February 19, 2026
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Human Cellular/Tissue-based Products, 4. Human Induced Pluripotent Stem Cell-processed Products
Non-proprietary Name	Raguneprocel
Brand Name	AMCHEPRY
Applicant	Sumitomo Pharma Co., Ltd.
Date of Application	August 5, 2025 (Application for marketing approval)

Results of Deliberation

In its meeting held on February 19, 2026, the Committee on Regenerative Medicine Products and Biotechnology reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product may be approved. The conditional and time-limited approval is applicable to the product. The approval conditions and duration of approval are as follows. The product should be designated as a Designated Regenerative Medical Product.

Approval Conditions

1. The applicant is required to conduct post-marketing approval condition assessment, for example through post-marketing surveillance covering all patients treated with the product, until the submission of an application for standard marketing approval of the product to which the conditional and time-limited approval has been granted.
2. The applicant is required to take necessary measures, such as provision of seminars, to ensure that physicians with adequate knowledge and experience in the diagnosis and treatment of Parkinson's disease as well as in stereotactic neurosurgical procedures have a full understanding of relevant information, including the results of the clinical study of the product and adverse events reported, to use the product in compliance with the "Indication or Performance" and "Dosage and Administration or Method of Use" at medical institutions with an established system for the treatment of Parkinson's disease.

Duration of Approval

7 years

Review Report

February 10, 2026
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following regenerative medical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	AMCHEPRY
Classification	Human Cellular/Tissue-based Products, 4. Human Induced Pluripotent Stem Cell-processed Products
Non-proprietary Name	Raguneprocel
Applicant	Sumitomo Pharma Co., Ltd.
Date of Application	August 5, 2025

Shape, Structure, Active Ingredients, Quantities, or Definition
The product (AMCHEPRY) consists of aggregates of dopaminergic neuronal progenitor cells generated by culturing, differentiating, and aggregating induced pluripotent stem (iPS) cells derived from human (allogeneic) peripheral blood mononuclear cells following transfection of episomal vectors.

Application Classification	(1-1) New regenerative medical product
Items Warranting Special Mention	Orphan Regenerative Medical Product (Orphan Regenerative Medical Product Designation No. 38 of 2025 [*R7 sai*]; PSB/MDED Notification No. 1212-3 dated December 12, 2025, by the Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare) SAKIGAKE Designation Regenerative Medical Product (SAKIGAKE Regenerative Medical Product Designation No. 2 of 2016 [*28 sai*]; PSEHB/MDED Notification No. 0228-21 dated February 28, 2017, by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare), SAKIGAKE comprehensive assessment consultation conducted for regenerative medical products
Reviewing Office	Office of Cellular and Tissue-based Products

Results of Review
On the basis of the data submitted, PMDA has concluded that the product is expected to have some efficacy in improving motor symptoms in patients with Parkinson's disease who have an inadequate

response to conventional pharmacotherapies, including levodopa-containing drug products, and that the product has acceptable safety (see Attachment). However, because the available information is currently limited, the efficacy of the product should continue to be evaluated and confirmed after marketing approval.

As a result of its review, PMDA has concluded that the product may be approved for the indication or performance and dosage and administration or method of use shown below, with the following approval conditions, and that specifically, a conditional and time-limited approval under Article 23-26 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices may be granted to the product.

Indication or Performance

Improvement of motor symptoms in patients with Parkinson's disease who have an inadequate response to conventional pharmacotherapies, including levodopa-containing drug products

Dosage and Administration or Method of Use

1. Transplantation of AMCHEPRY

Usually, in adults, AMCHEPRY consisting of allogeneic iPS cell-derived dopaminergic progenitor cells is transplanted stereotactically into the bilateral putamen, with a target of 5.4×10^6 cells per hemisphere. The cells are administered through 3 injection tracts passing through a single burr hole in the skull, and approximately 1.8×10^6 cells per tract are transplanted into 6 to 9 sites at intervals of 1 to 2 mm. The infusion rate is approximately 0.1 μL/sec.

2. Administration of tacrolimus hydrate before and after transplantation of AMCHEPRY for the purpose of suppressing immune responses to AMCHEPRY

Usually, tacrolimus is initially administered orally at a dose of 0.03 to 0.15 mg/kg twice daily starting in the morning of the transplantation day. Thereafter, the dose should be adjusted to maintain the blood tacrolimus trough level in the range of 5 to 10 ng/mL while monitoring the blood trough level.

If rejection is observed, the trough blood tacrolimus level should be maintained in the range of 10 to 20 ng/mL.

As a general rule, approximately 1 year after the start of tacrolimus administration, the dose should be gradually tapered over the subsequent 12 weeks and then discontinued; however, the duration of administration may be extended as necessary.

Approval Conditions

1. The applicant is required to conduct post-marketing approval condition assessment, for example through post-marketing surveillance covering all patients treated with the product, until the submission of an application for standard marketing approval of the product to which the conditional and time-limited approval has been granted.

2. The applicant is required to take necessary measures, such as provision of seminars, to ensure that physicians with adequate knowledge and experience in the diagnosis and treatment of Parkinson's disease as well as in stereotactic neurosurgical procedures have a full understanding of relevant information, including the results of the clinical study of the product and adverse events reported, to use the product in compliance with the "Indication or Performance" and "Dosage and Administration or Method of Use" at medical institutions with an established system for the treatment of Parkinson's disease.

Attachment

Review Report (1)

November 20, 2025

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	AMCHEPRY
Classification	Human Cellular/Tissue-based Products, 4. Human Induced Pluripotent Stem Cell-processed Products
Non-proprietary Name	Raguneprocel
Applicant	Sumitomo Pharma Co., Ltd.
Date of Application	August 5, 2025

Shape, Structure, Active Ingredients, Quantities, or Definition

AMCHEPRY consists of aggregates of dopaminergic neuronal progenitor cells generated by culturing, differentiating, and aggregating iPS cells derived from human (allogeneic) peripheral blood mononuclear cells following transfection of episomal vectors.

Proposed Indication or Performance

Improvement of OFF-state motor symptoms in patients with advanced Parkinson’s disease

Proposed Dosage and Administration or Method of Use

The usual adult dosage is approximately 5.4×10^6 dopaminergic neuronal progenitor cells derived from allogeneic iPS cells administered per hemisphere into the bilateral putamen (approximately 10.8×10^6 cells in total).

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

AMCHEPRY is a cell-based product containing aggregates of dopaminergic neuronal progenitor cells generated through directed differentiation from induced pluripotent stem (iPS) cells established from peripheral blood mononuclear cells obtained from a healthy adult donor. Following transplantation of AMCHEPRY into the putamen of the striatum in patients with Parkinson's disease (PD), AMCHEPRY is expected to differentiate and mature into dopaminergic neurons, thereby restoring dopaminergic neuronal function. The resulting increase in endogenous dopamine produced and released by dopaminergic neurons is anticipated to improve motor symptoms.

AMCHEPRY was designated, on February 28, 2017, as a SAKIGAKE therapy under the SAKIGAKE Designation System for regenerative medical products with the intended indication of Parkinson's disease (SAKIGAKE Regenerative Medical Product Designation No. 2 of 2016 [*28 sai*]).

1.2 Development history, etc.

PD is a neurodegenerative disorder characterized by the progressive degeneration and loss of dopaminergic neurons projecting from the substantia nigra to the striatum. Dopamine deficiency in the striatum results in motor symptoms including akinesia, tremor, rigidity, and postural instability. As the disease progresses, degeneration extends beyond dopaminergic neurons to involve non-dopaminergic neuronal systems. Consequently, in addition to motor symptoms, a wide range of non-motor manifestations emerges, including autonomic dysfunction, depressive symptoms, sleep disturbances, and dementia.

Conventional treatments for PD include dopaminergic pharmacotherapy centered on levodopa. However, in approximately 5 years after disease onset, the duration of drug efficacy shortens, and motor complications such as the wearing-off phenomenon develop, in which symptoms fluctuate in association with changes in drug concentration (*Parkinson's Disease Clinical Practice Guideline 2018* [in Japanese], Igaku-Shoin; 2018:p110). When motor complications can no longer be adequately controlled with pharmacotherapy, the introduction of device-aided therapies, including deep brain stimulation (DBS), levodopa-carbidopa intestinal gel (LCIG) therapy, and continuous subcutaneous levodopa infusion therapy, is considered. However, DBS requires continuous management, including procedures under local anesthesia every few years for battery replacement, and LCIG therapy carries risks related to gastrostomy and device-associated infection. Moreover, neither pharmacotherapy nor device-aided therapies are intended to restore dopaminergic neuronal function that has declined as a result of disease progression.

A Japanese clinical study of AMCHEPRY in patients with PD was conducted by Takahashi and colleagues at the Kyoto University Hospital (Study IACT16049-01), and an application for marketing approval of AMCHEPRY has now been submitted with Study IACT16049-01 as the pivotal clinical study. Study IACT16049-01 was initiated in August 2018 as an investigator-initiated clinical study supported by the Research Project for Practical Applications of Regenerative Medicine of the Japan Agency for Medical Research and Development.

As of October 2025, AMCHEPRY has not been approved or marketed in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

AMCHEPRY is a cell-based product containing aggregates of dopaminergic neuronal progenitor cells manufactured by preparing an iPS cell bank from an iPS cell stock (QHJI01s04) established from peripheral blood mononuclear cells obtained from a healthy adult donor following transfection of episomal vectors, isolating Corin-positive cells obtained after directed differentiation culture, and subsequently subjecting these cells to maturation culture.

2.1 iPS cell bank

The iPS cell bank (master cell bank [MCB]003) used for manufacture of AMCHEPRY is prepared by expansion culture of the iPS cell stock [redacted].

2.1.1 Establishment of the iPS cell stock

The source cells used for AMCHEPRY are iPS cells derived from peripheral blood mononuclear cells of a healthy adult donor carrying the most frequent haplotype in the Japanese population[1)] (human leukocyte antigen [HLA]-A*24:02, HLA-B*52:01, HLA-C*12:02, HLA-DR*15:02, HLA-DQ*06:01, and HLA-DP*09:01). At the Center for iPS Cell Research and Application (CiRA), human peripheral blood collected in 20[redacted] was used as the starting material, and 5 episomal vectors [see Section 2.1.1.1]. From the cells, a clone QHJI01s04 was selected based on the results of [redacted], [redacted], [redacted], [redacted], and [redacted] to establish the iPS cell stock. No regeneration of the iPS cell stock is planned.

The determined characterization consists of [redacted], [redacted], [redacted], [redacted] ([redacted], [redacted]), [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

2.1.1.1 Episomal vectors

The iPS cell stock was generated using 5 episomal vectors (pCE-hSK, pCE-hUL, pCE-hOCT3/4, pCE-mouse p53 carboxy-terminal dominant-negative fragment [mp53DD], and pCXB-Epstein-Barr nuclear antigen 1 [EBNA1]). pCE-hSK contains a gene expression cassette encoding human SRY-box transcription factor (SOX) 2 (hSOX2) and human kruppel like factor 4 (hKLF4); pCE-hUL contains a gene expression cassette encoding human v-myc-1 proto-oncogene protein (hL-MYC) and human RNA-binding protein that acts as a posttranscriptional regulator (hLIN28); pCE-hOCT3/4 contains a gene expression cassette encoding POU class 5 homeobox 1 (OCT3/4); and pCE-mp53DD contains a gene expression cassette encoding mp53DD, each designed to express the respective genes together with EBNA-1 under the control of the CAG promoter (hybrid construct consisting of the cytomegalovirus [CMV] enhancer fused to the chicken beta-actin promoter). pCXB-EBNA1 contains a gene expression cassette encoding EBNA-1 alone under the control of the CAG promoter. All the episomal vectors were prepared at [redacted], using [redacted] constructed by [redacted], as the starting material.

[1] Corresponds to 17% of the population in Japan (*Nature*. 2025;641:971-7).

The control tests include [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

2.1.2 Safety evaluation of adventitious agents in the iPS cell bank

2.1.2.1 Human peripheral blood mononuclear cells

The human peripheral blood mononuclear cells used as the starting material for the iPS cell bank comply with the Standards for Biological Raw Materials (MHLW Public Notice No. 210 of 2003). Donor eligibility was confirmed by a medical interview (medical history, travel history, and prior transplantation and blood transfusion) and by testing of blood samples collected from the donor for viruses and other infectious agents (syphilis, HBV, HCV, HIV-1, HIV-2, HTLV-1, PVB19, and CMV).

2.1.2.2 Biological raw materials other than human peripheral blood mononuclear cells

A biological raw material other than human peripheral blood mononuclear cells used up to the preparation of the iPS cell bank is Raw Material A, which is used for establishment of the iPS cell stock and preparation of the iPS cell bank. The material has been confirmed to comply with the Standards for Biological Raw Materials (MHLW Public Notice No. 210 of 2003).

2.1.3 Control of the iPS cell bank

The characterization tests for the iPS cell bank are shown in Table 1. Within the scope of the tests performed for adventitious agents, no viral or non-viral adventitious agents were detected.

The iPS cell bank is stored in [redacted]. No [redacted] of the iPS cell bank is planned.

Table 1. Characterization tests for the iPS cell bank

[redacted]	
Bacterial endotoxin	
Mycoplasma	
Sterility	
Virus test	Electron microscopy
	Reverse transcriptase activity
	Infectivity test (co-culture assay with HEK293 cells)
	In vitro assays (MRC-5 cells, Vero cells, and HeLa cells)
	In vivo assays (suckling mice, mature mice, guinea pigs, and embryonated chicken eggs)
	Human virus test (RT-PCR) ([redacted])
	Human virus test (qPCR) ([redacted])
[redacted]	

2.2 Product

2.2.1 Product and formulation, and product design

The product contains cell aggregates equivalent to 1×10^6 dopaminergic progenitor cells per container. The product contains physiological saline as an excipient.

2.2.2 Manufacturing process

2.2.2.1 Manufacturing process

The manufacturing process of the product consists of [redacted] of the iPS cell bank, [redacted], [redacted], [redacted], maturation culture, filling, packaging and labeling, and storage and testing.

