surgery is infeasible.

7.9 Criteria for Discontinuing Study Treatment

If one of the following conditions occurs, study treatment shall be discontinued, and the date and reason for discontinuation shall be described in the medical chart:

1) The subject makes a request to discontinue study treatment.
2) The subject dies.
3) The investigator or subinvestigator concludes that study treatment should be discontinued due to an adverse event.
4) The subject withdraws his or her consent.
5) The study cannot be continued due to transfer to another hospital.
6) The investigator or subinvestigator concludes that study treatment should be discontinued due to poor response to tacrolimus.
7) The investigator or subinvestigator concludes that the study cannot be continued.

7.10 Post-study Treatment

If immunosuppressive therapy is deemed necessary after discontinuation of study treatment, use of immunosuppressants other than tacrolimus, including sirolimus, Prednisolone, and mycophenolate mofetil, shall be considered.

8. Evaluation and Reporting of Adverse Events

8.1 Definitions

8.1.1 Definitions of Adverse Event and Defect

In this study, an adverse event (AE) is defined as any illness, disorder, or sign thereof occurring in a subject after the examination for the second registration. Note, however, that any AE suspected to be affected by usage of cell injector occurring in people other than subjects shall be also included in this study.

A defect of the study product is defined as any problem in a broad sense, including malfunction of the test product in the study and adverse effects of cells on the human body, whether it occurs during manufacture, delivery, storage, or use.

A defect of the cell injector is defined as any problem of the injector with regard to the quality, safety, performance, etc. in a broad sense, including damage and poor operation, whether it occurs during design, delivery, storage, or use.

A defect or equivalent is defined as any defect of the study product, any defect of the cell injector, or any adverse event occurring in a subject (related to study treatment or not). Note, however, that any AE suspected to be affected by usage of cell injector occurring in people other than subjects shall be also included in this study.

Any defect or equivalent occurring between the examination for the second registration and 24 months after transplantation shall be monitored, whether it is related to study treatment or not. It should be noted that any defect of the study product or the cell injector shall be monitored only after delivery. Any defect or equivalent occurring later than 24 months after transplantation shall be monitored only if it is related to study treatment.

The following shall not be handled as a defect or equivalent:

- Symptoms that occur during the natural course of PD and can be predicted before the start of study treatment
- Signs or symptoms that have persisted since before the start of study treatment without exacerbation
- Surgery or hospitalization planned before participation in the study or transplantation
  (Any new defect or equivalent occurring during the hospitalization shall be handled as an adverse event.)
- Social hospitalization required after informed consent

8.1.2 Seriousness of Adverse Events and Serious Adverse Events

The seriousness of adverse events shall be categorized as follows:

1. Not serious
2. Serious

A serious adverse event (SAE) is defined as any adverse event, as specified in Section 8.1.1, “Definitions of Adverse Event and Defect,” that meets at least one of the following:

a. Results in death
b. Is life-threatening
c. Requires inpatient hospitalization or prolongation of existing hospitalization for treatment
d. Results in disability/incapacity
e. May result in disability/incapacity
f. Is serious according to the criteria described in a to e above
g. Results in congenital anomaly/birth defect

8.1.3Severity of Adverse Events

The severity of adverse events shall be categorized as follows:

1. Mild: not or mildly symptomatic and not interfering with daily life
2. Moderate: interfering with daily life
3. Severe: severely interfering with daily life

8.1.4Assessment of Causal Relationship

The causal relationship of adverse events to study treatment shall be assessed and categorized as follows:

1. Not related: not reasonably related to study treatment
2. Related: reasonably related to study treatment

Adverse events can be assessed as related to study treatment by reference to resolution after discontinuation of treatment, recurrence after resumption of treatment, established causal relationship to the test drug or similar drugs, no confounding risk factor, consistency with exposure and/or duration of exposure, accurate medical history that almost completely explains the involvement of the test drug, no reasonable possibility of involvement of concurrent treatment, etc. The causal relationship shall be assessed by the investigator or subinvestigator.

8.1.5Outcome of Adverse Events

The outcome of adverse events shall be categorized as follows:

1. Resolved: The adverse event has resolved and the subject has recovered.
2. Resolving: The adverse event has almost resolved and the subject has almost recovered.
3. Not resolved: The adverse event has not resolved and the subject is in the same condition as at the onset of the adverse event (unchanged).
4. Resolved with sequelae: The adverse event has resolved, but the subject has sequelae.
5. Death: The subject died (related to study treatment or not).

6. Unknown: The outcome is unknown with no information available.

8.2 Evaluation and Reporting of Adverse Events, etc.

In this study, any event that may occur or worsen after the examination for the second registration shall be recorded and reported as an adverse event in the study. Abnormal laboratory values shall be handled in the same manner. Any preexisting event that worsens after the start of study treatment shall be reported as an adverse event in the CRF.

The seriousness, severity, causal relationship, and outcome of adverse events shall be assessed as specified in Section 8.1, “Definitions.”

The investigator or subinvestigator shall treat any subject experiencing an adverse event, report the adverse event in the CRF, monitor the event related or unrelated to study treatment until the end of the study period, and further follow it up, if not resolved, until resolution wherever possible. Any adverse drug reaction (adverse event related to study treatment) occurring after the end of the study period shall be monitored wherever possible.

However, this does not necessarily apply when any symptom resulting from exacerbation of the primary disease or associated with complications becomes chronic, or continuous monitoring is difficult due to transfer to another hospital or initiation of post-study treatment.

8.3 Expected Adverse Events

Adverse events that may occur in relation to cell transplantation or drugs used in this study are listed below.

Refer to the latest investigator’s brochure and package insert for possible adverse events.

8.3.1 Adverse Events Associated with Cell Transplantation

- Intracerebral hemorrhage, subdural hemorrhage, epidural hemorrhage, and subcutaneous hemorrhage
- Venostasis and brain edema
- Development of neurological deficit symptoms:
  Consciousness disturbance, movement disorder, sensory disturbance, dysarthria, character change, and memory impairment
- Infection
- Epileptic fit
- Liquorrhea
- Allergy to drugs or devices used
- Wound suture failure
- Surgery-related death

8.3.2Adverse Events Associated with General Anesthesia

- Sore throat, hoarseness, injury to teeth, pneumonia (aspiration pneumonia), and bronchospasm (asthmatic attack)
- Laryngospasm, allergy, malignant hyperthermia, brain disorder, cardiac arrest, and death

8.3.3Adverse Events Caused by Transplanted Cells

- Infection
- Tumor formation: Neurological deficit symptoms due to expansion
- Allergic reaction
- Involuntary movement
- Psychiatric symptoms due to excessive secretion of dopamine

8.3.4[^{18}F]FDOPA (PET Agent)

According to Public Assessment Report Iasodopa issued by the French authorities, the safety profile of IASOdopa has been well established, with no product-specific concerns detected in post-marketing surveillances. However, given reported cases of carcinoid symptoms following rapid infusion of IASOdopa, careful administration such as infusion over at least 1 minute is recommended.

8.3.5[^{18}F]FLT (PET Agent)

For non-radioactive FLT, the safety and efficacy were evaluated for the treatment of acquired immunodeficiency syndrome (AIDS), and a Phase I study revealed no bone-marrow toxicity or hepatotoxicity after administration at a daily dose of 100 mg (11,000 times the maximum dose of [^{18}F]FLT as FLT) for several weeks in HIV patients [Reference 22]. In addition, no adverse drug reaction has been reported in many individuals who clinically received [^{18}F]FLT in Japan or overseas. After being taken up by cells, [^{18}F]FLT is phosphorylated by thymidine kinase-1 (TK1), but hardly distributed to the nucleus and thus not introduced into DNA, unlike thymidine. Accordingly, [^{18}F]FLT may have little effect on any genes.

8.3.6[^{18}F]GE180 (PET Agent)

No adverse drug reaction has been reported in individuals who clinically received [^{18}F]GE180 overseas. In Japan, [^{18}F]GE180 will be administered after the safety has been confirmed in 4 subjects receiving [^{18}F]GE180 and undergoing PET in a clinical research at Kyoto University.

8.3.7Carbidopa (DOPA Decarboxylase Inhibitor)

Reported significant adverse drug reactions to the combination of levodopa and carbidopa include daytime sleepiness, malignant hyperthermia, and confusion, which may be mostly attributed to levodopa contained in the combination. Other significant adverse drug reactions include dyskinesia, nausea, hallucination/delusion, depressed state, decreased cognitive function, and convulsion, all of which have been reported as adverse drug reactions to the oral combination.

8.3.8Tacrolimus

Reported significant adverse drug reactions are acute kidney injury, nephrotic syndrome, cardiac failure, arrhythmia, myocardial infarction, angina pectoris, pericardial effusion, myocardial disorder, central nervous system disorder such as posterior reversible encephalopathy syndrome and hypertensive encephalopathy, cerebrovascular disorder, thrombotic microvascular disorder, pancytopenia, thrombocytopenic purpura, agranulocytosis, hemolytic anemia, pure red cell aplasia, ileus, oculomucocutaneous syndrome (Stevens-Johnson syndrome), dyspnea, interstitial pneumonia, infection, progressive multifocal leukoencephalopathy (PML), BK virus nephropathy, malignant tumor such as lymphoma, pancreatitis, diabetes mellitus, hyperglycemia, hepatic function disorder, and jaundice.

If any abnormality is found, appropriate measures such as dose reduction or interruption should be taken.

As hyperkalemia may occur, serum potassium should be regularly measured. Avoid the concomitant use of potassium-conserving diuretics (spironolactone, potassium canrenoate, and Triteren) and excessive potassium ingestion. Hepatitis due to reactivation of hepatitis B virus may occur in hepatitis B virus carrier patients who are receiving an immunosuppressant. Hepatitis onset due to reactivation of hepatitis B virus following the initiation of immunosuppressant administration has been reported in HBs antigen-negative patients. Precautions for reactivation of hepatitis B virus should be taken while monitoring liver function test values or hepatitis markers.