[redacted] and [redacted] has been defined as the critical steps.

2.2.2.2 In-process control tests

The in-process control tests in the manufacturing process of the product are shown in Table 2.

Table 2. In-process control tests in the manufacturing process of the product

Process	Test item
[redacted]	

*1, [redacted]

2.2.3 Safety evaluation for adventitious agents other than those in iPS cell bank

Table 3 shows biological raw materials used in the manufacturing process of the product. All the materials have been confirmed to comply with the Standards for Biological Raw Materials (MHLW Public Notice No. 210, 2003).

Table 3. Biological raw materials used in the manufacturing process of the product

Raw material		Animal species	Tissue used	Process used
Raw Material A		Hamster ([redacted] cells)	-	[redacted]
Raw Material B	Bovine albumin	Bovine	Blood	
	Porcine transferrin	Porcine	Blood	
Raw Material C	Bovine catalase	Bovine	Liver	
	Bovine superoxide dismutase	Bovine	Erythrocytes Kidney	
	Human transferrin	Human	Blood	
	Bovine albumin	Bovine	Blood	
Raw Material D		Hamster ([redacted] cells)	-	

2.2.4 Manufacturing process development

Table 4 shows main changes to the manufacturing process during development.

Table 4. Main changes to manufacturing process

Process change	Description of change
From [redacted] to [redacted]	• Extension of [redacted]
From [redacted] to [redacted]	• Change to [redacted]
From [redacted] to [redacted]	• Shortening of [redacted] • Addition of [redacted]
From [redacted] to [redacted]	• Change of [redacted] • Change of [redacted] • Change in [redacted] • Shortening of [redacted] • Change to [redacted]
From [redacted] to [redacted] ([redacted])	• Change of [redacted] • Change in [redacted]

The manufacturing process of the products used in each non-clinical study and clinical study is shown in Table 5.

Table 5. Manufacturing process of the products used in non-clinical and clinical studies

Manufacturing process	Non-clinical or clinical study which used the product
[redacted]	Non-clinical studies
	Study IACT16049-01
	Study IACT16049-01
	Study IACT16049-01
	Study IACT16049-01, non-clinical studies

In response to these process changes, quality attributes were assessed for comparability. For each of the process changes, pre- and post-change products have been confirmed to be comparable.

2.2.5 Characterization

2.2.5.1 Structure and characterization

Using the product, the following studies were conducted: [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], genome analyses, evaluation of residual plasmid, and [redacted]. In the genome analyses, it was confirmed that no mutations were detected in cancer-related genes.[2)]

2.2.6 Evaluation of the manufacturing process

2.2.6.1 Process-related impurities

The following impurities were identified as process-related impurities: Raw Material E, Raw Material F, Raw Material G, Raw Material H, Raw Material I, Raw Material J, Raw Material K, Raw Material L, Raw Material M, Raw Material N, Raw Material O, Raw Material P, Raw Material A, Raw Material Q, Raw Material B, Raw Material C, Raw Material R, Raw Material S, Raw Material D, and Raw Material T. For all process-related impurities, the assessment of exposures calculated from the measured or

2) Genes included in the COSMIC census (ver. [redacted], [redacted], or [redacted]) and the Shibata list (PMDA Science Board [Cellular and Tissue-based Products Subcommittee], "Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from induced Pluripotent Stem Cells (iPSCs) and iPSCs as Their Starting Materials," August 20, 2013).

estimated residual amounts demonstrated that the residual impurities are unlikely to result in safety concerns in humans.

2.2.6.2 Contamination with undifferentiated iPS cells

Because AMCHEPRY consists of cells differentiated from iPS cells, which are undifferentiated pluripotent stem cells, the risk of residual undifferentiated iPS cells in the final product was evaluated. To control undifferentiated iPS cells, which constitute off-target cells, the contamination rate of marker-positive cells has been set at [redacted]%, as determined by [redacted] markers ([redacted]positivity rate [redacted]) in specification testing using [redacted] as the test sample [see Section 2.2.7].

Furthermore, in view of the results of a tumorigenicity study involving intrastriatal transplantation in NOD.Cg-*Prkdc*^{scid}*Il2rg*^{tm1Sug}/ShiJic (NOG mice) [see Section 5.2], controlling the contamination level based on this specification ensures that the tumorigenic risk attributable to contamination with undifferentiated iPS cells is manageable, according to the applicant.

2.2.6.3 Contamination with epithelial-like cells

In the toxicity study in which AMCHEPRY was transplanted into NOG mice, epithelial-like cells and related structures considered to be choroid plexus epithelial cells were observed at the transplantation site in the AMCHEPRY group [see Sections 5.1 and 5.2].

The applicant's explanation about the risk attributable to contamination with epithelial-like cells:
Transcription factors that are critical for the differentiation of Corin-positive cells into dopaminergic neuronal progenitor cells are also known to be involved in differentiation into choroid plexus epithelial cells (*Nat Rev Neurosci.* 2015;16:445-57). This suggested that a subset of Corin-positive cells differentiated into choroid plexus epithelial cells under conditions intended to induce differentiation into dopaminergic neuronal progenitor cells. In the clinical study, no adverse events attributable to choroid plexus epithelial cells contained in AMCHEPRY were observed [see Section 6.R.2]. In specification testing using [redacted] as the test sample, the specification for [redacted] markers ([redacted]positivity rate [redacted]) has been set at [redacted]% based on the results of the study product used in the clinical study. By controlling the contamination rate of off-target cells, including epithelial-like cells, the potential risk attributable to contamination with epithelial-like cells is considered to be manageable.

2.2.6.4 Verification

Because it is difficult to perform prospective process validation for the manufacturing process to ensure that a product of the intended quality can be manufactured consistently, the applicant plans to conduct continuous process verification during commercial manufacturing. Through this verification consisting of the following elements, it will be confirmed for each batch that a product of the intended quality has been manufactured:

- [redacted]
- [redacted]

- [redacted]
- [redacted]

2.2.7 Control of the product

The specifications for the product are shown in Table 6.

Table 6. Specifications for the product

Test items	Testing methods
[redacted]	
Mycoplasma testing	Nucleic acid amplification test method (General Information in the Japanese Pharmacopoeia)
Bacterial endotoxin test	Turbidimetric technique (Japanese Pharmacopoeia)
Sterility test*2	BACT/ALERT method

*1 [redacted].

*2 [redacted] In addition to the specification testing, a sterility test (membrane filtration method) using the final product is performed as an identification test after release, and the results are confirmed after transplantation.

2.2.8 Stability

An outline of the stability studies of the product is shown in Table 7.

Table 7. Outline of stability studies of the product

Study name	Number of batches	Manufacturing process	Storage conditions	Study period	Storage form
Storage stability testing	3	[redacted] (proposed process)	5 ± 3°C	31 hours	Cyclo-olefin polymer tube body sealed with a chlorobutyl rubber stopper and a polypropylene cap

In the storage stability testing, no clear changes in quality attributes were observed throughout the study period. In addition, a transport stability testing confirmed that there was no impact attributable to transportation.

Based on the above results, the shelf life of 31 hours has been proposed for the product when stored at 5°C ± 3°C in a cyclo-olefin polymer tube body sealed with a chlorobutyl rubber stopper and a polypropylene cap.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the iPS cell bank and the product is adequately controlled.

3. Primary Pharmacodynamics or Performance and Outline of the Review Conducted by PMDA

The applicant submitted the results of the *in vitro* and *in vivo* studies as data relating to the primary pharmacodynamics or performance of AMCHEPRY.

3.1 *In vitro* study (CTD 3.2.P.2.3)

3.1.1 Dopamine release

After AMCHEPRY was subjected to maturation culture for 28 days to induce differentiation into dopaminergic neurons, the amount of dopamine released into the supernatant following potassium stimulation was measured by LC-MS or LC-MS/MS. The dopamine level (mean ± standard error) was 1.2 ± 0.4 pmol/DNA μg,[3)] confirming that AMCHEPRY differentiates and matures into dopaminergic neurons capable of secreting dopamine.

3.2 *In vivo* study (CTD 4.2.1.1-01)

3.2.1 Efficacy study in 6-OHDA-induced PD model immunodeficient rats

In male 6-hydroxydopamine (6-OHDA)-induced PD model immunodeficient rats,[4)] 4×10^5 cells of AMCHEPRY were transplanted into the striatum on the 6-OHDA-lesioned side in the AMCHEPRY group (15 animals), or physiological saline was administered in the control group (10 animals). Methamphetamine-induced rotational behavior[5)] before transplantation and up to 24 weeks post-transplantation was evaluated using a rotation measurement system. In addition, at 25 weeks after transplantation, the number of human dopaminergic neurons (hNu/TH double-positive cells) at the transplantation site was assessed by immunohistochemical staining.

The results of the methamphetamine-induced rotational behavior assessment are shown in Table 8. From 16 weeks after transplantation onward, the number of methamphetamine-induced rotations in the AMCHEPRY group tended to be lower than that in the control group, and at 24 weeks after transplantation, a statistically significant reduction in methamphetamine-induced rotations was observed in the AMCHEPRY group compared with the control group.

Table 8. Methamphetamine-induced rotations in 6-OHDA-induced PD model rats

Time point	Control[*1] (n = 10)	AMCHEPRY (n = 15[*2])
Before transplantation	985.9 ± 153.8	1031.3 ± 208.4
4 weeks after transplantation	966.5 ± 312.1	993.2 ± 374.2
8 weeks after transplantation	1135.8 ± 255.9	984.7 ± 445.7
12 weeks after transplantation	1276.2 ± 214.1	1264.5 ± 461.2
16 weeks after transplantation	1321.7 ± 353.8	1053.5 ± 402.3
20 weeks after transplantation	1140.2 ± 523.8	787.5 ± 479.2
24 weeks after transplantation	1210.6 ± 499.3	473.8 ± 645.8[*3]

Values are expressed as mean ± standard deviation (SD) (rotations per 90 minutes).
*1 Physiological saline
*2 At 8 and 12 weeks after transplantation, n = 14; from 16 weeks onward, n = 13. Drop-out was due to death or debilitation.
*3 $P < 0.01$ (Wilcoxon test)

Based on immunohistochemical staining, the number of human dopaminergic neurons (hNu/TH double-positive cells) at the transplantation site at 25 weeks after transplantation was 2312.0 ± 676.5 cells per animal (mean ± standard deviation [SD]).

3) The amount of dopamine released per unit was calculated by quantifying DNA obtained from cells subjected to potassium stimulation and subsequent ultrasonic disruption.
4) PD model rats in which 6-OHDA (a neurotoxin affecting dopaminergic and noradrenergic neurons) and desipramine (a norepinephrine transporter inhibitor) were administered unilaterally into the medial forebrain bundle, resulting in the loss of dopaminergic neurons in the ipsilateral nigrostriatal pathway.
5) Administration of methamphetamine, a dopamine release-inducing agent, produces rotational behavior in a single direction due to an imbalance of dopamine levels between the 2 sides of the brain.

3.R Outline of the review conducted by PMDA

The applicant's explanation about the mechanism of action of AMCHEPRY:

Based on the results of the dopamine release assay [Section 3.1.1] and the efficacy study using 6-OHDA-induced PD model immunodeficient rats [see Section 3.2.1], the dopaminergic neuronal progenitor cells engraft in the transplanted striatum, differentiate and mature into dopaminergic neurons, and secrete dopamine.

PMDA accepted the applicant's explanation.

4. Biological Disposition and Outline of the Review Conducted by PMDA

The applicant submitted results of a single-dose *in vivo* distribution study using male 6-OHDA-induced PD model immunodeficient rats[4)] relating to the non-clinical biological disposition data for AMCHEPRY. The applicant also submitted engraftment assessment results from Study IACT16049-02.[6)] relating to clinical pharmacokinetic data of AMCHEPRY.

4.1 Non-clinical biological disposition

4.1.1 Analytical methods

For non-clinical biological disposition of AMCHEPRY, human nuclei (hNu)-positive cells in the brain were detected by immunohistochemistry, and human genomic DNA in non-brain tissues was quantified using human Alu-quantitative polymerase chain reaction (qPCR).

4.1.2 *In vivo* distribution

The study of AMCHEPRY shown in Table 9 was conducted to evaluate the distribution of hNu-positive cells in brain tissue and human genomic DNA in other tissues. Transplanted cells were confined to the transplantation site and were not detected at distant locations.

Table 9. Single-dose intrastriatal transplantation study of AMCHEPRY – *in vivo* distribution

Test system	Observation period	Dose (cells)	Summary of results	Attached document
Male 6-OHDA-induced PD model immunodeficient rats	25 weeks	4×10^5	• At 25 weeks after transplantation, hNu-positive cells were detected around the transplantation site in all 13 animals.*1 In 5 of the 13 animals, hNu-positive cells were also detected in the right cerebral peduncle, but in smaller numbers compared with the transplantation site. • The Ki-67 positivity rate within the graft (mean ± SD) was 0.26% ± 0.29%.	4.2.1.1
			• At 25 weeks after transplantation, human genomic DNA in all tissues (blood, cerebrospinal fluid, spinal cord, liver, kidney, lung, heart, spleen, and lymph nodes) was below the lower limit of quantification in all 13 animals.*1	4.2.2.3

*1 Fifteen animals received AMCHEPRY, but 2 animals were excluded due to death or debilitation; as a result, 13 animals were analyzed.

4.1.3 Metabolism and excretion

No non-clinical studies were conducted to evaluate metabolism and excretion of AMCHEPRY.

6) Clinical study conducted to evaluate the efficacy and safety of tacrolimus co-administered at the time of AMCHEPRY transplantation. The subjects who received AMCHEPRY were the same as in Study IACT16049-01.

4.2 Clinical biological disposition

4.2.1 Analytical methods

For clinical pharmacokinetic evaluation, engraftment of AMCHEPRY in the striatum was assessed in 6 subjects in the efficacy analysis population of Study IACT16049-02 using head magnetic resonance imaging (MRI) and positron emission tomograph (PET) imaging (6-[^{18}F]-fluoro-L-dopa, [^{18}F]FDOPA).