8.4 Expedited Reporting of Adverse Events and Actions to Be Taken

8.4.1Reporting to the Hospital Director (First Report)

1) The investigator or subinvestigator shall treat any serious adverse event appropriately. The subinvestigator shall report the event to the investigator promptly, whether it is related to the study product, etc. or not. Subjects living too far away to visit the study site immediately shall be instructed to consult a predetermined primary care physician. The investigator shall contact the relevant primary care physician immediately to ask for appropriate treatment and collect information necessary for safety evaluation.
2) The investigator shall report any serious adverse event to the head of the study site within 24 hours of knowledge of the event, in principle, and also report it to the study product supplier, etc. In addition, the investigator shall provide additional information at the request of the head of the study site, the study product supplier, etc.
3) The investigator shall report any serious adverse event to the data and safety monitoring board if necessary.
4) The report format and procedure for reporting serious adverse events shall be in accordance with the written procedures for safety information.

Emergency contact information:
Investigator: Ryosuke Takahashi
Department of Neurology, Kyoto University Hospital
54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507

8.4.2Adverse Events that Need to be Reported to the Minister of Health, Labour and Welfare and Reporting Thereof

1) The investigator shall assess the predictability of any adverse event and the causal relationship of it to the study product, etc. promptly in accordance with the written procedures for safety information (study product), written procedures for safety information (study drug), written procedures for safety information (cell injector), and written procedures for safety information (PET agents and carbidopa).
2) The investigator shall report any adverse event subject to reporting to the regulatory authorities to the Minister of Health, Labour and Welfare.

8.4.3Reporting to the Hospital Director (Second and Subsequent Reports)

After the first report [reporting to the hospital director (first report)], the investigator shall provide any new information to the head of the study site, the study product supplier, etc. in written form as promptly as possible (within three business days).

8.5 Reporting of Pregnancies

As a general rule, if a subject discovers that she is pregnant while participating in the study, the investigator will report the pregnancy along with information such as the estimated date of birth to the head of the study site within 24 hours. The investigator will discontinue study drug treatment if the subject is on study drug treatment. The investigator will follow up until delivery or the termination of pregnancy, and will report the outcome as additional information to the head of the study site. If a baby is born, the newborn will be checked for external malformations at birth.

9. Observation/Examination/Report Items and Schedule

9.1 Study Period

For each subject, the study period will start with the first registration and end on the day of final observation. The study treatment period will start with the second registration and end with the completion or discontinuation of treatment with tacrolimus, and the observation period will start with cell transplantation and end at 24 months after transplantation. For the first subject, the observation period will end at 24 months after bilateral administration. Observations and examinations will be

repeated before bilateral administration.

Study-specific observations and examinations will be performed on an inpatient basis at registration (first and second), admission for cell transplantation, 4 weeks after cell transplantation, 12 weeks after cell transplantation, 6 months after cell transplantation, 12 months after cell transplantation, 18 months after cell transplantation, and 24 months after cell transplantation.

It may sometimes not be possible to perform every PET on time due to test equipment malfunctions, for example, or a test may sometimes unavoidably be stopped if the test reagent has not been delivered due to weather or traffic, for example. Consider performing PET even if outside the acceptable window for post-operative visit.

9.2 Notation and precautions

In case that the subjects cannot visit the study site to receive the study drug during the COVID-19 pandemic, the study site is permitted to deliver the study drug to the subject after contacting via phone and confirming the subject safety as long as the consent is obtained from the subject (Refer to “Q&A on how to manage clinical trials during the COVID-19 pandemic”). In this case, specified clinical laboratory tests will be performed in the assigned study site. The blood concentration will be measured in the study site or in the Kyoto University Hospital when the study site will send the blood sample to the Kyoto University Hospital.

If it is difficult to give an in-person explanation to a remote subject due to concerns about COVID-19 infection, it is acceptable to obtain remote consent regarding the "Informed Consent Form for Handling of Clinical Trial Data" from the viewpoint of subject protection.

9.3 Examination/Observation/Investigation Items before First Registration

Items listed below will be examined, observed, or investigated within 28 days before registration. Results of any examination performed before informed consent may be employed only with the agreement of the relevant subject.

Results of any examination, observation, or investigation performed before informed consent will be employed.

1) Subject baseline characteristics:

   Sex, date of birth, medical history (especially head trauma, stroke, psychosis, epilepsy, tumor, and drug intoxication), occupational history (e.g., exposure to agrichemicals or chemicals), medication history, concurrent disease, allergy, family history, ethnicity, years of education, and information of the target disease (date of initial diagnosis applicable information regarding diagnostic criteria, and information about treatment)

   Information about treatment: Date of onset, symptoms at onset, date symptoms initially confirmed by physician, date of initial treatment, confirmation of parkinsonism (bradykinesia, presence or absence of resting tremor, presence or absence of muscle rigidity

2) Physical findings: height, body weight, blood pressure, and pulse rate

3) Laboratory tests [within 7 days before registration]
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
   - Qualitative urinalysis: urine protein, urinary occult blood, and urine glucose
4) Tumor markers: CA19-9, CEA, CA125, PSA, AFP, SCC, and SLX
5) Coagulation: bleeding time, prothrombin time (PT), and activated partial thromboplastin time (APTT)
6) Immunology: C-reactive protein (CRP) and immunoglobulins (IgM, IgG, and IgA)
7) Infection tests: HBs antigen, HBs antibody, HBc antibody, HBV-DNA, HCV antibody, anti-HIV antibody, anti-HTLV-1 antibody, syphilis (STS/TPHA), parvovirus B19-IgM, and cytomegalovirus IgM

   *HBV-DNA will be measured if the subject is positive for at least either HBs antibody or HBc antibody.
8) HLA typing [Results obtained more than 28 days before registration are acceptable.]
9) Chest x-ray
10) Physiological function tests
    - ECG: standard 12-lead ECG
    - Pulmonary function test
11) MMSE
12) Hoehn and Yahr severity: ON duration, OFF duration
13) MDS-UPDRS (by a qualified physician): The patient's clinical state will be recorded as ON, OFF, or ON-OFF.
14) Average daily ON duration and OFF duration
    (painful dyskinesia, negligible dyskinesia, no dyskinesia)
15) Dyskinesia score (MDS-UDysRS)
16) Parkinson's Disease Questionnaire-39 (PDQ-39) (assessment of QOL)
17) Response to L-dopa without influence of antiparkinsonian drugs [Results obtained more than 28 days before registration are acceptable.]

    See Appendix 4, "Acute dopaminergic challenge test."
18) Head CT
19) Chest CT
20) Head MRI (plain/contrast) (determination of insertion site and tracts): OFF duration
21) Head MRA
22) PET: [^{18}F]FDG

23) DAT scan (^{123}I-ioflupane) [Results obtained more than 28 days before registration are acceptable.]
24) ^{123}I-MIBG myocardial scintigraphy
25) Pregnancy test (female only)
    (Excluding females who have experienced menarche and are considered menopausal based on a period of 12 months or more since the last menstruation, not medically)
26) Subjective and objective symptoms
27) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date)
28) L-dopa equivalent dose

9.4 Examination/Observation/Investigation Items before Second Registration

Items listed below will be examined, observed, or investigated within 28 days before the second registration.

1) Subject baseline characteristics:
   Medical history (especially head trauma, stroke, psychosis, epilepsy, tumor, and drug intoxication), occupational history (e.g., exposure to agrichemicals or chemicals), medication history, concurrent disease, allergy, family history, ethnicity, years of education, and information of the target disease
2) Physical findings: body weight, blood pressure, and pulse rate [first subject: unnecessary if performed within 28 days]
3) Laboratory tests [first subject: unnecessary if performed within 28 days]
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, albumin, γ-GTP, Al-P, LDH, total bilirubin, serum creatinine, BUN, Na, K, and Cl
   - Qualitative urinalysis: urine protein, urinary occult blood, and urine glucose
4) Tumor markers: CA19-9, CEA, CA125, PSA, AFP, SCC, and SLX [only second and subsequent subjects]
5) Coagulation: bleeding time, prothrombin time (PT), and activated partial thromboplastin time (APTT) [only second and subsequent subjects]
6) Immunology: C-reactive protein (CRP) and immunoglobulins (IgM, IgG, and IgA) [only second and subsequent subjects]
7) Infection tests [first subject: unnecessary if performed within 28 days]:
   HBs antigen, HBs antibody, HBc antibody, HBV-DNA, HCV antibody, anti-HIV antibody, anti-HTLV-1 antibody, syphilis (STS/TPHA), parvovirus B19-IgM, and cytomegalovirus IgM
   *HBV-DNA will be measured if the subject is positive for at least either HBs antibody or HBc

antibody.

8) Chest x-ray [first subject: unnecessary if performed within 28 days]
9) Physiological function tests [first subject: unnecessary if performed within 28 days]
   - ECG: standard 12-lead ECG
   - Pulmonary function test
10) MMSE [first subject: unnecessary if performed within 12 weeks]
11) Hoehn and Yahr severity: ON duration, OFF duration
    [first subject: unnecessary if performed within 12 weeks]
12) MDS-UPDRS (by a qualified physician) [first subject: unnecessary if performed within 12 weeks]:
    The patient's clinical state will be recorded as ON, OFF, or ON-OFF.
13) Average daily ON duration and OFF duration
    (painful dyskinesia, negligible dyskinesia, no dyskinesia)
14) Dyskinesia score [first subject: unnecessary if performed within 12 weeks]
15) PDQ-39 [first subject: unnecessary if performed within 12 weeks]
16) EQ-5D-5L
17) WPAI
18) Nursing care category
19) Head MRI [second and subsequent subjects only] (if necessary): OFF duration
20) PET: [^{18}F]FDOPA
    *For the first subject, [^{18}F]FDOPA PET will be performed within 28 days after DAT scan for the first registration.
21) DAT scan (^{123}I-ioflupane) [first subject: unnecessary if performed within 28 days]
22) Pregnancy test (female only) [only second and subsequent subjects]
    (Excluding females who have experienced menarche and are considered menopausal based on a period of 12 months or more since the last menstruation, not medically)
23) Subjective and objective symptoms/adverse events
24) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date)
25) L-dopa equivalent dose

9.5 Day before Cell Transplantation (Acceptable Range: -3 Days)

1) Head MRI (if necessary)
2) Physical findings: body weight, blood pressure, and pulse rate
3) Subjective and objective symptoms/adverse events
4) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)