4.2.2 Engraftment assessment at the transplantation site

At both 12 and 24 months after transplantation into the putamen, engraftment of AMCHEPRY was confirmed in all subjects (6 of 6 subjects).

4.R Outline of the review conducted by PMDA

The applicant's explanation about the biodistribution of AMCHEPRY:

The data of the non-clinical studies showed that AMCHEPRY transplanted into the striatum remained confined to the transplantation site and surrounding tissue at 25 weeks post-transplantation, with low proliferative activity. The likelihood of distribution to other organs was considered low.

Clinical study results confirmed engraftment of AMCHEPRY in the striatum up to 24 months after transplantation.

PMDA accepted the applicant's explanation.

5. Non-clinical Safety and Outline of the Review Conducted by PMDA

The applicant submitted results of a single-dose transplantation general toxicity study, a tumorigenicity study, and a teratoma formation study using immunodeficient mice as non-clinical safety data for AMCHEPRY. Unless otherwise specified, physiological saline was used as vehicle.

5.1 Single-dose transplantation toxicity study

A single-dose transplantation toxicity study (26-week observation period) was conducted in male and female NOG mice receiving bilateral intrastriatal transplantation of AMCHEPRY, as shown in Table 10.

Table 10. Single-dose transplantation toxicity study

Test system	Route of administration	Observation period	Dose (cells/ transplantation site)	Main findings	Attached document
Male and female mice (NOG)	Intrastriatal	26 weeks	0, 2×10^5 on each side bilaterally	Deaths: 2 of 16 males, 1 of 16 females Detection of bacteria in systemic organs[*1] (male), abscess in the left atrium[*1] (male), malignant lymphoma (female)[*2] Neural-like cells and glial-like cells,[*3] epithelial-like cells,[*4] cholesterol clefts, gliosis,[*5] brown pigment within macrophages,[*5] bone fragments/calcification[*5] at the transplantation site	4.2.3.1-01

*1 Bacteria were detected in the adrenal gland, gallbladder, heart, kidney, liver, and mesenteric/submandibular lymph nodes, and an abscess was observed in the left atrium. The findings were considered spontaneous changes attributable to the immunodeficiency of NOG mice or changes related to procedural stress associated with transplantation.
*2 The lesion was Ku80-negative, was also observed in the control group, and malignant lymphoma has been reported as a spontaneous lesion in NOG mice (e.g., *Exp Anim*. 2017;66:425-35), which suggested that the death was unrelated to transplantation of AMCHEPRY.
*3 Determined morphologically.
*4 Positive for anti-keratin antibody and anti-transthyretin (TTR) antibody.
*5 Observed at similar frequencies in both the control and AMCHEPRY groups.

At the transplantation site, in addition to neural-like cells and glial-like cells differentiated from dopaminergic neuronal progenitor cells, epithelial-like cells derived from AMCHEPRY were observed, and tubular structures were formed in some animals. No compression or injurious changes of surrounding tissues attributable to epithelial-like cells were observed. Although a subset of epithelial-like cells was positive for Ki-67, the positivity rate (mean ± SD) was 0.9% ± 1.23%, and the finding was confined to the transplantation site; therefore, it was not considered indicative of abnormal proliferation [see Section 5.R.1].

Cholesterol clefts were observed at the transplantation site of AMCHEPRY. The findings were considered attributable to cholesterol crystals resulting from necrotic cells that failed to engraft or from necrosis or inflammation of brain parenchyma associated with the transplantation procedure. No effects on surrounding tissues were observed, and cholesterol crystals are expected to resolve through phagocytosis by macrophages. Thus, the findings were not considered to raise safety concerns in humans. Gliosis and brown pigment within macrophages, and bone fragments/calcification were observed at the transplantation sites in both the AMCHEPRY and control groups. Gliosis and brown pigment within macrophages were considered findings secondary to haemorrhage or inflammation associated with the transplantation procedure. As their severity was minimal or mild, the findings were not considered to raise safety concerns in humans. Bone fragments/calcification are not typically observed in human neurosurgical procedures and were considered mouse-specific findings attributable to the transplantation procedure in mice; they were not considered to raise safety concerns in humans.

5.2 Tumorigenicity study

The tumorigenicity studies using NOG mice shown in Table 11 were conducted. In cell suspensions containing AMCHEPRY and iPS cells (MCB003), which are the raw material of AMCHEPRY, added up to the maximum amount calculated from the specification limit [see Section 2.2.6.2], no tumor formation or teratoma formation was observed.

Table 11. Tumorigenicity study

Test system	Outline/results	Attached document
Male and female mice (NOG)	The following test articles were transplanted into the right striatum of 8-week-old NOG mice. Animals were necropsied 39 weeks after transplantation, and examinations including histopathological evaluation (all organs throughout the body) and immunohistochemical analyses were performed. • AMCHEPRY group: 0, 2×10^5 cells/transplantation site • Spike group[*1]: AMCHEPRY 2×10^5 cells + MCB003 cells [redacted] cells/transplantation site • MCB003 cell group: 2×10^5 cells/transplantation site In the AMCHEPRY group and the spike group, no tumor formation or teratoma formation related to transplantation of AMCHEPRY was observed at the transplantation site or in any systemic organs.[*2] Formation of epithelial-like cells derived from AMCHEPRY was observed at the transplantation site; however, these cells did not exhibit abnormal proliferative characteristics and were not considered indicative of tumor formation. In the MCB003 cell group, teratoma formation was observed at the transplantation site.	4.2.3.1-02
Male and female mice (NOG)	AMCHEPRY (0 or 2×10^5 cells/transplantation site) was transplanted into the right striatum of 7- to 8-week-old NOG mice. Animals were necropsied 52 weeks after transplantation, and examinations including histopathological evaluation (all organs throughout the body) and immunohistochemical analyses were performed. No tumor formation or teratoma formation related to transplantation of AMCHEPRY was observed at the transplantation site or in any systemic organs.[*3] Ki-67-positive neuron-like cells and glia-like cells presumed to be derived from AMCHEPRY were observed at the transplantation site; however, no findings suggested involvement of these cells in tumor formation. Formation of epithelial-like cells derived from AMCHEPRY was observed at the transplantation site, and some of the cells were Ki-67-positive; however, the findings were localized to a limited area of the transplantation site and were not considered indicative of abnormal proliferation.	4.2.3.1-03 (reference)
Male mice (NOG)	The following test articles, mixed with Matrigel matrix, were transplanted subcutaneously into the dorsal region of 5- to 9-week-old NOG mice. Matrigel matrix alone was used in a control group. Animals were necropsied 26 weeks after transplantation, and examinations including histopathological evaluation (subcutaneous tissue of the dorsal region and surrounding tissues, as well as macroscopically abnormal sites) and immunohistochemical analyses were performed. • AMCHEPRY group: 0, 6×10^5 cells/transplantation site • Spike group: AMCHEPRY 6×10^5 + MCB003 cells 6×10^0 to 6×10^4 cells/transplantation site • MCB003 cell group: 6×10^5 cells/transplantation site • HeLa cell group: 6×10^5 cells/transplantation site • 201B7 cell group[*4]: 6×10^5 cells/transplantation site In the AMCHEPRY group and the spike group, masses were observed at the transplantation site. A small number of Ki-67-positive cells were included in the human cell populations identified at the transplantation site, but no increase in mass volume was observed and a tendency toward regression was noted. Based on histopathological findings, they were not considered indicative of tumor formation or teratoma formation. The masses were considered attributable to Matrigel or to inflammatory reactions associated with Matrigel. In the MCB003 cell group, no tumor formation or teratoma formation was observed during the 16-week observation period after subcutaneous transplantation of 6×10^5 cells.[*5] In the HeLa cell group and the 201B7 cell group, increases in mass volume suggestive of tumor formation or teratoma formation were observed at the transplantation site by 16 weeks after transplantation.	4.2.3.1-05 (reference)

*1 The maximum amount of iPS cells (MCB003 cells) calculated from the specification limit of AMCHEPRY ([redacted] marker, [redacted]%) was added.

*2 Neoplastic lesions, including lymphoma, were observed systemically in animals that died in the AMCHEPRY transplantation group; however, the lesions were Ku80-negative and were considered spontaneous findings.

*3 Neoplastic lesions were observed systemically in both surviving and deceased animals; however, the lesions were Ku80-negative and were considered spontaneous findings.

*4 iPS cells different from the iPS cells (MCB003 cells) used as the raw material of AMCHEPRY; these cells are known to proliferate and form teratomas when transplanted into subcutaneous tissue. Because an increase in mass volume suggestive of cell proliferation and teratoma formation in subcutaneous tissue was confirmed by 16 weeks after transplantation of 6×10^5 of 201B7 cells, the validity of this test system for evaluating tumor formation or teratoma formation was considered demonstrated.

*5 After transplantation of 6×10^5 of MCB003 cells into the testes of NOG mice, an increase in mass volume at the transplantation site was observed by 16 weeks, indicating potential teratoma-forming capability. In contrast, when a positive control group in which MCB003 cells were transplanted subcutaneously alone was included, no tumor formation or teratoma formation was observed in subcutaneous tissue by 26 weeks after subcutaneous transplantation of 6×10^5 cells.

5.3 Safety evaluation of process-derived impurities

The safety of impurities derived from the manufacturing process of AMCHEPRY was evaluated based on the levels of impurities remaining in AMCHEPRY, published literature, and the results of the single-dose transplantation toxicity study using AMCHEPRY ([redacted]) [see Section 5.1]. In view of the results of the safety evaluation, the applicant explained that residual impurities in AMCHEPRY do not pose a safety risk to humans.

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA concluded that there are no particular concerns regarding the non-clinical safety of AMCHEPRY.

5.R.1 Epithelial-like cells observed at the transplantation site of AMCHEPRY

In the single-transplantation toxicity study and the tumorigenicity study, epithelial-like cells were observed at the transplantation site in NOG mice that received intrastriatal transplantation of AMCHEPRY, and tubular structures were formed in some animals.

The applicant's explanation about the above:

The epithelial-like cells observed were considered to be choroid plexus epithelial cells, based on their histological architecture and positive immunoreactivity for anti-cytokeratin antibody and anti-transthyretin (TTR) antibody. The epithelial-like cells observed after transplantation of AMCHEPRY were not differentiated from dopaminergic neuronal progenitor cells; rather, it is considered that a subset of Corin-positive cells differentiated into choroid plexus epithelial cells during the manufacturing process and remained in AMCHEPRY [see Section 2.2.6.3]. The presence of epithelial-like cells and tubular structures composed of epithelial-like cells was not considered indicative of toxicity of AMCHEPRY for the following reasons:

- In the tumorigenicity study (39-week observation) using male and female NOG mice that received intrastriatal transplantation of AMCHEPRY, histopathological examination showed no compression of surrounding tissues by aggregates of epithelial-like cells, no papillary proliferation, and no injury to adjacent tissues [see Section 5.2]. The number of transplanted cells per striatal volume in NOG mice exceeded the transplantation dose per striatal volume in humans.
- A subset of epithelial-like cells was positive for Ki-67, but the proportion of positive cells (mean ± SD) was approximately 0.9% ± 1.23% [see Section 5.1], and no findings suggestive of tumorigenic transformation were observed in the tumorigenicity studies of AMCHEPRY up to the longest evaluation period of 52 weeks [see Section 5.2].

Epithelial-like cells may also be present in commercial products but, based on the above considerations, the potential safety concerns in clinical use of AMCHEPRY are considered to be low.

PMDA accepted the applicant's explanation that the epithelial-like cells and tubular structures composed of epithelial-like cells observed in studies using NOG mice are findings associated with a low safety concern, given the absence of effects on normal tissues and the absence of tumor formation. However, because there remains a possibility that epithelial-like cells and related structures may also form in

commercial products, the safety of AMCHEPRY following transplantation into the human striatum will continue to be discussed in the clinical section [see Section 6.R.2].

5.R.2 Tumorigenic risk of AMCHEPRY

Because AMCHEPRY consists of cells differentiated from iPS cells, which are undifferentiated pluripotent stem cells, there is a theoretical risk of tumorigenicity and teratoma formation associated not only with the intended cells but also with contaminating undifferentiated iPS cells and off-target cells.

The applicant's explanation about the above:
When iPS cells (MCB003 cells), which are the raw material of AMCHEPRY, were transplanted alone into the brain parenchyma (striatum) of NOG mice, teratoma formation was observed. In contrast, when AMCHEPRY alone, or a test article consisting of AMCHEPRY mixed with the maximum amount of iPS cells (MCB003 cells) calculated from the specification limit of AMCHEPRY, was transplanted into the striatum, no tumor formation or teratoma formation was observed up to 39 weeks of observation, even at approximately 7.3 times the planned clinical dose in humans (based on striatal volume) or 40 times the planned clinical dose (based on body weight). In an additional reference evaluation data with 52 weeks of observation, no tumor formation or teratoma formation was observed [see Section 5.2]. In addition to undifferentiated iPS cells, potential off-target cells may include malignantly transformed cells, epithelial-like cells, or progenitors of epithelial-like cells. However, no tumorigenicity or teratoma formation attributable to such off-target cells was observed. Thus, although residual iPS cells in AMCHEPRY may have a potential risk of teratoma formation, the risk of tumorigenicity and teratoma formation is considered low under the anticipated content of undifferentiated iPS cells (which is managed by AMCHEPRY's quality control), the proposed dosage and administration or method of use, and the route of administration.

PMDA accepted the applicant's explanation. With respect to the tumorigenic and teratoma-forming risk of epithelial-like cells or their progenitors among off-target cells other than undifferentiated iPS cells, this is as described in Section 5.R.1.

6. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the results of 1 Japanese clinical study shown in Table 12 as the efficacy and safety evaluation data of AMCHEPRY.