9.6 Day of Cell Transplantation (Preoperative)

1) Physical findings: body weight (if necessary), blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
3) Measurement of blood drug concentration: blood collection immediately before oral administration in the morning (to measure trough concentration)
   See Section 9.25, "Measurement of Blood Concentrations (Tacrolimus)."
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Head CT
6) Subjective and objective symptoms/adverse events
7) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)

9.7 Day of Cell Transplantation (Immediately after Operation)

1) Information of operation
   Date of operation, duration of operation, surgeon, duration of anesthesia, anesthetic technique, blood loss, presence or absence of defect, information of graft (weight or volume)
2) Measurement of blood drug concentration: blood collection immediately before oral administration in the morning or evening (to measure trough concentration)
   See Section 9.25, "Measurement of Blood Concentrations (Tacrolimus)."
3) Head CT
4) Subjective and objective symptoms/adverse events
5) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)

9.8 Day after Cell Transplantation

1) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
   - Qualitative urinalysis: urine protein, urinary occult blood, and urine glucose

2) Measurement of blood drug concentration: blood collection immediately before oral administration in the morning or evening (to measure trough concentration)
   See Section 9.25, “Measurement of Blood Concentrations (Tacrolimus).”
3) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
4) Head CT
5) Head MRI
6) Subjective and objective symptoms/adverse events
7) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)

9.9 1 Week after Cell Transplantation (Acceptable Range: ±3 Days)

1) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
   - Qualitative urinalysis: urine protein, urinary occult blood, and urine glucose
2) Measurement of blood drug concentration: blood collection immediately before oral administration in the morning or evening (to measure trough concentration)
   See Section 9.25, “Measurement of Blood Concentrations (Tacrolimus).”
3) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
4) Subjective and objective symptoms/adverse events
5) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)

9.10 4 Weeks after Cell Transplantation (Acceptable Range: ±3 Days)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
   - Qualitative urinalysis: urine protein, urinary occult blood, and urine glucose
3) Measurement of blood drug concentration
   See Section 9.25, “Measurement of Blood Concentrations (Tacrolimus).”

4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Hoehn and Yahr severity: ON duration, OFF duration
6) MDS-UPDRS (by a qualified physician): The patient's clinical state will be recorded as ON, OFF, or ON-OFF.
7) Average daily ON duration and OFF duration
   (painful dyskinesia, negligible dyskinesia, no dyskinesia)
8) Dyskinesia score
9) PDQ-39
10) EQ-5D-5L
11) Head MRI (if necessary): OFF duration
12) Subjective and objective symptoms/adverse events
13) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)
14) L-dopa equivalent dose

9.11 8 Weeks after Cell Transplantation (Acceptable Range: ±7 Days)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
   - Qualitative urinalysis: urine protein, urinary occult blood, and urine glucose
3) Measurement of blood drug concentration
   See Section 9.25, "Measurement of Blood Concentrations (Tacrolimus)."
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Subjective and objective symptoms/adverse events
6) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)

9.12 12 Weeks after Cell Transplantation (Acceptable Range: ±7 Days)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)

- Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
- Qualitative urinalysis: urine protein, urinary occult blood, and urine glucose

3) Measurement of blood drug concentration
   See Section 9.25, "Measurement of Blood Concentrations (Tacrolimus)."
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Hoehn and Yahr severity: ON duration, OFF duration
6) MDS-UPDRS (by a qualified physician): The patient's clinical state will be recorded as ON, OFF, or ON-OFF.
7) Average daily ON duration and OFF duration
   (painful dyskinesia, negligible dyskinesia, no dyskinesia)
8) Dyskinesia score
9) PDQ-39
10) EQ-5D-5L
11) Head MRI (if necessary): OFF duration
12) PET: [^{18}F]GE180
13) Subjective and objective symptoms/adverse events
14) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)
15) L-dopa equivalent dose

9.13 16 Weeks after Cell Transplantation (Acceptable Range: ±7 Days)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
   - Qualitative urinalysis: urine protein, urinary occult blood, and urine glucose
3) Measurement of blood drug concentration
   See Section 9.25, "Measurement of Blood Concentrations (Tacrolimus)."
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Subjective and objective symptoms/adverse events
6) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)

9.14 6 Months after Cell Transplantation (Acceptable Range: ±14 Days)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
   - Qualitative urinalysis: urine protein, urinary occult blood, and urine glucose
3) Measurement of blood drug concentration
   See Section 9.25, "Measurement of Blood Concentrations (Tacrolimus)."
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Hoehn and Yahr severity: ON duration, OFF duration
6) MDS-UPDRS (by a qualified physician): The patient's clinical state will be recorded as ON, OFF, or ON-OFF.
7) Average daily ON duration and OFF duration
   (painful dyskinesia, negligible dyskinesia, no dyskinesia)
8) Dyskinesia score
9) PDQ-39
10) EQ-5D-5L
11) WPAI
12) Nursing care category
13) Head MRI (if necessary): OFF duration
14) PET: [^{18}F]FDOPA, [^{18}F]FLT, and [^{18}F]GE180
15) Subjective and objective symptoms/adverse events
16) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)
17) L-dopa equivalent dose

9.15 8 Months after Cell Transplantation (Acceptable Range: ±14 Days)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, Cl

- Qualitative urinalysis: urine protein, urinary occult blood, and urine glucose

3) Measurement of blood drug concentration
   See Section 9.25, “Measurement of Blood Concentrations (Tacrolimus).”
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Subjective and objective symptoms/adverse events
6) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)

9.16 10 Months after Cell Transplantation (Acceptable Range: ±14 Days)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
   - Qualitative urinalysis: urine protein, urinary occult blood, and urine glucose
3) Measurement of blood drug concentration
   See Section 9.25, “Measurement of Blood Concentrations (Tacrolimus).”
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Subjective and objective symptoms/adverse events
6) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)

9.17 12 Months after Cell Transplantation (Acceptable Range: ±14 Days)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
   - Qualitative urinalysis: urine protein, urinary occult blood, and urine glucose
3) Measurement of blood drug concentration
   See Section 9.25, “Measurement of Blood Concentrations (Tacrolimus).”
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Hoehn and Yahr severity: ON duration, OFF duration

6) MDS-UPDRS (by a qualified physician): The patient's clinical state will be recorded as ON, OFF, or ON-OFF.
7) Average daily ON duration and OFF duration
(painful dyskinesia, negligible dyskinesia, no dyskinesia)
8) Dyskinesia score
9) PDQ-39
10) EQ-5D-5L
11) WPAI
12) Nursing care category
13) Head MRI (if necessary): OFF duration
14) PET: [^{18}F]FDOPA and [^{18}F]GE180
15) DAT scan (^{123}I-ioflupane)
16) Subjective and objective symptoms/adverse events
17) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)
18) L-dopa equivalent dose

9.18 14 Months after Cell Transplantation (Acceptable Range: ±14 Days)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
3) Measurement of blood drug concentration
See Section 9.25, "Measurement of Blood Concentrations (Tacrolimus)."
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Subjective and objective symptoms/adverse events
6) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)

9.19 16 Months after Cell Transplantation (Acceptable Range: ±14 Days)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils,

basophils, lymphocytes, and monocytes)

- Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl

3) Measurement of blood drug concentration (only under treatment with tacrolimus)
   See Section 9.25, "Measurement of Blood Concentrations (Tacrolimus)."
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Head MRI (if necessary)
6) PET: [^{18}F]GE180
7) Subjective and objective symptoms/adverse events
8) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)

9.20 18 Months after Cell Transplantation (Acceptable Range: ±14 Days)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
3) Measurement of blood drug concentration (only under treatment with tacrolimus)
   See Section 9.25, "Measurement of Blood Concentrations (Tacrolimus)."
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Hoehn and Yahr severity: ON duration, OFF duration
6) MDS-UPDRS (by a qualified physician): The patient's clinical state will be recorded as ON, OFF, or ON-OFF.
7) Average daily ON duration and OFF duration
   (painful dyskinesia, negligible dyskinesia, no dyskinesia)
8) Dyskinesia score
9) PDQ-39
10) EQ-5D-5L
11) WPAI
12) Nursing care category
13) Head MRI (if necessary) : OFF duration
14) PET: [^{18}F]FDOPA
15) Subjective and objective symptoms/adverse events
16) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date

and end date or under treatment)

17) L-dopa equivalent dose

9.21 20 Months after Cell Transplantation (Acceptable Range: ±14 Days)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
3) Measurement of blood drug concentration (only under treatment with tacrolimus)
   See Section 9.25, "Measurement of Blood Concentrations (Tacrolimus)."
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Subjective and objective symptoms/adverse events
6) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)

9.22 22 Months after Cell Transplantation (Acceptable Range: ±14 Days)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl
3) Measurement of blood drug concentration (only under treatment with tacrolimus)
   See Section 9.25, "Measurement of Blood Concentrations (Tacrolimus)."
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Subjective and objective symptoms/adverse events
6) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)

9.23 24 Months after Cell Transplantation (Acceptable Range: ±14 Days)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin,

hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)

- Biochemistry: AST, ALT, γ-GTP, Al-P, LDH, albumin, total bilirubin, serum creatinine, BUN, Na, K, and Cl

3) Measurement of blood drug concentration (only under treatment with tacrolimus)
   See Section 9.25, "Measurement of Blood Concentrations (Tacrolimus)."
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)
5) Hoehn and Yahr severity: ON duration, OFF duration
6) MDS-UPDRS (by a qualified physician): The patient's clinical state will be recorded as ON, OFF, or ON-OFF.
   The response will be assessed as excellent or good in MDS-UPDRS Part III at OFF time.
7) Average daily ON duration and OFF duration
   (painful dyskinesia, negligible dyskinesia, no dyskinesia)
8) Dyskinesia score
9) PDQ-39
10) EQ-5D-5L
11) WPAI
12) Nursing care category
13) Head MRI (if necessary): OFF duration
14) PET: [^{18}F]FDOPA
15) DAT scan (^{123}I-ioflupane)
16) Subjective and objective symptoms/adverse events
17) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)
18) L-dopa equivalent dose

9.24 Discontinuation (within 14 Days after Decision of Discontinuation)

1) Physical findings: body weight, blood pressure, and pulse rate
2) Laboratory tests
   - Hematology: red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and differential leukocyte count (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
   - Biochemistry: AST, ALT, albumin, γ-GTP, Al-P, LDH, total bilirubin, serum creatinine, BUN, Na, K, and Cl
3) Measurement of blood drug concentration (if necessary)
   See Section 9.25, "Measurement of Blood Concentrations (Tacrolimus)."
4) Immunology: CRP and immunoglobulins (IgM, IgG, and IgA)

5) Hoehn and Yahr severity: ON duration, OFF duration
6) MDS-UPDRS (by a qualified physician): The patient's clinical state will be recorded as ON, OFF, or ON-OFF.
7) Average daily ON duration and OFF duration
   (painful dyskinesia, negligible dyskinesia, no dyskinesia)
8) Dyskinesia score
9) PDQ-39
10) EQ-5D-5L
11) WPAI
12) Nursing care category
13) Head MRI (if necessary)
14) Subjective and objective symptoms/adverse events
15) Information of concomitant therapy: name of the drug, purpose, and treatment period (start date and end date or under treatment)
16) L-dopa equivalent dose

9.25 Examination Methods

9.25.1 MMSE, Hoehn and Yahr Severity, MDS-UPDRS, Dyskinesia Score, and Average Daily ON Duration and OFF Duration

Each subject will be evaluated by the same physician throughout the study period, in principle. MDS-UPDRS and Hoehn and Yahr severity of neurological findings will be assessed while being videotaped.

1) MMSE
   The MMSE will be assessed at ON time.
2) Hoehn and Yahr severity
   The Hoehn and Yahr severity will be assessed at both ON time and OFF time.
   Definition of OFF: See Appendix 4, "Acute dopaminergic challenge test."
3) MDS-UPDRS
   The MDS-UPDRS will be assessed at ON time and OFF time (Part 3 only).
   Definition of OFF: See Appendix 4, "Acute dopaminergic challenge test.".
4) Dyskinesia score
   The dyskinesia score will be assessed at ON time.
5) Average daily ON duration (with or without dyskinesia) and OFF duration
   The average over 7 days before visit will be calculated based on a symptom diary.
   Patients will be trained about how to complete a symptom diary during screening hospitalization before registration.

9.25.2 PDQ-39 Assessment

The PDQ-39 will be assessed at ON time.

9.25.3 Diagnostic Imaging by MRI, SPECT, and PET

Each imaging test will be performed in accordance with the procedure described below.

- Head MRI

Images such as high-resolution T1-weighted images, high-resolution T2-weighted images, T2* images, FLAIR images, diffusion-weighted images, and/or functional MRI images will be acquired using a 3-tesla MRI scanner (e.g., Skyra manufactured by Siemens Healthcare) at Kyoto University Hospital. Sedatives will be administered if necessary.

[Purposes]

1) Determination of the graft site in the brain before transplantation

Preoperatively, images such as high-resolution T1-weighted images, T2-weighted images, FLAIR-weighted images, diffusion-weighted images, and/or contrast T1 images will be acquired and used together with information from other modalities ([^{18}F]FDOPA PET images and CT images) to determine the precise graft site and formulate a surgical plan.

2) Estimation of post-transplantation volume of transplanted cells or tissue

Post-transplantation graft expansion will be estimated using high-resolution MRI images. Our previous non-human primate experiments have shown that T1- and T2-weighted images can be used to fractionate the site corresponding to the transplanted tissue quite accurately. Given this finding, not only T1- and T2-weighted images, but also diffusion-weighted and FLAIR images, which are useful for tissue characterization, will be acquired to extract the fraction corresponding to the graft site (estimated graft volume) for follow-up of change in volume. In case of suspected rejection or graft expansion, contrast MRI will be performed if necessary.

3) Assessment of rejection and graft expansion

If peri-graft edema or graft expansion is identified on T2-weighted images, etc., PET will be considered for comprehensive assessment.

[Image analysis]

Estimation of “graft volume” by MRI

T1-weighted images, T2-weighted images, FLAIR images, diffusion-weighted images, etc. will be used to fractionate the site deemed to be transplanted cells or tissue and then calculate the estimated volume of the graft fraction.

- SPECT (DAT scan)

SPECT images will be acquired using a SPECT scanner (e.g., Infinia manufactured by GE

Healthcare) at Kyoto University Hospital.

1) Drugs listed below will be interrupted for DAT scanning.
   For the duration of interruption, see the clinical guidelines for DAT-SPECT, 2nd edition [References 24 and 25].
   Paroxetine, duloxetine, escitalopram, fluvoxamine, sertraline, imipramine, clomipramine, pimozide, memantine, amantadine, ephedrine hydrochloride, phenylephrine hydrochloride, pseudoephedrine hydrochloride, cocaine hydrochloride, methamphetamine hydrochloride, methylphenidate, mazindol, modafinil, and flunarizine hydrochloride
2) An intravenous line will be established to administer [^{123}I]-ioflupane injection (DAT scan) intravenously.
3) SPECT images will be acquired via a gamma camera over approximately 30 minutes starting 3 hours after administration.

[Image analysis]

Accumulation of ioflupane in the corpus striatum will be qualitatively assessed on reconstructed SPECT images and quantitatively assessed by calculating the specific binding ratio (SBR), etc. with the corpus striatum and occipital lobe or background as regions of interest.

- PET

Three PET modalities will be performed using FDOPA (i), FLT (ii), and GE180 (iii).

Images will be acquired using a combined PET/CT scanner (e.g., Discovery IQ manufactured by GE Healthcare).

i) [^{18}F]FDOPA

1) Cabergoline (Cabaser) and selegiline hydrochloride will be interrupted no later than 72 hours before administration of [^{18}F]FDOPA.
2) Sustained-release preparations of pramipexole hydrochloride, ropinirole hydrochloride, etc. will be interrupted no later than 48 hours before administration of [^{18}F]FDOPA.
3) All antiparkinsonian drugs other than L-DOPA will be interrupted no later than 24 hours before administration of [^{18}F]FDOPA.
4) Rotigotine patch will be removed no later than around 20:00 on the day before PET.
5) L-DOPA (+ DOPA decarboxylase inhibitor) will be interrupted no later than 12 hours before administration of [^{18}F]FDOPA.
6) The subject will be fasted from 4 hours before administration of [^{18}F]FDOPA.
7) The following drug will be orally administered 1 hour before administration of [^{18}F]FDOPA:
   - Carbidopa (DOPA decarboxylase inhibitor): 150 mg
8) An intravenous line will be established to administer approximately 185 MBq of [^{18}F]FDOPA injection slowly over approximately 1 minute.

9) Dynamic PET images of the head will be acquired over 90 minutes after administration of [^{18}F]FDOPA.
10) The duration of imaging will be determined after confirming that the subject will not feel great discomfort during a long-term examination.

[Image analysis]

Accumulation of FDOPA in the corpus striatum will be qualitatively assessed on reconstructed PET images and quantitatively assessed by calculating the standardized uptake value (SUV) in the corpus striatum and occipital lobe as regions of interest. If necessary, time activity curves will be generated from dynamic data to perform a graphic analysis.

ii) [^{18}F]FLT

1) No premedication or fasting is required for PET.
2) An intravenous line will be established to administer approximately 185 MBq of [^{18}F]FLT injection as the standard dose of radioactivity slowly over approximately 1 minute.
3) Static PET images of the head will be acquired over 10 to 15 minutes starting at 60 minutes after administration of [^{18}F]FLT.

[Image analysis]

Accumulation of FLT at the treatment site will be qualitatively assessed on reconstructed PET images. If necessary, the accumulation will be quantitatively assessed by calculating the standardized uptake value (SUV) in appropriate regions of interest.

iii) [^{18}F]GE180

1) No premedication or fasting is required for PET.
2) Images will be acquired with the subject breathing quietly in the supine position in a test bed.
3) An intravenous line will be established to administer approximately 185 MBq of [^{18}F]GE180 injection slowly over approximately 1 minute.
4) Dynamic PET images of the head will be acquired over 90 minutes after administration of [^{18}F]GE180.
5) The duration of imaging will be determined after confirming that the subject will not feel great discomfort during a long-term examination.

[Image analysis]

Images will be reconstructed using data collected from 60 to 90 minutes to qualitatively assess the presence or absence of increased accumulation of [^{18}F]GE180 at the treatment site and measure the SUV. If necessary, time activity curves will be generated from dynamic data to perform a graphic

analysis.

9.26 Measurement of Blood Concentrations (Tacrolimus)

To measure blood tacrolimus concentrations, blood will be collected immediately before oral administration in the morning or evening (to measure trough concentration). The target trough blood concentration is 5 to 10 ng/mL.

Blood drug concentration will be measured every day for 3 days after the start of oral treatment with tacrolimus. Thereafter, blood drug concentration will be measured once or twice a week up to discharge, as a rule, but more or less frequently depending on the stability of blood concentrations. After discharge following cell transplantation, trough blood concentration will be measured as scheduled to achieve the target concentration by titrating the dose level.

Using the criteria described below, rejection treated with tacrolimus will be comprehensively assessed based on findings of [^{18}F]GE180 PET, MRI, time course of parkinsonian symptoms, and blood tests. Assessment will be made by the cranial neurologist and the radiologist through discussion at 12 weeks, 6 months, 12 months, and 16 months.

Table 9.25 Criteria for assessing rejection treated with tacrolimus

Examination item	12 weeks	6 months	12 months Tacrolimus (+)	16 months Tacrolimus (-)	Examiner	Assessment criteria
[^{18}F]GE180 PET	○	○	○	○	Radiologist Neurologist	Findings of GE180 accumulation consistent with the graft
MRI	○	○	○	○	Radiologist Neurologist	In view of the clinical course, peri-graft edema associated with rejection is detected as T2 high signal.
Time course of parkinsonian symptoms	○	○	○	○	Neurologist	In view of the clinical course, exacerbation of parkinsonian symptoms may be due to reduced function of transplanted cells associated with rejection.
[^{18}F]FDOPA PET		○	○		Radiologist Neurologist	In view of the clinical course, decreased accumulation due to reduced function of transplanted cells associated with rejection is observed.
Blood tests	○	○	○	○	Neurologist	Abnormally high white blood cell count and CRP, etc.

9.27 Storage of Blood Samples for Future Research

9.27.1 Intended Use of Blood Samples

Blood samples will be stored for exploratory analysis of biological reactions and immunoresponse during cell transplantation.