Table 12. Clinical study on the efficacy and safety of AMCHEPRY (evaluation data)

Phase	Study identifier (jRCT number)	Study population	No. of transplanted patients	Dosage regimen	Observation period	Endpoints
I/II	Study IACT16049-01 (jRCT2090220384)	Patients with PD	7	**AMCHEPRY** (Patients 1-3)[*1] 4.8×10^6 cells transplanted into the bilateral putamen (2.4×10^6 cells per hemisphere) (Patients 4-7) 8.4×10^6 to 10.8×10^6 cells transplanted into the bilateral putamen ($4.2\text{-}5.4 \times 10^6$ cells per hemisphere) **Tacrolimus** Oral dose for 52 weeks from the day of transplantation of AMCHEPRY. Treatment is initiated at 0.03 to 0.15 mg/kg (standard dose, 0.06 mg/kg) twice daily, and the dose is adjusted to maintain the trough blood level in the range of 5 to 10 ng/mL. Thereafter, the dose is tapered over 12 weeks.	24 months after transplantation of AMCHEPRY	Safety Efficacy

*1 In the first patient, for safety considerations, AMCHEPRY was transplanted into only one hemisphere. At 6 months after transplantation, after confirmation by the Efficacy and Safety Evaluation Committee that there were no major safety concerns, AMCHEPRY was transplanted into the contralateral hemisphere. From the second patient onward, bilateral transplantation was performed simultaneously.

In Study IACT16049-01, the efficacy and safety of tacrolimus administered at the time of transplantation of AMCHEPRY were also evaluated. This evaluation was conducted as Study IACT16049-02 (Japan registry of clinical trials [jRCT] number, jRCT2091220385), and the results of Study IACT16049-02 were also submitted as evaluation data.

6.1 Evaluation data

6.1.1 Japanese clinical study

6.1.1.1 Study IACT16049-01 (CTD 5.3.5.2-01, August 2018 to December 2023)

An open-label, uncontrolled Japanese clinical study (Study IACT16049-01) was conducted at a single center to evaluate the safety and efficacy of AMCHEPRY in patients with PD whose symptoms had become difficult to control with pharmacotherapy alone but who had not completely lost responsiveness to levodopa preparations (target sample size, 7 patients). The main inclusion and exclusion criteria were as shown in Table 13.

Table 13. Main inclusion and exclusion criteria

Inclusion criteria	• Diagnosed with PD (clinically confirmed or clinically probable) according to the MDS clinical diagnostic criteria for PD (*Mov Disord*. 2015;30:1591-601) • Inadequate symptom control with conventional pharmacotherapy • Aged ≥50 and <70 years at the time of informed consent • Duration of PD ≥5 years • Presence of ON and OFF states (confirmed by MDS-UPDRS Part III and symptom diary assessments) • OFF-state H&Y stage ≥3 • OFF-state H&Y stage ≤3 • ≥30% responsiveness to L-dopa during withdrawal of anti-PD drugs • DAT scan showing a pattern of decreased uptake characteristic of PD in the basal ganglia region • Within 7 days before enrollment, adequate organ function as demonstrated by clinical laboratory tests: ➢ Neutrophils: ≥2,000/μL ➢ Platelets: ≥5.0 × 10^4/μL ➢ AST and ALT: ≤3.0 × upper limit of normal at the study site ➢ Total bilirubin: ≤1.5 × upper limit of normal at the study site ➢ eGFR: ≥60 mL/min/1.73 m²
Exclusion criteria	• Symptomatic organic lesions on brain MRI • Considered to have dementia or be at high risk for dementia • Presence of any of the following comorbidities: ➢ Malignant neoplasm ➢ Epilepsy ➢ Psychiatric disorders (including depression, bipolar disorder, and schizophrenia) ➢ Other serious comorbidities (including cerebrovascular disorder, cardiac disease, chronic respiratory disease, poorly controlled hypertension, or diabetes mellitus) • History of any of the following: ➢ Malignant neoplasm ➢ Epilepsy ➢ Cerebral haemorrhage ➢ Psychiatric disorders (including depression, bipolar disorder, and schizophrenia) ➢ Pallidotomy, thalamotomy, or deep brain stimulation

In Study IACT16049-01, the study period for each patient was defined as from primary registration[7)] to the last observation date. The treatment period was defined as from secondary registration[7)] to the end date of tacrolimus administration or discontinuation of the study. The observation period was defined as up to 24 months[8)] after transplantation of AMCHEPRY.

The dosage and administration or method of use was defined as a single transplantation of 2.4 × 10^6 cells of AMCHEPRY per hemisphere into the bilateral putamen under general anesthesia using a stereotactic neurosurgical system. In the first patient, for safety considerations, AMCHEPRY was transplanted only into one putamen. At 6 months after transplantation, upon confirmation by the Efficacy and Safety Evaluation Committee that there were no major safety concerns, AMCHEPRY was transplanted into the contralateral side. From the second patient onward, bilateral transplantation of AMCHEPRY into the putamen was performed simultaneously. In addition, the dose was modified during the study, and from the fourth patient onward, 4.2 to 5.4 × 10^6 cells per hemisphere were transplanted (Patients 1-3 constituted the low-dose group, and Patients 4-7 constituted the high-dose group).

To promote engraftment of AMCHEPRY *in vivo*, tacrolimus was administered orally for 52 weeks starting on the morning of the day of transplantation. Tacrolimus was initiated at 0.03 to 0.15 mg/kg per

7) Primary registration was defined as the time when screening was performed and eligibility was confirmed. Secondary registration was defined as the time when eligibility was reconfirmed after repeat examinations, observations, and assessments. AMCHEPRY was transplanted within 28 days after secondary registration.

8) For the first patient, the observation period was defined as up to 24 months after completion of bilateral transplantation.

dose (standard dose, 0.06 mg/kg) twice daily, with dose adjustment to maintain the trough blood level in the range of 5 to 10 ng/mL. After 52 weeks of administration, the dose was tapered over 12 weeks.

In Study IACT16049-01, 8 patients underwent primary registration. Of these, 1 patient discontinued the study before transplantation of AMCHEPRY at the investigator's discretion, and the remaining 7 patients underwent secondary registration. All 7 patients received transplantation of AMCHEPRY and were included in the safety analysis population. Among them, 6 patients who underwent simultaneous bilateral transplantation were included in the efficacy analysis population.

Table 14 shows a patient-by-patient summary of demographic characteristics and other baseline characteristics in Study IACT16049-01.

Table 14. Patient-by-patient summary of demographic and other baseline characteristics

Item	Low-dose			High-dose			
	PD01	PD02	PD03	PD04	PD05	PD06	PD08
Sex	Male	Female	Female	Male	Male	Male	Female
Age (years)	50	62	60	61	69	58	56
HLA matching*1	Complete	Partial	Partial	Complete	Partial	Complete	Partial
Improvement rate in levodopa responsiveness (%)	69.7	89.7	67.3	57.4	75.8	68.0	67.0
Disease duration (years)	10.3	8.8	9.5	10.3	8.7	12.2	9.5
LEDD (mg)	665.5	1137.9	957.6	1276.5	839.4	1514.0	1027.5

*1 Complete matching was defined as concordance at all 6 loci (HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, and HLA-DP) between the iPS cell donor and the. PD02 and PD08 matched at 2 loci (HLA-A and HLA-DQ), and PD03 and PD05 each matched at 1 locus (HLA-A or HLA-DQ, respectively).

The primary endpoints were defined as (1) the incidence and severity of adverse events and (2) the presence or absence of graft overgrowth in the brain (>3 cm^3)[9] at 24 months after transplantation, as assessed by MRI. The results for the primary endpoints were as shown below.

(1) Incidence and severity of adverse events

The incidence of adverse events was 100% (7 of 7 patients), the incidence of adverse reactions to AMCHEPRY was 14.3% (1 of 7 patients), and the incidence of other adverse events related to the study treatment was 71.4% (5 of 7 patients). Adverse events observed in ≥2 patients were application site pruritus (4 patients [2 in the low-dose group, 2 in the high-dose group]), renal dysfunction (3 patients [2, 1]), claustrophobia (2 patients [2, 0]), fall and urine occult blood positive (2 patients each [0, 2]), dental caries, nausea, wound complication, and dystonia (2 patients each [1, 1]) (Table 15).

[9] In accordance with the guidelines of the Japan Neurosurgical Society (The Joint Committee on Guidelines for the Management of Stroke. Japanese Guidelines for the Management of Stroke 2009), which specifies a haematoma volume of ≥31 cm^3 as the surgical indication threshold for putaminal haemorrhage, a criterion of 3.1 cm^3 at 2 years was established to ensure that, even assuming linear graft growth, the graft volume would not exceed 31 cm^3 after 20 years.

Table 15. Incidence of adverse events

MedDRA/J v26.1 System organ class (SOC) Preferred term (PT)	Low-dose (N = 3) n (%)	High-dose (N = 4) n (%)	Overall (N = 7) n (%)
Blood and lymphatic system disorders			
Anaemia	0	1 (25.0)	1 (14.3)
Ear and labyrinth disorders			
Tinnitus	1 (33.3)	0	1 (14.3)
Vertigo	0	1 (25.0)	1 (14.3)
Eye disorders			
Vitreous floaters	0	1 (25.0)	1 (14.3)
Gastrointestinal disorders			
Abdominal discomfort	1 (33.3)	0	1 (14.3)
Abdominal pain upper	1 (33.3)	0	1 (14.3)
Dental caries	1 (33.3)	1 (25.0)	2 (28.6)
Diarrhoea	0	1 (25.0)	1 (14.3)
Nausea	1 (33.3)	1 (25.0)	2 (28.6)
Vomiting	1 (33.3)	0	1 (14.3)
General disorders and administration site conditions			
Application site pruritus	2 (66.7)	2 (50.0)	4 (57.1)
Chills	0	1 (25.0)	1 (14.3)
Discomfort	0	1 (25.0)	1 (14.3)
Pyrexia	1 (33.3)	0	1 (14.3)
Therapeutic product effect decreased	1 (33.3)	0	1 (14.3)
Hepatobiliary disorders			
Hepatic function abnormal	1 (33.3)	0	1 (14.3)
Hyperbilirubinaemia	0	1 (25.0)	1 (14.3)
Infections and infestations			
Conjunctivitis	0	1 (25.0)	1 (14.3)
Cystitis	1 (33.3)	0	1 (14.3)
Dermatophytosis of nail	1 (33.3)	0	1 (14.3)
Nasopharyngitis	1 (33.3)	0	1 (14.3)
Sinusitis	0	1 (25.0)	1 (14.3)
Conjunctivitis bacterial	0	1 (25.0)	1 (14.3)
Injury, poisoning and procedural complications			
Fall	0	2 (50.0)	2 (28.6)
Rib fracture	0	1 (25.0)	1 (14.3)
Pneumocephalus	0	1 (25.0)	1 (14.3)
Postoperative hypertension	0	1 (25.0)	1 (14.3)
Wound	0	1 (25.0)	1 (14.3)
Wound complication	1 (33.3)	1 (25.0)	2 (28.6)
Investigations			
C-reactive protein increased	1 (33.3)	0	1 (14.3)
Gamma-glutamyltransferase increased	1 (33.3)	0	1 (14.3)
Weight decreased	0	1 (25.0)	1 (14.3)
Urinary occult blood positive	0	2 (50.0)	2 (28.6)
Magnetic resonance imaging head	0	1 (25.0)	1 (14.3)
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (33.3)	0	1 (14.3)
Back pain	1 (33.3)	0	1 (14.3)
Lumbar spinal stenosis	0	1 (25.0)	1 (14.3)
Muscle tightness	1 (33.3)	0	1 (14.3)
Nervous system disorders			
Dyskinesia	0	1 (25.0)	1 (14.3)
Dystonia	1 (33.3)	1 (25.0)	2 (28.6)
Headache	1 (33.3)	0	1 (14.3)
Hypoaesthesia	0	1 (25.0)	1 (14.3)
Psychiatric disorders			
Anxiety	0	1 (25.0)	1 (14.3)
Claustrophobia	2 (66.7)	0	2 (28.6)
Hallucination, olfactory	0	1 (25.0)	1 (14.3)
Renal and urinary disorders			
Hypertonic bladder	0	1 (25.0)	1 (14.3)
Pollakiuria	0	1 (25.0)	1 (14.3)
Renal dysfunction	2 (66.7)	1 (25.0)	3 (42.9)

MedDRA/J v26.1 System organ class (SOC) Preferred term (PT)	Low-dose (N = 3) n (%)	High-dose (N = 4) n (%)	Overall (N = 7) n (%)
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea	1 (33.3)	0	1 (14.3)
Skin and subcutaneous tissue disorders			
Alopecia	0	1 (25.0)	1 (14.3)
Eczema	1 (33.3)	0	1 (14.3)
Vascular disorders			
Orthostatic hypotension	0	1 (25.0)	1 (14.3)
Peripheral coldness	0	1 (25.0)	1 (14.3)
Product issues			
Device breakage	1 (33.3)	0	1 (14.3)

No severe adverse events were observed. Moderate dyskinesia occurred in 1 patient (PD0[redacted] in the high-dose group). The outcome of this event was “not recovered”; however, it was assessed as not related to AMCHEPRY. All other events were mild in severity. No deaths, serious adverse events, or adverse events leading to graft removal were observed.

(2) Presence or absence of graft overgrowth in the brain (>3 cm^3) at 24 months after transplantation (MRI)

Table 16 shows the changes in graft fraction volume for each patient. Regarding graft volume after transplantation of AMCHEPRY, none of the 7 patients showed graft overgrowth exceeding 3 cm^3 (3,000 μL) in either hemisphere at 24 months after transplantation.