9.27.2 Blood Samples to Be Stored

Blood samples for future research from subjects who meet the following conditions will be stored.

- Subjects who provide informed consent to participate in this study and informed consent to "the use and storage of blood samples for future research"
- Subjects from whom blood samples for future research are collected based on the above informed consent

9.27.3 Method for Collecting and Storing Blood Samples (for future research)

1) Blood sample collection time points

See "9.27 Study Calendar."

2) Blood sample collection

The following blood samples will be collected.

For storage of serum: 6 mL whole blood

For storage of PBMCs: 8 mL whole blood

3) Blood treatment and storage

Blood samples will be stored by separately specified procedures.

Samples will also be stored permanently in Center for iPS Cell Research and Application, Kyoto University, unless limited by specifications or ethical requirements.

9.27.4 Action Taken when Subject Withdraws Consent

If a subject withdraws consent for the storage of blood samples for future research, the samples will be disposed of. However, if data has already been obtained at the time that consent is withdrawn, storage will continue in order to ensure the integrity of existing data.

9.28 Study Calendar

		First	Second	Day before trans-planta-tion	Day of trans-planta-tion	Observation period																Discontin-uation
		Regis-tration	Regis-tration			Day after trans-planta-tion	1W	4W	8W	12W	16W	6M	8M	10M	12M	14M	16M	18M	20M	22M	24M	
		In-patient	In-patient		Inpatient			In-patient	Out-patient	In-patient	Out-patient	In-patient	Out-patient	Out-patient	In-patient	Out-patient	In-patient	In-patient	Out-patient	Out-patient	In-patient	
Acceptable range (day)				-3			±3	±3	±7	±7	±7	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	
Human iPSC-derived dopaminergic progenitors					●																	
Administration of tacrolimus					●	●	●	●	●	●	●	●	●	●	●	●	▲	▲	▲	▲	▲	
Subject baseline characteristics		●	○																			
Physical findings		●	○	●	●			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Laboratory tests	Blood	●	○		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	Qualitative urinalysis	●	○			●	●	●	●	●	●	●	●	●	●							
Future Research	For storage of serum	●			●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	For storage of PBMCs	●								●					●		●					
Measurement of blood tacrolimus concentration					See Section 9.25.				●	●	●	●	●	●	●	●		▲	▲	▲	▲	▲
Tumor markers/coagulation		●	○																			
Immunology		●	○		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Infection tests/HLA typing		●	○																			
Chest x-ray/physiological tests		●	○																			
MMSE		●	○																			
Hoehn and Yahr severity, MDS-UPDRS, PDQ-39, dyskinesia score		●	○					●		●		●			●			●			●	●
EQ-5D-5L			●					●		●		●			●			●			●	●
WPAI/nursing care category			●									●			●			●			●	●
L-dopa response test		●																				
Head CT		●			●																	

	First	Second	Day before trans-planta-tion	Day of trans-planta-tion	Observation period																Discontin-uation
	Regis-tration	Regis-tration			Day after trans-planta-tion	1W	4W	8W	12W	16W	6M	8M	10M	12M	14M	16M	18M	20M	22M	24M	
	In-patient	In-patient		Inpatient			In-patient	Out-patient	In-patient	Out-patient	In-patient	Out-patient	Out-patient	In-patient	Out-patient	In-patient	In-patient	Out-patient	Out-patient	In-patient	
Chest CT	●																				
Head MRI[1)]	●	▲			●		●		●		●			●		●	●			●	●
Head MRA	●																				
FDG PET	●																				
[^{18}F]FDOPA PET		●									●			●			●			●	
[^{18}F]FLT PET											●										
[^{18}F]GE180 PET									●		●			●		●					
DAT scan (^{123}I-ioflupane)	●	○												●						●	
^{123}I-MIBG myocardial scintigraphy	●																				
Pregnancy test (female only)	●	○																			
Subjective and objective symptoms/ adverse events	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Information of concomitant therapy	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
L-dopa equivalent dose	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

●: mandatory ○: second and subsequent subjects

1) Head MRI will be performed with contrast before registration and if necessary thereafter..

2) Performed before and after surgery on the day of surgery.

3) Changing from inpatient to outpatient and vice versa will be affordable depending on the circumstances.

10. Target Sample Size and Study Period

10.1 Target Sample Size

In this study, the target sample size is 7 subjects (who have undergone cell transplantation).

The primary objective of the study is to evaluate the safety at 24 months after cell transplantation. With focus on a possible increase in graft size to > 3 cm^3, the expansion was simulated using nonclinical graft data in 8 monkeys (16 grafts) [Reference 10]. In this simulation using data in 6 animals (12 grafts on a bilateral basis), a mixed effects model for the graft size including time point and plateau as effects [Reference 23] was applied to calculate the confidence interval for the maximum 95% confidence upper limit for the mean estimated graft size at each time point. More specifically, 1000 random samples with replacement were generated from 6 (12 grafts) of 8 animals (16 grafts) to calculate the confidence upper limit for the estimated size of each graft at each time point and determine the maximum confidence upper limit. For 1000 maximum values obtained from 1000 samples, 2.5 percentile and 97.5 percentile were designated as the confidence lower limit and the confidence upper limit for the maximum confidence upper limit for the estimated graft size, respectively. Assuming that the effect of the study product on graft data in monkeys would be similar to that in the study population of the present study, and the aforementioned statistical model would be valid for study data, the graft size was estimated to be at most approximately 110 mm^3.

10.2 Study Period

Patient registration period: August 2018 to March 2022 according to the plan

Follow-up period: 24 months after cell transplantation

Study period: August 2018 to March 2024 according to the plan

11. Definitions of Endpoints

11.1 Primary Endpoints

1) Incidence and severity of adverse events

For adverse events reported, the severity will be assessed, and the incidence in the treatment period will be determined.

2) Presence or absence of graft expansion in the brain at 24 months after transplantation

Definition of graft expansion: > 3 cm^3

Modality: head MRI

11.2 Secondary Endpoints

11.2.1 Secondary Safety Endpoints

1) Uptake of [^{18}F]FLT

This endpoint is defined as the presence or absence of accumulation of [^{18}F]FLT at the graft site at

6 months after transplantation.

2) Uptake of [^{18}F]GE180

This endpoint is defined as the presence or absence of accumulation of [^{18}F]GE180 at the graft site at 12 weeks, 6 months, and 12 months after transplantation.

3) Dyskinesia score

This endpoint is defined as the change in dyskinesia score from the second registration to each post-transplantation time point.

4) Graft size

The graft size on MRI will be assessed at each time point of measurement (day before immediately after transplantation, day after transplantation, and 4 weeks, 12 weeks, 6 months, 12 months, 18 months, and 24 months after transplantation) as defined separately (see Section 9.24.3).

11.2.2 Secondary Efficacy Endpoints

1) MDS-UPDRS Part III total score (at OFF time)

This endpoint is defined as the change in UPDRS Part III score at OFF time from the second registration to each post-transplantation time point.

The efficacy will be assessed based on MDS-UPDRS Part III total score at OFF time at 24 months after cell transplantation.

- Excellent response defined as a decrease of ≥ 5
- Good response defined as a decrease of 0 to 4

2) MDS-UPDRS Part III total score (at ON time)

This endpoint is defined as the change in UPDRS Part III score at ON time from the second registration to each post-transplantation time point.

3) Average daily ON duration (with or without dyskinesia) and OFF duration

This endpoint is defined as the change in daily ON duration (with or without dyskinesia) or OFF duration from the second registration to each post-transplantation time point.

4) L-dopa equivalent dose

This endpoint is defined as the change in L-dopa equivalent dose from the second registration to 4 weeks, 12 weeks, 6 months, 12 months, 18 months, or 24 months after transplantation.

Formula to convert to the L-dopa dose [Reference 26]:

L-dopa 100 mg = pramipexole salt 1 mg = ropinirole 5 mg = rotigotine 7.5 mg = bromocriptine 10 mg = pergolide 1 mg = cabergoline 1.5 mg = selegiline 10 mg = amantadine 100 mg = apomorphine 10 mg

5) MDS-UPDRS Part II total score

This endpoint is defined as the change in UPDRS Part II score from the second registration to each post-transplantation time point.

6) MDS-UPDRS Part I total score

This endpoint is defined as the change in UPDRS Part I score from the second registration to each post-transplantation time point.

7) MDS-UPDRS Part I, Part II, and Part III (at ON time)

This endpoint is defined as the change in sum score of UPDRS Part I, Part II, and Part III (at ON time) from the second registration to each post-transplantation time point.

8) MDS-UPDRS Part I, Part II, and Part III (at OFF time)

This endpoint is defined as the change in sum score of UPDRS Part I, Part II, and Part III (at OFF time) from the second registration to each post-transplantation time point.

9) Hoehn and Yahr severity

This endpoint is defined as the change in Hoehn and Yahr severity from the second registration to 4 weeks, 12 weeks, 6 months, 12 months, 18 months, or 24 months after transplantation.

10) Bradykinesia subscale

This endpoint is defined as the change in sum of scores of the following aspects at OFF time in UPDRS Part III from the second registration to each post-transplantation time point:
speech (3.1), facial expression (3.2), finger tapping (3.4), hand movements (3.5), leg agility (3.8), and global spontaneity of movement (body bradykinesia) (3.14)

11) Uptake of [^{18}F]FDOPA

This endpoint is defined as the change in accumulation of [^{18}F]FDOPA at the graft site from the second registration to each post-transplantation time point.

12) Uptake on DAT scan

This endpoint is defined as the change in each quantitative measure at the graft site (including SBR) from the second registration to each post-transplantation time point.

13) PDQ-39 (Parkinson's Disease Questionnaire)

This endpoint is defined as the change in score from the second registration to each post-transplantation time point.

14) EQ-5D-5L

At the second registration and 4 weeks, 12 weeks, 6 months, 12 months, 18 months, and 24 months after transplantation, each subject will be asked to select one of five levels that most accurately describes his or her health status (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on the day of observation. The Japanese version of the tariff will be used to calculate the QOL value.