Table 16. Graft fraction volume in the brain as measured by cranial MRI at 24 months after transplantation (μL[*1])

	Time point	Low-dose			High-dose			
		PD01	PD02	PD03	PD04	PD05	PD06	PD08
Right	Week 4 (after bilateral surgery)	78.27	150.39	68.53	75.74	154.50	22.90	118.90
	Week 12 (after bilateral surgery)	75.71	212.40	105.38	129.90	86.40	33.20	75.80
	Month 6 (after bilateral surgery)	38.66	216.80	98.50	167.80	158.80	68.80	139.90
	Month 12 (after bilateral surgery)	93.83	314.40	128.63	248.70	127.10	112.90	176.10
	Month 16 (after bilateral surgery)	83.54	380.90	197.40	134.30	67.70	159.10	216.40
	Month 18 (after bilateral surgery)	79.65	385.20	137.13	248.30	95.80	117.60	180.60
	Month 24 (after bilateral surgery)	131.33	433.60	180.90	293.30	70.80	143.20	207.00
Left	Week 4 (first patient only)	0.00	-	-	-	-	-	-
	Week 12 (first patient only)	0.00	-	-	-	-	-	-
	Month 6 (first patient only)	4.00	-	-	-	-	-	-
	Week 4 (after bilateral surgery)	-	46.47	107.68	34.34	103.10	44.80	28.40
	Week 12 (after bilateral surgery)	-	85.90	72.14	137.80	134.20	79.60	30.00
	Month 6 (after bilateral surgery)	11.00	185.40	142.48	166.60	106.70	118.80	42.90
	Month 12 (after bilateral surgery)	13.93	299.70	247.48	177.70	183.10	318.20	154.60
	Month 16 (after bilateral surgery)	8.83	372.80	291.11	362.40	204.20	224.10	279.30
	Month 18 (after bilateral surgery)	17.52	302.20	210.36	186.80	215.80	191.50	95.00
	Month 24 (after bilateral surgery)	11.34	411.00	278.40	241.90	182.00	173.70	428.10

-, Not evaluated
*1 Graft fraction volume was measured in microliters (μL).

6.1.1.2 Study IACT16049-02 (CTD 5.3.5.2-02, August 2018 to December 2023)

In Study IACT16049-01, the efficacy and safety of tacrolimus administered at the time of transplantation of AMCHEPRY were also evaluated, and the applicant submitted the results as those of Study IACT16049-02.

Tacrolimus was administered orally for 52 weeks starting on the morning of the day of transplantation of AMCHEPRY. Treatment was initiated at 0.03 to 0.15 mg/kg per dose (standard dose, 0.06 mg/kg) twice daily, and the dose was adjusted to maintain the trough blood level in the range of 5 to 10 ng/mL. After 52 weeks of administration, the dose was tapered over 12 weeks.

The primary efficacy endpoint was the cumulative rejection suppression rate (non-occurrence rate)[10] at 12 weeks and 12 months after transplantation of AMCHEPRY. At both time points, the cumulative rejection suppression rate (non-occurrence rate) was 100% (6 of 6 patients), and all 6 patients in the efficacy analysis population were assessed as having no rejection.

Regarding safety, the incidence of adverse reactions to tacrolimus was 42.9% (3 of 7 patients). Adverse reactions observed in ≥2 patients were renal dysfunction (2 patients). Other adverse reactions included hepatic function abnormal, gamma-glutamyltransferase increased, dermatophytosis of nail, and cystitis (1 patient each). All events were mild in severity; except for 1 event each of renal dysfunction and dermatophytosis of nail that had not recovered, all events resolved. There were no deaths, serious adverse events, or adverse events leading to discontinuation of treatment. An adverse event leading to dose reduction occurred in 1 patient with renal dysfunction, which developed on Day 243 after initiation of treatment and had not resolved.

6.R Outline of the review conducted by PMDA

6.R.1 Efficacy

6.R.1.1 Review policy for evaluation of efficacy

The applicant's explanation about the rationale for describing the efficacy of AMCHEPRY based on the results of Study IACT16049-01:

(1) Efficacy endpoints

The primary objective of Study IACT16049-01 was to confirm the safety of AMCHEPRY, but efficacy was also evaluated. In assessing the efficacy of AMCHEPRY, it is considered important to evaluate imaging findings ([^{18}F]FDOPA PET and engraftment) and OFF-state motor symptoms excluding the effects of anti-PD disease drugs (International Parkinson and Movement Disorder Society [MDS]-Unified Parkinson's Disease Rating Scale [UPDRS] Part III total score, Hoehn and Yahr staging [H&Y stage], and the Bradykinesia subscale), based on the following considerations:

- Evaluation of graft size by MRI and assessment of [^{18}F]FDOPA uptake at the transplantation site can confirm that AMCHEPRY has engrafted, differentiated into dopaminergic neurons, and is functioning. [^{18}F]FDOPA PET is a useful modality for evaluating dopamine synthesis capacity in the striatum of patients with PD. In patients with PD, [^{18}F]FDOPA uptake decreases in the putamen followed by the caudate nucleus with disease progression; therefore, the Ki value,[11] a quantitative index, has been used to assess disease progression (*Brain.* 2002;125:2248-56; *Neuroimage*. 2011;56:1463-8).
- The OFF-state MDS-UPDRS Part III total score provides an objective evaluation of motor symptoms in the absence of pharmacological intervention and reflects the extent of dopaminergic neuronal loss.

[10] The proportion of patients who experienced no rejection during the 12 weeks and 12 months after transplantation of AMCHEPRY.

[11] The Ki value represents the rate constant for [^{18}F]FDOPA uptake into the brain and reflects [^{18}F]FDOPA uptake in the striatal region and its metabolism to 6-[18F]-fluoro-dopamine ([^{18}F]FDA).

Accordingly, in several cell transplantation studies and clinical studies of disease-modifying agents, it has been adopted as a primary efficacy endpoint as an indicator of disease progression in motor symptoms (*Ann Neurol*. 2003;54:403-14; *Parkinsonism Relat Disord*. 2025;132:107257, etc.). In addition, as bradykinesia is a cardinal symptom required for the diagnosis of PD, the Bradykinesia subscale of OFF-state MDS-UPDRS Part III was evaluated.

- H&Y stage is an index that classifies the stage of PD into 5 levels, with each stage representing a substantial change in disease status. In advanced PD that has become difficult to treat with medication, the disease progresses irreversibly, and conventional agents without disease-modifying effects do not improve OFF-state H&Y stage. Evaluating whether improvement in the H&Y stage is observed is considered meaningful.

(2) Study design

Study IACT16049-01 was initially planned as a first-in-human study (FIH study) with the primary objective of safety evaluation. Taking the following points into consideration, the study was conducted as an open-label, uncontrolled study:

- If a sham surgery group was to be established as a control group, ethical concerns would arise due to the invasiveness of sham surgery.
- The efficacy of AMCHEPRY needs to be evaluated in the practically defined off state after withdrawal of anti-PD drugs; establishment of a sham surgery group or a standard therapy group would impose a substantial burden on patients.
- In PD, which is designated as an intractable disease in Japan, a system is in place to reduce the financial burden on patients through medical expense subsidies. In a study including a sham surgery group or a standard therapy group, patient enrollment would be difficult and a high dropout rate during the study would be anticipated; thus, feasibility would be low.

Study IACT16049-01 enrolled patients whose symptoms were inadequately controlled despite optimized conventional pharmacotherapy. PD is a progressive disorder with irreversible worsening of pathology; motor symptoms in the practically defined off state can be evaluated to a certain extent even without a control group. Although the potential influence of a placebo effect on efficacy evaluation is a concern, the placebo effect is considered as follows:

- [^{18}F]FDOPA PET provides an objective assessment and is not considered to be affected by the placebo effect. In a meta-analysis (*J Parkinsons Dis*. 2022;12:759-71), results of [^{18}F]FDOPA PET were reported in 4 of 9 studies (evaluation period, 6-24 months); no significant improvement in [^{18}F]FDOPA uptake in the putamen or caudate nucleus was observed in the sham surgery groups.
- The placebo effect on the OFF-state MDS-UPDRS Part III total score is considered to be limited for the following reasons:
  - In the placebo groups of 2 clinical studies of disease-modifying agents without surgical intervention (*N Engl J Med*. 2022;387:408-20; *N Engl J Med*. 2022;387:421-32), the mean change from baseline in the OFF-state MDS-UPDRS Part III total score at Week 52 was +6.1 points [95% confidence interval (CI), 4.0-8.2] and +5.6 points [standard error, 0.9], showing no improvement and indicating worsening over time.
  - In sham surgery groups of clinical studies involving surgical procedures, both improvement and worsening of the OFF-state MDS-UPDRS Part III total score have been reported. In a meta-

analysis (*J Parkinsons Dis*. 2022;12:759-71), the weighted mean change from baseline in the OFF-state UPDRS Part III total score at approximately 1 year after transplantation in sham surgery groups across 9 studies [95% CI] was −4.3 [−3.1 to −5.6], indicating improvement. In the study showing the greatest improvement in the OFF-state UPDRS Part III total score, the mean change from baseline at 1 year after surgery [SD] was −10.1 [12.26] (*Lancet Neurol*. 2011;10:509-19). In contrast, in another study with a sham surgery procedure similar to that study, the mean change from baseline in the OFF-state UPDRS Part III total score at 2 years after surgery [standard error] was +8.4 [5.5] (*Ann Neurol*. 2003;54:403-14). As described above, the placebo effect associated with sham surgery has not been consistent. Considering reports indicating that a placebo effect driven by patients' expectations of therapeutic benefit does not persist long term without an actual treatment effect (*Arch Gen Psychiatry*. 2004;61:412-20; *Lancet Neurol*. 2011;10:509-19), the likelihood that a placebo effect would persist over a prolonged period is considered low.

PMDA's view:

Study IACT16049-01 was initially planned as a FIH study with the primary objective of safety evaluation. Because no control group was established and the number of enrolled patients was limited to 7, there are inherent limitations in evaluating the efficacy of AMCHEPRY solely on the basis of the results of Study IACT16049-01. In particular, regarding the potential impact of a placebo effect on the OFF-state UPDRS Part III total score, no improvement has been observed in placebo groups of multiple clinical studies of pharmacological therapies without surgical intervention. In contrast, in a sham surgery group of a clinical study involving surgical treatment, the mean change from baseline in the OFF-state UPDRS Part III total score at 2 years after surgery was reported to be −8.2 (*Lancet Neurol.* 2011;10:509-19). The applicant's explanation that the likelihood of a long-lasting placebo effect is low is understandable to some extent, but it should be noted that even at 2 years after transplantation, which was the evaluation time point in Study IACT16049-01, the possibility of a certain degree of placebo effect associated with the surgical procedure (stereotactic brain surgery) at the time of transplantation of AMCHEPRY cannot be excluded. The results should be interpreted with caution.

The applicant explained that imaging assessments ([^{18}F]FDOPA PET and engraftment) and evaluation of OFF-state motor symptoms excluding the effects of anti-PD drugs (MDS-UPDRS Part III total score, H&Y stage, and the Bradykinesia subscale) are important for evaluating the efficacy of AMCHEPRY, which is understandable. Accordingly, PMDA decided to focus primarily on these endpoints as key efficacy measures and to comprehensively evaluate the efficacy of AMCHEPRY, taking into account the results of other efficacy endpoints as well.

6.R.1.2 Results of efficacy evaluation

6.R.1.2.1 Results of key efficacy endpoints

The applicant's explanation about the results of imaging assessments ([^{18}F]FDOPA PET and engraftment) and OFF-state motor symptoms excluding the effects of anti-PD drugs (MDS-UPDRS Part III total score, H&Y stage, and the Bradykinesia subscale):

(1) Results of imaging assessments ([^{18}F]FDOPA PET and engraftment)

1) [^{18}F]FDOPA uptake in the putamen

Table 17 shows the results of [^{18}F]FDOPA uptake in the 6 patients in the efficacy analysis population. Accumulation of [^{18}F]FDOPA was confirmed qualitatively in the putamen, the transplantation site of AMCHEPRY. At 24 months after transplantation, the Ki value in the putamen increased from baseline in 5 of 6 patients. In addition, the putamen-to-caudate ratio[12)] increased from baseline in all 6 patients.

Table 17. List of patient-level results of [^{18}F]FDOPA uptake (putamen and putamen-to-caudate ratio, bilateral mean)

Item	Time point	Ki: putamen (bilateral mean)						Putamen-to-caudate ratio (bilateral mean)*2					
		Low-dose		High-dose				Low-dose		High-dose			
		PD02	PD03	PD04	PD05	PD06	PD08	PD02	PD03	PD04	PD05	PD06	PD08
Observed value	Secondary registration	0.0044	0.0046	0.0027	0.0024	0.0027	0.0023	0.4582	0.5382	0.3916	0.3470	0.3758	0.3687
	Month 6	0.0040	0.0058	0.0026	0.0046	0.0032	0.0034	0.4595	0.5948	0.3540	0.6195	0.4225	0.4190
	Month 12	0.0047	0.0055	0.0035	0.0040	0.0044	0.0037	0.5089	0.6303	0.4974	0.5058	0.5647	0.5125
	Month 18	0.0042	0.0053	0.0033	0.0045	0.0045	0.0032	0.4847	0.6256	0.5027	0.6567	0.5717	0.4426
	Month 24	0.0042	0.0054	0.0041	0.0049	0.0032	0.0042	0.4966	0.6498	0.6110	0.7065	0.4616	0.6186
Change from baseline*1	Secondary registration	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Month 6	-0.0004	0.0012	-0.0001	0.0022	0.0005	0.0011	0.0013	0.0566	-0.0376	0.2725	0.0467	0.0503
	Month 12	0.0003	0.0009	0.0008	0.0016	0.0017	0.0013	0.0507	0.0922	0.1058	0.1588	0.1889	0.1438
	Month 18	-0.0001	0.0007	0.0006	0.0020	0.0018	0.0009	0.0264	0.0874	0.1111	0.3097	0.1959	0.0739
	Month 24	-0.0002	0.0008	0.0014	0.0025	0.0005	0.0019	0.0384	0.1117	0.2194	0.3595	0.0858	0.2498

*1 Baseline was defined as the time of secondary registration.
*2 Ratio of Ki values between the putamen and caudate nucleus (bilateral mean).

Table 18 shows the results of [^{18}F]FDOPA uptake in the patient (PD01) who underwent unilateral transplantation at a time and was excluded from the efficacy analysis population. In this patient as well, accumulation of [^{18}F]FDOPA was confirmed qualitatively in the transplanted putamen at 24 months after bilateral transplantation. Furthermore, at 24 months after transplantation, the Ki value in the putamen increased from baseline, and the putamen-to-caudate ratio[12)] increased from baseline.

12) The Ki value in the transplanted putamen to that in the non-transplanted caudate nucleus.

Table 18. Results of [^{18}F]FDOPA uptake (putamen and putamen-to-caudate ratio, bilateral mean, PD01)

Item	Time point	Ki: putamen (bilateral mean)	Putamen-to-caudate ratio (bilateral mean)*4
Observed value	Secondary registration	0.004332	0.4909
	Month 6*2	0.003263	0.4339
	Month 6*3	0.003287	0.4073
	Month 12*3	0.004347	0.5214
	Month 18*3	0.003724	0.5107
	Month 24*3	0.004859	0.6119
Change from baseline*1	Secondary registration	0	0
	Month 6*2	-0.001069	-0.0570
	Month 6*3	-0.001045	-0.0836
	Month 12*3	0.000015	0.0305
	Month 18*3	-0.000608	0.0198
	Month 24*3	0.000527	0.1209

*1 Baseline was defined as the time of secondary registration.
*2 After transplantation to one hemisphere.
*3 After transplantation to the remaining hemisphere.
*4 Ratio of Ki values between the putamen and caudate nucleus (bilateral mean).

2) Engraftment of AMCHEPRY

Assessment of engraftment was performed in Study IACT16049-02 at 12 and 24 months after transplantation. To ensure objectivity, engraftment in the putamen was determined by consensus between neurologists and radiologists based on MRI and PET images ([^{18}F]FDOPA and [^{18}F]GE180[13]) obtained up to the respective evaluation time points. All 6 patients in the efficacy analysis population were judged to have engraftment in the putamen at both 12 and 24 months after transplantation. In the patient (PD01) who underwent unilateral transplantation at a time and was excluded from the efficacy analysis population, engraftment was also judged to be present in both putamina.

(2) Evaluation of OFF-state motor symptoms (MDS-UPDRS Part III total score, H&Y stage, and Bradykinesia subscale)

Table 19 and Figures 1 to 3 show the results for the OFF-state MDS-UPDRS Part III total score, OFF-state H&Y stage, and OFF-state Bradykinesia subscale.

[13]) A translocator protein antagonist, which is expected to emerge in activated microglia. This was used for neuroinflammation reaction assessment.

Table 19. List of patient-level results for OFF-state MDS-UPDRS Part III total score, OFF-state H&Y stage, and OFF-state bradykinesia subscale

Item	Time point	OFF-state MDS-UPDRS Part III total score						OFF-state H&Y stage						OFF-state Bradykinesia subscale					
		Low-dose		High-dose				Low-dos		High-dose				Low-dose		High-dose			
		PD02	PD03	PD04	PD05	PD06	PD08	PD02	PD03	PD04	PD05	PD06	PD08	PD02	PD03	PD04	PD05	PD06	PD08
Observed value	Primary registration*2	34	59	73	66	58	36	4	5	5	5	3	3	11	23	26	18	23	13
	Secondary registration	34	55	71	59	52	34	4	5	5	5	3	3	14	20	22	17	21	11
	Week 4	36	34	32	75	47	24	4	4	2	5	2	2	12	13	10	25	18	9
	Week 12	18	49	19	73	36	26	4	4	2	5	2	2	7	20	4	26	13	9
	Month 6	18	64	21	65	43	25	2	4	2	5	2	2	4	26	6	20	17	9
	Month 12	25	38	21	67	49	23	4	4	2	5	2	2	7	11	8	24	20	9
	Month 18	25	45	31	68	48	24	2	4	2	5	2	2	9	15	12	24	20	9
	Month 24	23	50	39	64	55	17	2	4	5	5	2	2	9	16	15	23	22	7
Change from baseline*1	Primary registration	0	4	2	7	6	2	0	0	0	0	0	0	-3	3	4	1	2	2
	Secondary registration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Week 4	2	-21	-39	16	-5	-10	0	-1	-3	0	-1	-1	-2	-7	-12	8	-3	-2
	Week 12	-16	-6	-52	14	-16	-8	0	-1	-3	0	-1	-1	-7	0	-18	9	-8	-2
	Month 6	-16	9	-50	6	-9	-9	-2	-1	-3	0	-1	-1	-10	6	-16	3	-4	-2
	Month 12	-9	-17	-50	8	-3	-11	0	-1	-3	0	-1	-1	-7	-9	-14	7	-1	-2
	Month 18	-9	-10	-40	9	-4	-10	-2	-1	-3	0	-1	-1	-5	-5	-10	7	-1	-2
	Month 24	-11	-5	-32	5	3	-17	-2	-1	0	0	-1	-1	-5	-4	-7	6	1	-4

*1 Baseline was defined as the time of secondary registration.

*2 Interval from primary registration to secondary registration: PD02 = 11.3 months; PD03 = 7.7 months; PD04 = 17.1 months; PD05 = 19.8 months; PD06 = 20.2 months (MDS-UPDRS Part III total score and Bradykinesia subscale), 20.5 months (H&Y stage); PD08 = 6.1 months.

1) OFF-state MDS-UPDRS Part III total score

Of the 6 patients in the efficacy analysis population, 4 patients were judged to have shown a marked response[14)] in the OFF-state MDS-UPDRS Part III total score. Among the 2 patients (PD05 and PD06 in the high-dose group) who did not show a marked response at 24 months after transplantation, 1 patient (PD06) showed improvement up to 18 months after transplantation but worsened to +3 at 24 months. The other patient (PD05) showed an increased score at 4 weeks after transplantation, followed by a decrease up to 24 months; however, the change from baseline was +5, indicating worsening.

14) In the clinical study protocol, based on the following reports on the 1 to 2-year course of the MDS-UPDRS Part III in the off state under sham surgery or standard treatment, an improvement of ≥5 points in the MDS-UPDRS Part III total score in the off state from baseline to 24 months after transplantation was defined as a marked response, and an improvement of 0 to 4 points was defined as a response.

- In clinical studies evaluating transplantation of dopaminergic neurons (*Ann Neurol.* 2003;54:403-14; *N Engl J Med.* 2001;8;344:710-9), symptoms remained unchanged or worsened.
- In a clinical study evaluating DBS (*Lancet Neurol.* 2010;9:581-91), no change was observed.

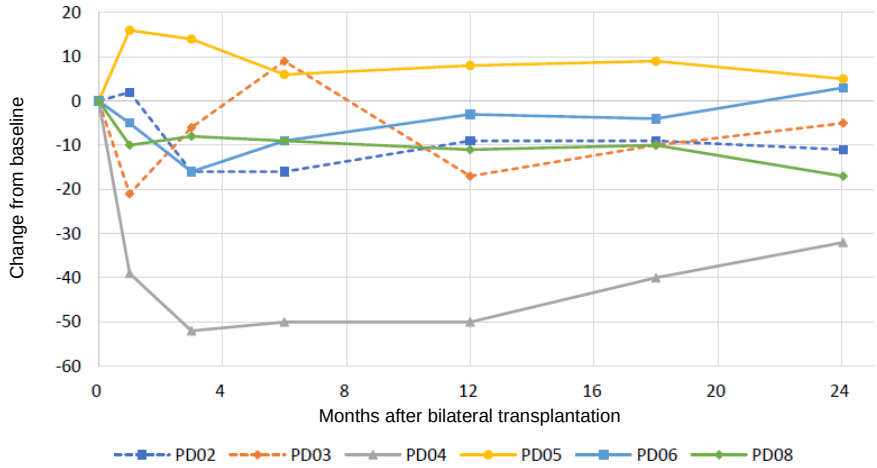

Figure 1. Change from baseline in OFF-state MDS-UPDRS Part III total score

2) OFF-state H&Y stage

Of the 6 patients in the efficacy analysis population, 4 patients showed a decrease in the H&Y stage at 24 months after transplantation compared with baseline; 1 patient improved by 2 stages (stage 4 to stage 2), and the other 3 patients improved by 1 stage (1 patient from stage 5 to stage 4, and 2 patients from stage 3 to stage 2). The remaining 2 patients (PD04 and PD05 in the high-dose group) showed the same stage at baseline and at 24 months after transplantation. Among them, 1 patient (PD04) improved from stage 5 at baseline to stage 2 between 4 weeks and 18 months after transplantation but returned to stage 5 at 24 months. The other patient (PD05) showed no change from baseline through 24 weeks after transplantation.

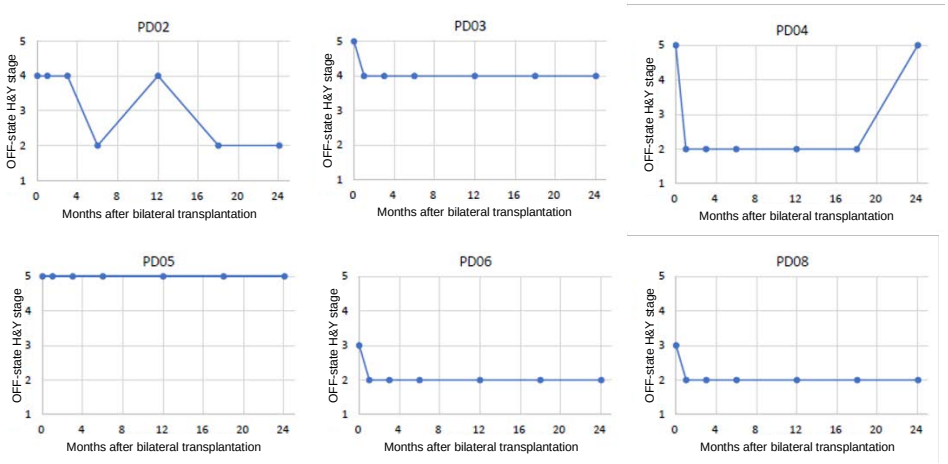

Figure 2. Severity according to OFF-state H&Y stage

3) OFF-state Bradykinesia subscale

Of the 6 patients in the efficacy analysis population, 4 patients showed improvement in the Bradykinesia subscale at 24 months after transplantation compared with baseline. Among the 2 patients who did not show improvement at Month 24, 1 patient (PD06) showed a change from baseline of −8 at 12 weeks after transplantation, followed by −4 at Month 6, −1 at 12 and Month 18, and +1 at Month 24. The other patient (PD05) showed the greatest increase in score at 12 weeks after transplantation, followed by a decrease up to 24 months; however, the change from baseline was +6.

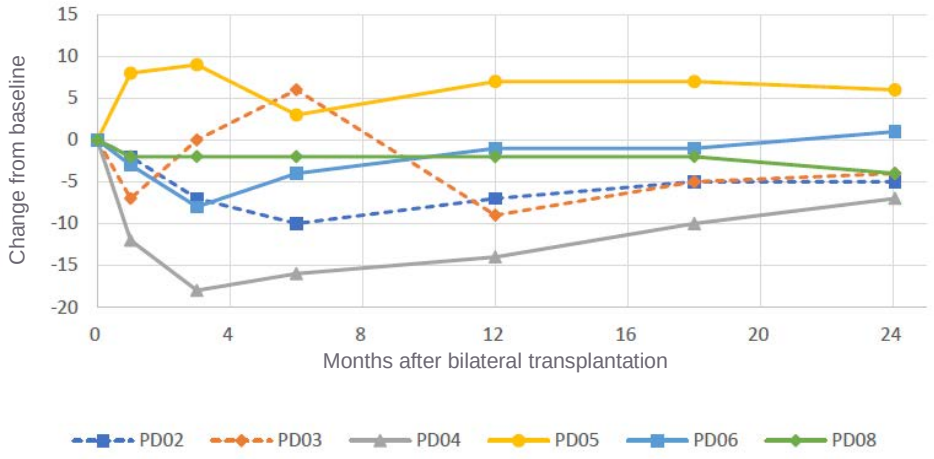

Figure 3. Change from baseline in OFF-state Bradykinesia subscale

Table 20 shows the OFF-state MDS-UPDRS Part III total score, OFF-state H&Y stage, and OFF-state Bradykinesia subscale in the patient (PD01) excluded from the efficacy analysis population, and improvement was observed in all endpoints.

Table 20. Results for OFF-state MDS-UPDRS Part III total score, OFF-state H&Y stage, and OFF-state Bradykinesia subscale (PD01)

Item	Time point	OFF-state MDS-UPDRS Part III total score	OFF-state H&Y stage	OFF-state Bradykinesia subscale
Observed value	Primary registration	43	3	14
	Week 4*2	16	2	3
	Week 12*2	36	3	8
	Month 6*2	39	3	12
	Week 4*3	23	2	6
	Week 12*3	19	2	3
	Month 6*3	31	3	9
	Month 12*3	31	2	12
	Month 18*3	28	2	12
	Month 24*3	38	2	12
Change from baseline*1	Primary registration	0	0	0
	Week 4*2	-27	-1	-11
	Week 12*2	-7	0	-6
	Month 6*2	-4	0	-2
	Week 4*3	-20	-1	-8
	Week 12*3	-24	-1	-11
	Month 6*3	-12	0	-5
	Month 12*3	-12	-1	-2
	Month 18*3	-15	-1	-2
	Month 24*3	-5	-1	-2

*1 Baseline was defined as the time of primary registration.
*2 After transplantation to one side.
*3 After transplantation to the contralateral side.

In summary, accumulation of [^{18}F]FDOPA and engraftment of AMCHEPRY were confirmed in all patients. Among the 6 patients in the efficacy analysis population, 4 patients showed a marked response in the OFF-state MDS-UPDRS Part III total score and improvement in the OFF-state Bradykinesia subscale. Furthermore, among the 4 patients, 3 patients showed a decrease in the OFF-state H&Y stage by 2 stages (1 patient) or 1 stage (2 patients). Taken together, the above findings suggest clinically meaningful improvement in disease status after transplantation of AMCHEPRY.