15) Work Productivity and Activity Impairment Questionnaire: General Health V2.2 (WPAI-GH)

At the second registration and 6 months, 12 months, 18 months, and 24 months after transplantation,

each subject will be asked to answer a questionnaire regarding his or her health problems over the 7 days immediately before travel to the study site (not including travel days).

16) Nursing care category

Each subject will be investigated as to whether he or she is certified as requiring nursing care under the nursing care insurance system, as well as the applicable nursing care category (support level 1, support level 2, nursing care level 1, nursing care level 2, nursing care level 3, nursing care level 4, or nursing care level 5) if certified.

12. Statistical Considerations

12.1 Analysis Sets

12.1.1 Efficacy Analysis Set

The efficacy analysis set consists of second and subsequent subjects who are enrolled in the study and undergo cell transplantation bilaterally and simultaneously. Those who are found to have a major protocol violation after registration or those who are found to be ineligible for the study after registration will be excluded from the study.

12.1.2 Safety Analysis Set

The safety analysis set consists of all subjects who are enrolled in the study and receive at least part of study treatment.

12.2 Handling of Data

12.2.1 Handling of Subjects

Any enrolled subject who may be ineligible for inclusion in the analysis set shall be discussed by the investigator and the person responsible for statistical analysis to decide how to handle the relevant subject, and the issue, contents, and date of decision shall be recorded. If the evaluation (conclusion) in the study is affected, the data and safety monitoring board shall be consulted.

12.2.2 Handling of Data

Data shall be handled as described below, in principle, for tabulation or analysis. Any doubt shall be discussed by the investigator and the person responsible for statistical analysis to decide how to handle the relevant data, and this process shall be documented. If the evaluation in the study is affected by exclusion of the data, the data and safety monitoring board shall be consulted.

Any missing examination or measurement data shall be handled as missing, rather than imputed.

If there are multiple observations in a given period, the observation nearest to the nominal day shall be used.

12.3 Statistical Analyses

In this study, statistical analyses are planned as described below. Technical details of analysis methods and detailed procedures for statistical analyses shall be described in a separately prepared statistical analysis plan.

12.3.1 Primary Analyses

1) Incidences of adverse events and adverse drug reactions

For the safety analysis set, the incidences of adverse events, adverse drug reactions, and serious adverse events reported up to the end of the observation period will be tabulated.

2) Presence or absence of graft expansion

For the safety analysis set, the proportion of subjects with graft expansion in the brain at 24 months after transplantation and its two-sided 95% confidence interval will be calculated. The accurate interval will be estimated based on binomial distribution. Analysis will be performed on a graft basis.

12.3.2 Secondary Analyses

(1) Analysis of safety

For the safety analysis set, each endpoint will be analyzed as described below.

1) Uptake of [^{18}F]FLT

The presence or absence of accumulation of [^{18}F]FLT at the graft site at 6 months after transplantation will be assessed.

2) Uptake of [^{18}F]GE180

The presence or absence of accumulation of [^{18}F]GE180 at the graft site at 12 weeks, 6 months, and 12 months after transplantation will be assessed.

3) Dyskinesia score

For dyskinesia score, time course from the registration to 24 months after transplantation will be presented. In addition, time course of change from the second registration to each time point will be presented. Analysis will be performed on a subject basis.

4) Graft size

For graft size, time course from day before immediately after transplantation to 24 months after transplantation will be presented. Analysis will be performed on a graft basis.

(2) Analysis of efficacy

For the efficacy analysis set, each endpoint will be analyzed as described below. All analyses will be performed on a subject basis.

1) Analyses of MDS-UPDRS scores

For (i) Part III total score (at OFF time), (ii) Part III total score (at ON time), (iii) Part II total

score, (iv) Part I total score, (v) sum score of Part I, Part II, and Part III (at ON time), and (vi) sum score of Part I, Part II, and Part III (at OFF time), time course from the registration to 24 months after transplantation will be presented. In addition, time course of change from the second registration to each time point will be presented.

2) Average daily ON duration (with or without dyskinesia) and OFF duration

For average daily ON duration (with or without dyskinesia) and OFF duration, time course from the registration to 24 months after transplantation will be presented. In addition, time course of change from the second registration to each time point will be presented.

3) L-dopa equivalent dose

For L-dopa equivalent dose, time course from the registration to 24 months after transplantation will be presented. In addition, time course of change from the second registration to each time point will be presented.

4) Hoehn and Yahr severity

For Hoehn and Yahr severity, time course from the registration to 24 months after transplantation will be presented. In addition, time course of change from the second registration to each time point will be presented.

5) Bradykinesia subscale

For bradykinesia subscale, time course from the registration to 24 months after transplantation will be presented. In addition, time course of change from the second registration to each time point will be presented.

6) Uptake of [^{18}F]FDOPA

For uptake of [^{18}F]FDOPA, time course from the registration to 24 months after transplantation will be presented for each graft site. In addition, time course of change from the second registration to each time point will be presented.

7) Uptake on DAT scan

For quantitative measures at the graft site (including SBR), time course of change from the registration to each post-transplantation time point will be assessed.

8) PDQ-39 (Parkinson’s Disease Questionnaire)

For PDQ-39 score, time course from the registration to 24 months after transplantation will be presented. In addition, time course of change from the second registration to each time point will be presented.

9) EQ-5D-5L

For EQ-5D-5L, time course from the second registration to 24 months after transplantation will be presented.

10) WPAI

For WPAI, time course from the second registration to 24 months after transplantation will be presented.

11) Nursing care category

For the presence or absence of certification for nursing care and nursing care category, time course from the registration to 24 months after transplantation will be presented.

(3) Demographic and other baseline characteristics

1) Composition of subjects

For each analysis set, disposition of subjects and number of ineligible subjects will be calculated and presented in flowchart.

2) Subject characteristics and summary statistics

Summary statistics or frequency will be presented.

13. Completion and Submission of Case Report Forms

In this study, CRFs shall be completed and submitted using the EDC system designed to complete CRFs electronically.

Prior to the use of the EDC system, the investigator, subinvestigator, and study collaborator will receive unique ID codes and passwords from the data center to complete and submit CRFs.

CRFs shall be completed, submitted, corrected, and read through the EDC system. These tasks shall be performed after personal authentication with ID codes and passwords, and will be electronically recorded with names of those involved. The investigator, subinvestigator, or study collaborator shall enter necessary data as scheduled. Data in the CRF shall be electronically stored in the EDC database throughout the study period. After completion of final data entry and correction, data in the CRF (including tracked changes) shall be output as a data set and stored in two electronic media. The two electronic media shall be appropriately retained until the end of the study-specified retention period, one by the study site, and the other by the coordinating investigator.

13.1 Identification of Source Documents

In this study, source documents are identified as follows:

1) Medical records, imaging films, questionnaire-related records, etc.
2) Subject ID code and registration number: list of subjects/list of ID codes/registration list
3) Date of informed consent or second informed consent: informed consent form

Other items: records of information provision to subjects, study drug log, etc.

14. Direct Access to Source Documents

The investigator and the study site shall cooperate in study-related monitoring and auditing as well as inspection by the IRB or the regulatory authorities by providing direct access to all study-related records, including source documents.

15. Quality Control and Quality Assurance

The sponsor-investigator shall implement the quality control and assurance system based on the written operational procedures in the organization described in Section 23, “Study Organization” to ensure that this study is conducted in compliance with the protocol and applicable regulatory requirements, including the Pharmaceutical and Medical Device Act (PMD Act), the Ministerial Ordinance on Good Clinical Practice for Regenerative Medicine Products, etc. (GCP ordinance for regenerative medicine products, etc.), and the Ministerial Ordinance on Good Clinical Practice for Drugs (GCP ordinance for drugs).

15.1 Monitoring

Monitoring shall be performed to confirm that this study is being conducted while protecting human rights and well-being of subjects and in accordance with the protocol, relevant regulations, etc., and that data are sufficiently reliable.

Details of monitoring, including the scope and methods, will be specified separately in written procedures for monitoring.

15.2 Audit

The auditor shall perform GCP auditing as part of quality assurance activities as a third party to assess whether this study is being conducted in compliance with the GCP ordinance, the protocol, written procedures, etc. independently and separately from routine monitoring and quality control operations.

Details of audit, including the scope and methods, will be specified separately in an audit plan and written procedures.

15.3 Data and Safety Monitoring Board

The data and safety monitoring board will be established to monitor whether this study is being conducted safely and appropriately. The data and safety monitoring board shall discuss the following issues to advise the investigator if necessary:

- Safety evaluation of unilateral administration in the first subject to determine whether to perform contralateral administration
- Safety evaluation after transplantation in the fourth subject
- Significant change to the protocol
- Serious adverse event
- Serious problem detected through monitoring, etc.
- Other issues that, in the opinion of the investigator, must be discussed by the data and safety monitoring board

Details will be specified separately in written procedures for the data and safety monitoring board.

16. Ethics

16.1 Rules to Comply with

This study will be conducted in compliance with the ethical principles based on the Declaration of Helsinki, the Pharmaceutical and Medical Device Act (PMD Act), the Ministerial Ordinance on Good Clinical Practice for Regenerative Medicine Products, etc. (GCP ordinance for regenerative medicine products, etc.), the Ministerial Ordinance on Good Clinical Practice for Drugs (GCP ordinance for drugs), other GCP-related regulations, and the protocol.

16.2 Creation and Revision of Written Information and Informed Consent Form

The investigator shall create the written information and informed consent form that will be used to obtain informed consent from each potential subject for participation in the study. In addition, the investigator shall submit the created written information and informed consent form as well as the protocol to the head of the study site before the start of the study to obtain approval from the IRB and the head of the study site.

Written information shall contain at least GCP ordinance-specified matters and should not be intended to solicit consent from subjects.

If deemed necessary to make any change to written information and informed consent based on new findings that may affect the subject's consent after the start of the study, the investigator shall revise the written information and informed consent form and obtain approval from the IRB and the head of the study site.

New findings include information of any new adverse event and information about development of any new treatment for the relevant disease.

16.3 Informed Consent

Prior to each subject's participation in the study, the investigator or subinvestigator shall provide a full and understandable explanation using written information to obtain his or her voluntary written consent for participation in the study. The subject shall be given ample time and opportunities for questions to decide whether to participate, and all questions shall be answered satisfactorily. The investigator or subinvestigator involved in explanation, the study collaborator, and the subject shall sign (or write name and seal) and date the informed consent form. The informed consent form shall be retained by the study site, and the written information and a copy of the informed consent form shall be provided to the subject. The investigator or subinvestigator shall explain any significant revision to written information to each participating subject to obtain his or her voluntary consent to continue to participate in the study.