PMDA's view:

Study IACT16049-01 was a single-center exploratory study, and the following issues should be noted when evaluating improvement in motor symptoms based on its results.

- All motor symptom endpoints are subjective measures, and in an open-label, uncontrolled study, expectations of treatment benefit on the part of both evaluators and patients may influence the assessment.
- Improvement in the OFF-state MDS-UPDRS Part III total score has been reported in association with surgical procedures (*Lancet Neurol*. 2011;10:509-19), and a certain degree of placebo effect associated with stereotactic brain surgery performed at the time of transplantation of AMCHEPRY cannot be excluded.
- Whereas the rate of disease progression varies considerably among patients with PD, the efficacy analysis population was limited to 6 patients (2 in the low-dose group and 4 in the high-dose group).

On the other hand, improvement in the OFF-state MDS-UPDRS Part III total score, the key efficacy endpoint, was observed in 4 of 6 patients at 24 months after transplantation. In particular, in 3 patients (PD02, −11; PD04, −32; PD08, −17), the magnitude of improvement exceeded the maximum placebo effect reported at 2 years after transplantation (−8.2), suggesting the efficacy of AMCHEPRY. Furthermore, the results for the ON-state MDS-UPDRS Part III total score and other endpoints [see Section 6.R.1.2.2] also suggest some efficacy of AMCHEPRY in patients with PD. However, as described in Section 6.R.1.1, there are limitations in evaluating the efficacy of AMCHEPRY solely on the basis of the results of Study IACT16049-01, and the current evaluation of efficacy of AMCHEPRY is highly limited. PMDA considers that the efficacy of AMCHEPRY should be re-evaluated in the post-marketing setting.

6.R.1.2.2 Results of other major efficacy endpoints

The applicant's explanation regarding the results of the major efficacy endpoints other than the key efficacy endpoints (other major efficacy endpoints):

(1) ON-state MDS-UPDRS Part III total score and ON-state H&Y stage

Table 21 and Figures 4 and 5 show the results of the ON-state MDS-UPDRS Part III total score and ON-state H&Y stage.

Table 21. List of patient-level results of ON-state MDS-UPDRS Part III total score and ON-state H&Y stage

Item	Time point	ON-state MDS-UPDRS Part III total score						ON-state H&Y stage					
		Low-dose		High-dose				Low-dose		High-dose			
		PD02	PD03	PD04	PD05	PD06	PD08	PD02	PD03	PD04	PD05	PD06	PD08
Observed value	Primary registration	9	20	12	32	25	9	2	2	2	2	2	2
	Secondary registration	8	13	23	27	25	10	2	2	2	2	2	2
	Week 4	4	12	8	18	18	14	1	2	1	2	2	2
	Week 12	5	13	8	20	26	12	2	2	2	2	2	2
	Month 6	6	12	13	24	31	5	2	2	2	2	2	2
	Month 12	7	11	9	25	34	5	1	2	2	2	2	2
	Month 18	9	7	10	23	32	3	2	2	2	2	2	1
	Month 24	5	4	12	25	32	2	2	1	2	2	2	2
Change from baseline[*1]	Primary registration	1	7	-11	5	0	-1	0	0	0	0	0	0
	Secondary registration	0	0	0	0	0	0	0	0	0	0	0	0
	Week 4	-4	-1	-15	-9	-7	4	-1	0	-1	0	0	0
	Week 12	-3	0	-15	-7	1	2	0	0	0	0	0	0
	Month 6	-2	-1	-10	-3	6	-5	0	0	0	0	0	0
	Month 12	-1	-2	-14	-2	9	-5	-1	0	0	0	0	0
	Month 18	1	-6	-13	-4	7	-7	0	0	0	0	0	-1
	Month 24	-3	-9	-11	-2	7	-8	0	-1	0	0	0	0

*1 Baseline was defined as the time of secondary registration.

The ON-state MDS-UPDRS Part III total score decreased at 24 months post-transplantation compared with baseline in 5 of 6 patients. In 1 patient (PD06), the change from baseline was −7 at 4 weeks post-transplantation; however, no improvement was observed from Week 12 onward.

The ON-state H&Y stage improved at 24 months post-transplantation compared with baseline in 1 patient, decreasing from stage 2 to stage 1. In the remaining 5 patients, no change from the baseline stage 2 was observed at 24 months post-transplantation.

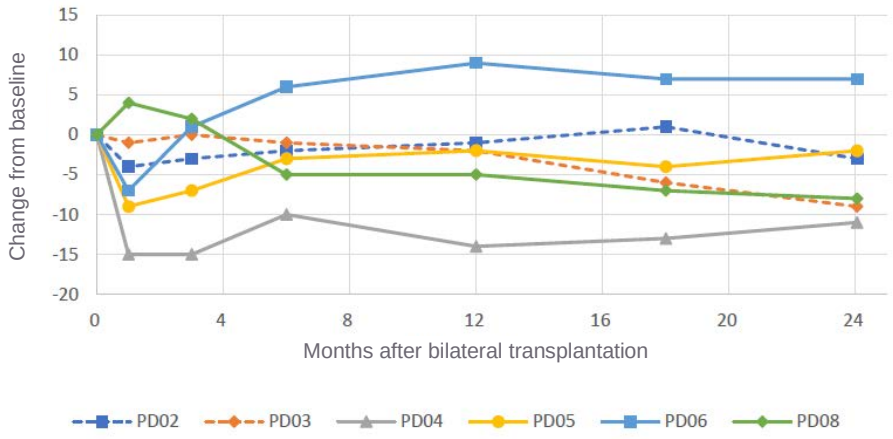

Figure 4. Change from baseline in ON-state MDS-UPDRS Part III total score

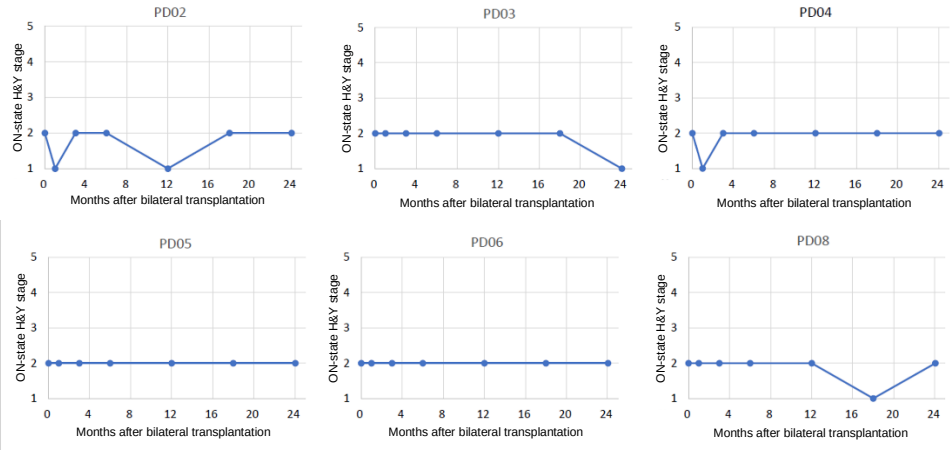

Figure 5. ON-state H&Y stage

(2) Mean daily on time, off time, and good on time

Table 22 and Figure 6 show the results of mean daily on time, off time, and good on time.

Table 22. List of patient-level results of mean daily on time, off time, and good on time

Item	Time point	On time						Off time						Good on time					
		Low-dose		High-dose				Low-dose		High-dose				Low-dose		High-dose			
		PD02	PD03	PD04	PD05	PD06	PD08	PD02	PD03	PD04	PD05	PD06	PD08	PD02	PD03	PD04	PD05	PD06	PD08
Observed value	Primary registration	7.6	10.9	12.3	11.5	7.9	10.1	8.6	6.5	2.9	2.0	7.9	6.9	7.6	10.9	12.3	11.5	7.9	7.4
	Secondary registration	7.7	11.4	13.1	10.4	8.6	10.5	9.2	6.6	3.6	1.3	8.5	6.7	7.7	11.4	12.9	9.9	8.6	9.5
	Week 4	11.2	11.5	12.6	11.2	12.1	11.1	5.4	6.7	4.5	1.4	5.4	6.3	11.2	11.5	11.4	10.2	12.1	6.5
	Week 12	13.3	9.8	12.7	10.3	11.9	11.5	4.0	9.0	3.6	2.4	3.7	5.8	13.3	9.8	12.7	10.2	10.3	10.2
	Month 6	12.9	8.4	10.4	11.1	11.1	11.1	3.3	10.1	6.5	2.1	6.9	6.9	12.9	8.4	10.2	11.1	10.8	7.6
	Month 12	12.9	11.2	11.0	11.0	9.6	10.1	3.1	7.1	6.1	2.0	7.5	7.0	12.9	11.2	10.6	11.0	9.6	5.2
	Month 18	14.0	11.5	11.3	11.2	10.3	10.1	2.6	6.2	5.6	1.1	6.6	7.1	13.3	11.5	11.2	10.7	10.3	3.2
	Month 24	11.8	9.2	10.3	11.3	7.4	8.6	4.3	9.1	6.2	1.4	9.3	8.5	11.2	9.2	8.9	11.1	7.4	2.6
Change from baseline[*1]	Primary registration	-0.1	-0.6	-0.8	1.1	-0.6	-0.4	-0.6	-0.1	-0.6	0.7	-0.6	0.1	-0.1	-0.6	-0.6	1.6	-0.6	-2.1
	Secondary registration	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Week 4	3.5	0.1	-0.4	0.9	3.5	0.6	-3.9	0.1	0.9	0.1	-3.1	-0.4	3.5	0.1	-1.5	0.4	3.5	-3.0
	Week 12	5.6	-1.6	-0.4	-0.1	3.3	1.0	-5.2	2.4	0.1	1.1	-4.8	-0.9	5.6	-1.6	-0.1	0.4	1.7	0.7
	Month 6	5.1	-3.0	-2.7	0.7	2.5	0.6	-5.9	3.5	2.9	0.8	-1.6	0.1	5.1	-3.0	-2.6	1.2	2.2	-1.9
	Month 12	5.2	-0.2	-2.1	0.6	1.1	-0.4	-6.1	0.5	2.6	0.7	-1.0	0.3	5.2	-0.2	-2.2	1.1	1.1	-4.3
	Month 18	6.3	0.1	-1.8	0.9	1.7	-0.4	-6.6	-0.4	2.0	-0.2	-1.9	0.4	5.6	0.1	-1.6	0.9	1.7	-6.3
	Month 24	4.1	-2.2	-2.8	0.9	-1.1	-1.9	-4.9	2.4	2.6	0.1	0.8	1.8	3.5	-2.2	-3.9	1.3	-1.1	-6.9

Unit: hours

*1 Baseline was defined as the time of secondary registration.

Among the 4 patients (PD02, PD03, PD04, and PD08) who were considered to have achieved a marked response, defined as an improvement of ≥5 points in the OFF-state MDS-UPDRS Part III total score at 24 months post-transplantation of AMCHEPRY, only 1 patient (PD02) showed an increase in mean daily on time, a decrease in off time, and an increase in good on time. No improvement was observed in PD03, PD04, or PD08.

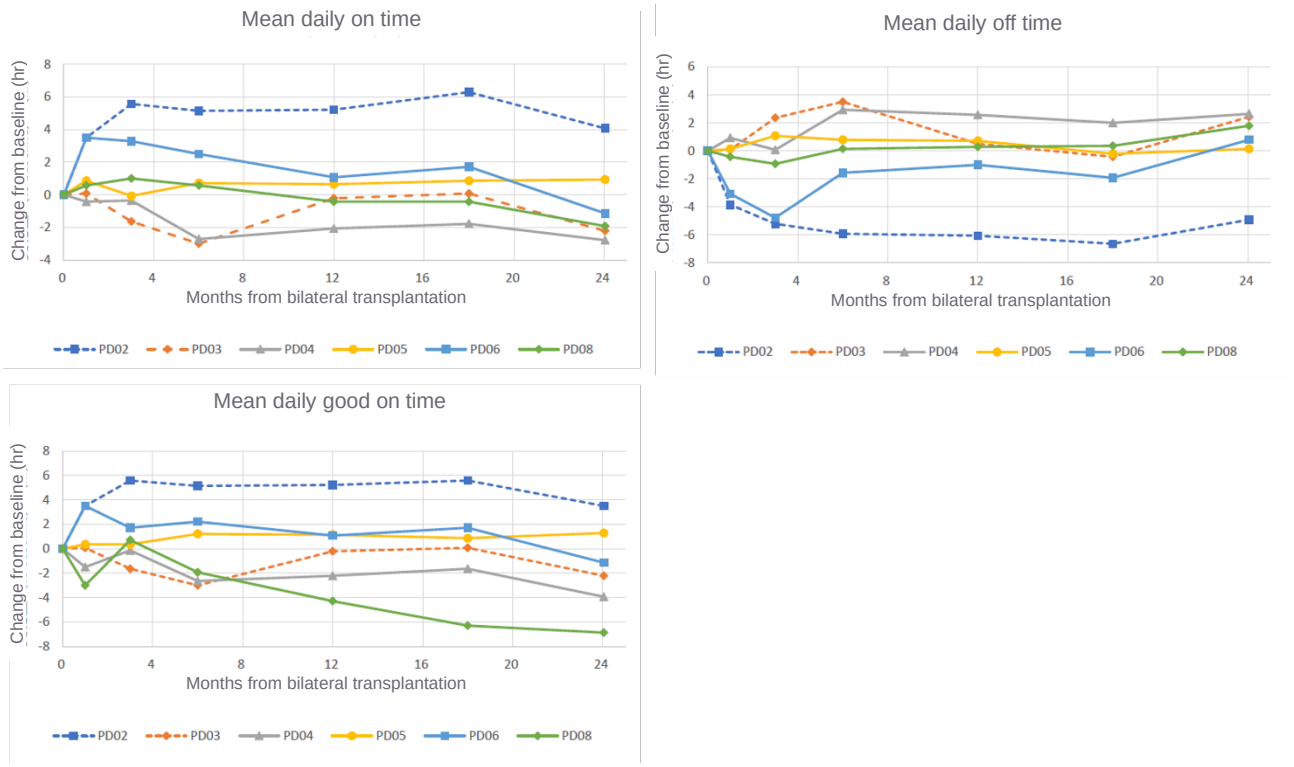

Figure 6. Change from baseline in mean daily on time, off time, and good on time

(3) MDS-UPDRS Part I total score and MDS-UPDRS Part II total score

Table 23 and Figure 7 show the results of the MDS-UPDRS Part I total score and the MDS-UPDRS Part II total score.