For any patient who is able to consent, but cannot date or sign the informed consent form due to disability, a witness shall sign (or write name and seal) and date the informed consent form to certify

that the patient voluntarily consents after receiving a full explanation in the presence of the witness. An honest witness is defined as a person who is independent from study conduct and free from undue influence by those involved in the study, and witnesses the informed consent process for a patient who cannot complete the process by himself or herself due to inability to read the informed consent form or any other reason. In this case, the name section for the subject shall be left blank rather than signed by the witness on behalf of the subject. Instead, the witness shall describe the name of the subject, the reason for the subject's inability to sign the informed consent form, and the relationship between the subject and the witness in the margin of the form.

16.4 Protection of Personal Information and Privacy

Those involved in the study shall protect personal information in compliance with applicable laws and regulations, local ordinances, etc. In addition, those individuals shall make every effort to protect the personal information and privacy of subjects and should not divulge any personal information learned during the course of the study without justifiable reason. This also applies after retirement.

The investigator, subinvestigator, and study collaborator shall submit the patient registration form, CRFs, etc. using the subject ID code or registration number rather than personally identifiable information (e.g., name, address, telephone number).

The data center shall manage data using the subject ID code or registration number. The investigator or subinvestigator may publish information generated in the study, but in such a manner that no subject can be identified.

17. Expenses for the Study

17.1 Funding Source and Financial Relations

This study will be funded by the Japan Agency for Medical Research and Development in the form of a research grant, which the principal investigator acquired, and by Sumitomo Pharma Co., Ltd. (former Sumitomo Dainippon Pharma Co., Ltd.)

Potential conflicts of interest between the principal investigator or the sponsor-investigator and Sumitomo Pharma Co., Ltd. (former Sumitomo Dainippon Pharma Co., Ltd.) regarding the conduct or results of the study shall be appropriately controlled based on the policy for the management of conflicts of interest at Kyoto University and Graduate School of Medicine, Kyoto University.

17.2 Study-related Expenses and Expenses Incurred by Subjects

The expenses for the study will be paid from the public research grant that the principal investigator acquired or the fund provided by Sumitomo Pharma Co., Ltd. (former Sumitomo Dainippon Pharma Co., Ltd.)

The study product, study drug, and unapproved concomitant instruments will be provided for free. The study product, unapproved concomitant drugs ([^{18}F]-FDOPA, [^{18}F]FLT, [^{18}F]GE180, and

carbidopa), operation costs, DAT scan (second and subsequent scans), and [^{18}F]FDG PET will be paid from the research grant. The system provided for healthcare services that combines insurance-covered and non-covered services will be applied to other expenses.

Payment to subjects for reducing the financial burden shall be approved by the IRB.

17.3 Compensation for Health Injury

The investigator or subinvestigator and the study site shall ensure that any subject suffering from health injury due to an adverse event resulting from study conduct (including health injuries attributable to preparation or management of study conduct, or partially contracted study conduct) can be immediately diagnosed, treated, and dealt with as necessary.

Any study-related health injury (disability of grade 1 or 2 as defined in the relief system for sufferers from adverse drug reactions and fatal accident) shall be financially compensated for (compensation for death or residual disability) based on the provisions of the clinical trial liability insurance purchased for the study. However, no out-of-pocket medical expenses, medical benefits, or other compensation (bereaved family compensation, funeral fees, disability compensation, and disabled child compensation) shall be paid in the study.

Any damage due to health injury incurred by a subject resulting from study operation shall be compensated for based on the provisions of the clinical trial liability insurance, excluding legal liability arising from medical practice, which shall be covered by the medical professional liability insurance purchased by the investigator or subinvestigator. Medical expenses for the treatment of health injury shall be covered by health insurance.

18. Protocol Deviations and Approval and Revision of the Protocol

18.1 Protocol Deviations

The investigator or subinvestigator shall promptly report any protocol deviation made for medically unavoidable reasons, such as to eliminate an immediate hazard to a subject, to the IRB in writing.

18.2 Approval of the Protocol

The investigator shall submit the protocol to the head of the study site before the start of the study to obtain approval of the conduct of the study from the IRB and the head of the study site.

18.3 Revision of the Protocol

If necessary, the investigator shall revise the protocol after discussion with the principal investigator and the investigator. If the revision may be influential in the safety or efficacy evaluation, the principal investigator and the investigator shall discuss with the person responsible for statistical analysis to decide whether to revise the protocol. For any significant change, temporary suspension of patient registration shall be considered to protect subjects if necessary, and discussed by the data and safety

monitoring board in advance.

The investigator shall submit the revised protocol to the head of the study site to obtain approval from the IRB and the head of the study site.

The investigator shall promptly communicate the revision to those involved in the study at the study site, including the subinvestigator and study collaborator.

19. Completion and Premature Discontinuation or Suspension of the Study

19.1 Completion of the Study

After completion of the study period in all subjects, submission of all CRFs, and finalization of data, the investigator shall report completion of the study to the head of the study site in writing.
The head of the study site shall promptly notify the IRB of completion of the study in writing.

19.2 Premature Discontinuation or Suspension of the Study

If one of the conditions listed below occurs, the investigator shall discuss whether to continue the study based on the protocol and decide to discontinue or suspend the entire study. A decision to discontinue the entire study shall be reported with the reason to the regulatory authorities in writing. In addition, the study product supplier, etc. shall be notified of the decision.

i) Information on the quality, efficacy, or safety of the study product, study drug, etc. or other important information for the proper conduct of the study is obtained.
ii) The data and safety monitoring board advises to discontinue or suspend the entire study.
iii) The IRB instructs to discontinue or suspend the study.
iv) Any other condition that may affect the continuation of the study occurs.

The investigator shall promptly notify the head of the study site of any decision to discontinue or suspend the study with the reason in writing. The investigator or subinvestigator shall promptly explain the decision to each subject and take appropriate measures.

The head of the study site shall promptly notify the IRB of the decision in writing.

20. Handling of Study-related Materials

Materials to be retained shall be retained until 1) or 2) described below, whichever is later. If the investigator requests that the materials be retained for a longer period of time, how long and how to retain them shall be discussed.

1) Day of marketing approval of the study drug (or day when 3 years have passed since receipt of notification that development is discontinued or results of the relevant study are not attached to a drug application)
2) Day when 3 years have passed since discontinuation or completion of the study

For each record to be retained, a person responsible for retention shall be appointed.
If study-related materials are no longer required to be retained, the investigator shall inform the study

site in writing.

21. Secondary Use of Data

In future, data generated in the study (including image data and recorded videos) may be used secondarily to develop treatments for PD. The investigator, etc. shall explain secondary use of study results to each subject. Prior to secondary use, a research protocol containing the details shall be submitted to the ethics committee for review and approval.

22. Agreements on Publication

Publication of study results at an academic meeting or in an academic journal shall be preceded by discussion of materials, abstract, draft of the paper, etc. between the investigator and the study product supplier, etc.

Study results should not be published without approval from all individuals involved, regardless of means or contents. Even after agreement of all individuals involved, any change to the contents for any reason, including review by the journal, shall be communicated to all individuals involved to obtain approval.

23. Study Organization

23.1 Principal Investigator

The principal investigator is responsible for all aspects of planning, conduct, and operational management of the study.

Jun Takahashi, Professor of Department of Clinical Application
Center for iPS Cell Research and Application, Kyoto University

53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507
TEL: 075-366-7052 Fax: 075-366-7071

23.2 Sponsor-investigator (Investigator)

Ryosuke Takahashi, Professor of Department of Neurology, Kyoto University Hospital

54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507

[Main duties]

- Submission of a clinical trial notification, etc. to the Minister of Health, Labour and Welfare
- Operations for dealing with information of adverse drug reactions, etc.
- Operations for creating the protocol, etc.
- Operations for taking actions in situations encountered in the study period
- Operations for handling problematic subjects and subject data
- Operations for ensuring the quality of the study drug and managing the study drug
- Operations such as monitoring, data management, statistical analysis, creation of a clinical study report, and auditing (including operations for contracting with contract research organizations, etc.)
- Operations for proceeding with the study
- Operations for establishing a board necessary for study conduct (data and safety monitoring board) and holding meetings of the board
- Operations for retaining records, etc.
- Operations for discontinuing the study
- Other necessary operations for the study
- Agreement on compliance with the protocol
- Creation of written information and consent form
- Selection and supervision of subinvestigators, etc.
- Application of study conduct, etc.
- Selection of subjects
- Informed consent from subjects
- Use of the study drug, etc.

- Medical care of subjects
- Reporting of serious adverse events
- Protocol deviations, etc.
- Creation and reporting of CRFs
- Acceptance of monitoring, auditing, inspections, etc.
- Discontinuation or suspension of the study, etc.

23.3 Study Sites and Departments

23.3.1 Study Sites

Kyoto University Hospital

54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507

23.3.2 Study Departments

1) Department of Neurology (responsible department)
2) Department of Neurosurgery (transplantation)
3) Department of Diagnostic Imaging and Nuclear Medicine (assessment of PET, SPECT, and MRI images)

23.4 Data and Safety Monitoring Board

Hideyuki Sawada*, Vice Director of National Hospital Organization Utano Hospital

Shigeru Kinoshita, Professor of Department of Frontier Medical Science and Technology for Ophthalmology, Kyoto Prefectural University of Medicine

Hiroki Toda, Manager of Department of Neurosurgery, Tazuke Kofukai, Medical Research Institute, Kitano Hospital

* Chairperson

[Main duties]

When any issue, according to the sponsor-investigator, must be discussed by the data and safety monitoring board after the start of the study, including serious adverse events and problems requiring premature discontinuation of the entire study, the data and safety monitoring board shall discuss the issue to advise in response to a consultation request from the sponsor-investigator.

23.5 Data Center

Department of Clinical Trial Science, Institute for Advancement of Clinical and Translational Science, Kyoto University Hospital

54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507

Person responsible for statistical analysis:

Satoshi Morita, Department of Clinical Trial Science, Institute for Advancement of Clinical and Translational Science, Kyoto University Hospital

Statistician

Kentaro Ueno, Department of Clinical Trial Science, Institute for Advancement of Clinical and Translational Science, Kyoto University Hospital

[Main duties]

The person responsible for statistical analysis and the statistician shall plan statistical analysis methods and create a statistical analysis plan for the study. In addition, they shall perform statistical analyses in accordance with the statistical analysis plan and create a statistical analysis report.

Person responsible for data management:

Akemi Kinoshita, Department of Clinical Trial Science, Institute for Advancement of Clinical and Translational Science, Kyoto University Hospital

[Main duties]

The person responsible for data management shall design CRFs, check CRFs, enter data, and control data quality.

23.6 Person Responsible for Monitoring

Kayoko Enomoto, Department of Clinical Trial Science, Institute for Advancement of Clinical and Translational Science, Kyoto University Hospital

[Main duties]

The person responsible for monitoring shall perform monitoring operations in accordance with study-specified written procedures, and manage and control monitoring operations carried out by sponsor-investigator-designated monitors.

23.7 Audit

Sumitomo Pharma Co., Ltd. (former Sumitomo Dainippon Pharma Co., Ltd.)

2-6-8 Doshomachi, Chuo-ku, Osaka 541-0045

[Duties]

The auditor shall investigate whether this study has been conducted in accordance with GCP and the protocol to ensure the reliability of materials collected in the study.

23.8 Study Product Supplier, etc.

23.8.1 Study Product Supplier

1) From the first to third subjects

Center for iPS Cell Research and Application (CiRA), Kyoto University
53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507
TEL: 075-366-7000

2) From the fourth to seventh subjects

Sumitomo Pharma Co., Ltd. (former Sumitomo Dainippon Pharma Co., Ltd.)
2-6-8 Doshomachi, Chuo-ku, Osaka 541-0045
TEL: 06-6203-5321 (main)

[Main duties]

The study product supplier shall provide the study product to the investigator.

The study product supplier shall collect and provide information, including the brochure of the study product and information on the safety of the study product.

The study product supplier shall provide other necessary information based on discussion with the investigator.

23.8.2 Study Drug Supplier

Towa Pharmaceutical Co., Ltd. (tacrolimus)
2-11 Shinbashi-cho, Kadoma, Osaka 571-8580
TEL: 06-6900-9100 (representative)

[Main duties]

The study drug supplier shall provide the study drug to the investigator.

The study drug supplier shall collect and provide information, including the brochure of the study drug and information on the safety of the study drug.

The study drug supplier shall provide other necessary information based on discussion with the investigator.

23.8.3 Cell Injector Supplier

TOP Corporation (needles)
19-10 Senjunakai-cho, Adachi-ku, Tokyo 120-0035
TEL: 03-3882-3101 (representative)

[Main duties]

The cell injector supplier shall provide the cell injector to the investigator.

The cell injector supplier shall collect and provide information, including the brochure of the study instrument and information on the safety of the study instrument.

The cell injector supplier shall provide other necessary information based on discussion with the investigator.

23.9 Contract Manufacturer of PET Agents

Nihon Medi-Physics Co., Ltd.

3-4-10 Shinsuna, Koto-ku, Tokyo 136-0075

TEL: 03-5634-7006 (representative)

[Duties]

i) Operations for procurement, inspection upon receipt, and storage of raw and other materials necessary to manufacture PET agents
ii) Operations for manufacturing and shipping PET agents
iii) Operations for distributing and delivering PET agents
iv) Operations for disposing of PET agents

23.10 Cell-Cultivating and -Processing Facility

1) From the first to third subjects

Center for iPS Cell Research and Application (CiRA), Kyoto University

53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507

TEL: 075-366-7000 FAX: 075-366-7023

2) From the fourth to seventh subjects

Sumitomo Dainippon Manufacturing Plant for Regenerative Medicine & Cell Therapy (SMaRT), Sumitomo Pharma Co., Ltd. (former Sumitomo Dainippon Pharma Co., Ltd.)

33-94 Enoki-cho, Suita-city, Osaka 564-0053

[Main duties]

The cell-cultivating and -processing facility shall manufacture and ship iPSCs and dopaminergic progenitors.

23.11 Image Assessment (MRI, SPECT, and PET)

Department of Radiology (Diagnostic Imaging and Nuclear Medicine), Graduate School of Medicine, Kyoto University

54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507

Responsible person: Yuji Nakamoto, Professor of Department of Radiology, Graduate School of Medicine, Kyoto University

[Main duties]

The assessor shall assess MRI, SPECT, and PET images in this study.

23.12 Adviser for Assessment of MRI Images

Takuya Hayashi, Team Leader, Laboratory for Brain Connectomics Imaging

RIKEN Center for Biosystems Dynamics Research

24. References

1) Survey of patients in 2014, Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare
2) Parkinson's disease and related disorders (3) Parkinson's disease (publicly paid) [Internet]. Japan Intractable Diseases Information Center: Japan Intractable Diseases Research Foundation/Japan Intractable Diseases Information Center; [updated on 8 July 2011; cited on 6 February 2012]. Available from: http://www.nanbyou.or.jp/entry/314
3) 2011 Practical Guideline for Parkinson's Disease [Internet]. Japanese Society of Neurology; [cited on 21 February 2012]. Available from: http://www.neurology-jp.org/guidelinem/parkinson.html
4) Freed CR, Greene PE, Breeze RE, et al: Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med 2001; 344: 710―719
5) Olanow CW, Goetz CG, Kordower JH, et al: A doubleblind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol 2003; 54: 403―414
6) Kefalopoulou Z, Politis M, Piccini P, Mencacci N, Bhatia K, Jahanshahi M, et al. Long-term clinical outcome of fetal cell transplantation for Parkinson disease: Two case reports. JAMA Neurol 2014, Jan; 71(1):83-7.
7) Kikuchi, T., Morizane, A., Doi, D., Onoe, H., et al. Survival of Human Induced Pluripotent Stem Cell--Derived Midbrain Dopaminergic Neurons in the Brain of a Primate Model of Parkinson's Disease. Journal of Parkinson's Disease 1, 395-412 (2011).
8) Doi, D., Morizane, A., Kikuchi, T., Onoe, H., et al. Prolonged Maturation Culture Favors a Reduction in the Tumorigenicity and the Dopaminergic Function of Human ESC-Derived Neural Cells in a Primate Model of Parkinson's Disease. Stem Cells 30, 935-945 (2012).
9) Doi, D., Samata, B., Katsukawa, M., Kikuchi, T., et al. Isolation of human induced pluripotent stem cell-derived dopaminergic progenitors by cell sorting for successful transplantation. Stem Cell Reports 2, 337-350 (2014).
10) Kikuchi, T., Morizane, A., Doi, D., Magotani, H., et al. Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model. Nature 548(7669): 592-6 (2017).
11) A. Schrag, et al. Minimal Clinically Important Change on the Unified Parkinson's Disease Rating Scale Movement disorders 21, 1200-2007,2006
12) A. Williams, S. Gill, T. Varma, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomized, open-label trial Lancet Neurol, 9 (2010)581-591
13) Ronald B. Postuma, et al. MDS Clinical Diagnostic Criteria for Parkinson's Disease Movement disorders 30, 1592-, 2015
14) Hoehn MM, Yahr MD: Parkinsonism: onset, progression, and mortality. Neurology, 1967, 17: 427-442.

15) Ikeda S, et al.: Developing a Japanese version of the EQ-5D-5L value set. Journal of the National Institute of Public Health 64: 47-55, 2015.
16) Reilly MC, Zbrozek AS, Dukes EM: The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 4: 353-365, 1996.
17) Lang AE, Houeto JL, Krack P, Kubu C, Lyons KE, Moro E, et al. Deep Brain Stimulation: Preoperative Issues. Movement Disorders 2006; 21(Sup.14):S171-S196.
18) Morizane A, Kikuchi T, Hayashi T, Mizuma H, Takara S, et al. MHC matching improves engraftment of iPSC-derived neurons in non-human primates. Nat Commun. 2017 Aug 30;8(1):385. 1-12.
19) Medawar PB, Immunity to homologous grafted skin; the fate of skin homografts transplanted to the brain, to subcutaneous tissue, and to the anterior chamber of the eye.1948 Br J Exp Pathol. 1948 Feb;29(1):58-69.
20) Barker RA, Drouin-Ouellet J, Parmar M: Cell-based therapies for Parkinson disease-past insights and future potential. Nat Rev Neurol 2015;11: 492-503
21) Barker RA, Parmar M, Studer L, Takahashi J: Human Trials of Stem Cell-Derived Dopamine Neurons for Parkinson's Disease: Dawn of a New Era. Cell Stem Cell 2017;21: 569-73
22) Shields AF. PET imaging with ^{18}F-FLT and thymidine analogs: Promise and pitfalls. J Nucl Med 2003, Sep;44(9):1432-4.
23) Warschausky, S., Kay, J.B., and Kewman, D.G. Hierarchical Linear Modeling of FIM Instrument Growth Curve Characteristics After Spinal Cord Injury. Archives of Physical Medicine and Rehabilitation, 2001, 82(3): 329-34.
24) Clinical guidelines for DAT-SPECT, 2nd edition. Japanese Society of Nuclear Medicine/The Japanese Council of Nuclear Neuroimaging
25) Kägi G, Bhatia KP, Tolosa E. The role of DAT-SPECT in movement disorders. J Neurol Neurosurg Psychiatry 2010, Jan; 81 (1):5-12.
26) Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Mov Disord 2010;25(15):2649-53.

25. Appendices

- Appendix 1: Mini Mental State Examination (MMSE)
- Appendix 2: Unified Dyskinesia Rating Scale (MDS-UDysRS) (dyskinesia score)
- Appendix 3: Parkinson Disease Questionnaire-39 (PDQ-39) (assessment of QOL)
- Appendix 4: Acute dopaminergic challenge test (testing of response to L-DOPA)
- Appendix 5: Japanese version of the Euro-QOL 5 Dimensions-5 Levels (EQ-5D-5L)
- Appendix 6: Work Productivity and Activity Impairment Questionnaire (WPAI)
- Appendix 7: Flowchart of immunosuppressive therapy