Table 23. List of patient-level results of MDS-UPDRS Part I total score and MDS-UPDRS Part II total score

Item	Time point	MDS-UPDRS Part I total score						MDS-UPDRS Part II total score					
		Low-dose		High-dose				Low-dose		High-dose			
		PD02	PD03	PD04	PD05	PD06	PD08	PD02	PD03	PD04	PD05	PD06	PD08
Observed value	Primary registration	6	5	4	1	7	6	10	9	9	4	9	0
	Secondary registration	7	7	7	1	6	4	11	17	6	9	14	4
	Week 4	8	9	4	1	3	2	14	22	6	3	15	2
	Week 12	5	11	5	2	8	2	8	22	2	14	12	2
	Month 6	5	9	8	2	10	4	7	23	8	15	17	4
	Month 12	5	7	10	1	5	5	9	14	8	16	15	4
	Month 18	5	11	7	2	12	0	9	14	8	18	23	5
	Month 24	6	8	10	1	8	4	10	18	25	14	19	8
Change from baseline*1	Primary registration	-1	-2	-3	0	1	2	-1	-8	3	-5	-5	-4
	Secondary registration	0	0	0	0	0	0	0	0	0	0	0	0
	Week 4	1	2	-3	0	-3	-2	3	5	0	-6	1	-2
	Week 12	-2	4	-2	1	2	-2	-3	5	-4	5	-2	-2
	Month 6	-2	2	1	1	4	0	-4	6	2	6	3	0
	Month 12	-2	0	3	0	-1	1	-2	-3	2	7	1	0
	Month 18	-2	4	0	1	6	-4	-2	-3	2	9	9	1
	Month 24	-1	1	3	0	2	0	-1	1	19	5	5	4

*1 Baseline was defined as the time of secondary registration.

The change from baseline in the MDS-UPDRS Part I total score showed an improvement of −1 at 24 months post-transplantation in 1 of 6 patients. Three other patients showed improvement at some time point between 4 weeks and 18 months post-transplantation; however, the changes from baseline at

Month 24 were +3, +2, and 0, respectively. The remaining 2 patients showed no improvement after transplantation, with changes from baseline at Month 24 of +1 and 0, respectively. All 6 patients showed improvement in the change from baseline in the MDS-UPDRS Part II total score at some time point between 4 weeks and 18 months post-transplantation; however, only 1 patient (PD02) demonstrated improvement at Month 24.

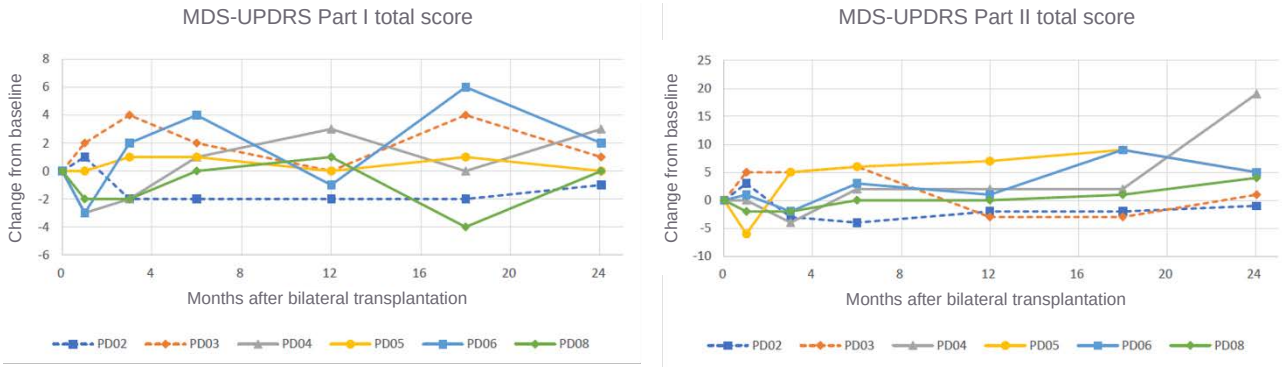

Figure 7. Change from baseline in MDS-UPDRS Part I total score and MDS-UPDRS Part II total score

(4) LEDD

Table 24 and Figure 8 show the results of levodopa equivalent daily dose (LEDD). LEDD decreased from baseline to 24 months post-transplantation in 3 of 6 patients (PD02, PD05, and PD08) and increased in the remaining 3 patients.

Table 24. List of patient-level results of LEDD

Item	Time point	Low-dose		High-dose			
		PD02	PD03	PD04	PD05	PD06	PD08
Observed value	Primary registration	1071.4	891.1	1464.0	1037.4	1248.0	861.0
	Secondary registration	1137.9	957.6	1276.5	839.4	1514.0	1027.5
	Week 4	1137.9	957.6	1276.5	839.4	1514.0	886.0
	Week 12	1137.9	957.6	1276.5	839.4	1514.0	923.5
	Month 6	1137.9	957.6	1396.5	789.4	1514.0	923.5
	Month 12	1018.2	1024.1	1558.5	839.4	1514.0	923.5
	Month 18	951.7	1024.1	1440.5	839.4	1514.0	971.4
	Month 24	951.7	1024.1	1573.5	779.6	1614.0	904.7
Change from baseline*1	Primary registration	-66.50	-66.50	187.50	198.00	-266.00	-166.50
	Secondary registration	0.00	0.00	0.00	0.00	0.00	0.00
	Week 4	0.00	0.00	0.00	0.00	0.00	-141.50
	Week 12	0.00	0.00	0.00	0.00	0.00	-104.00
	Month 6	0.00	0.00	120.00	-50.00	0.00	-104.00
	Month 12	-119.70	66.50	282.00	0.00	0.00	-104.00
	Month 18	-186.20	66.50	164.00	0.00	0.00	-56.10
	Month 24	-186.20	66.50	297.00	-59.85	100.00	-122.85

Unit: mg
*1 Baseline was defined as the time of secondary registration.

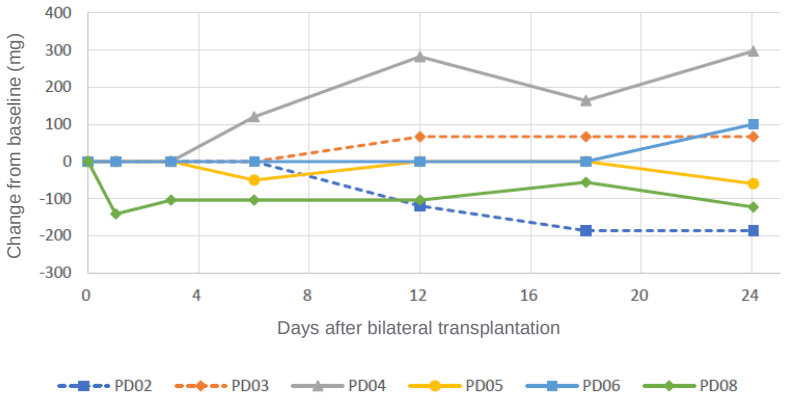

Figure 8. Change from baseline in LEDD

Table 25 shows the results of other major efficacy endpoints in the patient excluded from the efficacy analysis population (PD01).

Table 25. Results of other major efficacy endpoints (PD01)

Item	Time point	ON-state MDS-UPDRS Part III total score	ON-state H&Y stage	On time	Off time	Good on time	MDS-UPDRS Part I total score	MDS-UPDRS Part II total score	LEDD
Observed value	Primary registration	5	2	8.6	7.8	7.0	4	18	665.5
	Week 4[*2]	13	2	9.0	8.4	8.6	7	6	665.5
	Week 12[*2]	7	2	0.6	17.7	0.6	3	10	720.05
	Month 6[*2]	19	2	3.4	14.1	3.4	5	5	779.9
	Week 4[*3]	12	2	8.1	9.7	8.1	7	8	871.4
	Week 12[*3]	12	2	8.6	10.1	8.6	4	7	846.4
	Month 6[*3]	13	2	5.1	11.9	5.1	5	9	846.4
	Month 12[*3]	16	2	6.5	10.4	6.5	4	9	846.4
	Month 18[*3]	11	2	12.1	6.2	9.8	1	9	635.5
	Month 24[*3]	22	2	6.8	10.1	4.9	5	14	580.0
Change from baseline[*1]	Primary registration	0	0	0	0	0	0	0	0
	Week 4[*2]	8	0	0.4	0.6	1.6	3	-12	0
	Week 12[*2]	2	0	-8	9.9	-6.4	-1	-8	54.55
	Month 6[*2]	14	0	-5.2	6.3	-3.6	1	-13	114.4
	Week 4[*3]	7	0	-0.5	1.9	1.1	3	-10	205.0
	Week 12[*3]	7	0	0	2.3	1.6	0	-11	180.9
	Month 6[*3]	8	0	-3.5	4.1	-1.9	1	-9	180.9
	Month 12[*3]	11	0	-2.1	2.6	-0.5	0	-9	180.9
	Month 18[*3]	6	0	3.5	-1.6	2.8	-3	-9	-30
	Month 24[*3]	17	0	-1.8	2.3	-2.1	1	-4	-85.5

*1 Baseline was defined as the time of primary registration.
*2 After unilateral transplantation
*3 After contralateral transplantation

Among the 4 patients (PD02, PD03, PD04, and PD08) who were considered to have achieved a marked response, defined as an improvement of ≥5 points from baseline in the OFF-state MDS-UPDRS Part III total score at 24 months post-transplantation of AMCHEPRY, only 1 patient (PD02) showed improvement at 24 months post-transplantation in mean daily on time, off time, good on time, MDS-UPDRS Part I total score, and MDS-UPDRS Part II total score. No improvement was observed in the remaining 3 patients (PD03, PD04, and PD08). PMDA requested the applicant to explain the reasons for the above findings.

The applicant's response:
As an outcome measure for transplantation therapy with dopamine-producing cells, the OFF-state MDS-UPDRS Part III, which assesses motor function in the absence of anti-PD drugs, is considered most appropriate for evaluating the effects of endogenous dopamine produced and secreted by the transplanted cells (*Nat Med*. 2019;25:1045-53). On time and off time are commonly used indicators to evaluate the effects of anti-PD treatment, but they are influenced by the dosage, administration, and types of anti-parkinsonian drugs (hereinafter referred to as the "medication regimen"). In Study IACT16049-01, modification of the anti-PD medication regimen according to patients' motor symptoms was restricted in order to evaluate the effects of endogenous dopamine following transplantation of AMCHEPRY. Furthermore, on time and off time are subjective assessments evaluated by patients themselves, and their concordance with assessment indices evaluated by medical professionals, such as the MDS-UPDRS Part III, is not necessarily high (*NPJ Parkinsons Dis*. 2022;8:69-75; *Front Neurol*. 2022;13:935664). In addition, MDS-UPDRS Part IB within MDS-UPDRS Part I and MDS-UPDRS Part II are also subjective assessments completed by patients, similar to the evaluation of on time and off time, and are influenced by the anti-PD medication regimen.

For the above reasons, under the conditions of Study IACT16049-01, mean daily on time, off time, and good on time, as well as MDS-UPDRS Part I total score and MDS-UPDRS Part II total score, were not considered to have been adequately evaluated and did not correspond with the improvement observed in the OFF-state MDS-UPDRS Part III total score.

PMDA's view:
As explained by the applicant, improvement was observed in many patients in the OFF-state MDS-UPDRS Part III total score, which is considered the most appropriate endpoint for evaluating the efficacy of AMCHEPRY, and a trend toward improvement was also observed in the ON-state MDS-UPDRS Part III total score. Thus, AMCHEPRY can be expected to exhibit some efficacy in patients with PD. On the other hand, in addition to the OFF-state MDS-UPDRS Part III total score, improvement in indicators reflecting clinical symptoms in patients with PD, i.e., mean daily on time, off time, good on time, MDS-UPDRS Part I total score, and MDS-UPDRS Part II total score, was observed in only 1 of 6 patients, and most patients who achieved a marked response in the OFF-state MDS-UPDRS Part III total score did not show improvement in these measures. In the exploratory Study IACT16049-01, the primary objective was to evaluate endogenous dopamine production after transplantation of AMCHEPRY; adjustment of anti-PD drugs based on patients' motor symptoms was restricted, and the applicant's explanation that this restriction contributed to the findings is understandable. However, after marketing, there will be no restriction on modification of the anti-parkinsonian regimen. In patients with PD, in addition to motor symptoms assessed by physicians using the OFF-state MDS-UPDRS Part III total score, clinically important outcomes such as on time, off time, and the impact on activities of daily living should be confirmed.

6.R.2 Safety

PMDA evaluated the following adverse events as requiring attention in association with transplantation of AMCHEPRY, based on reports of clinical research in which human fetal ventral mesencephalic cells were transplanted into patients with PD (*N Engl J Med*. 2001;344:710-19; *Ann Neurol*. 2003;54:403-

14), as well as the package inserts of other cell-based products and anti-PD drugs: Dyskinesia, dystonia, and events of concern in dopamine replacement therapy (psychiatric symptoms due to excessive dopamine secretion, neuroleptic malignant syndrome, sudden onset of sleep, haemolytic anaemia, thrombocytopenia, malignant melanoma, and angle closure glaucoma), post-transplant graft overgrowth and tumorigenicity risk, and allergic reactions (including transplant rejection).

The applicant provided the following explanations about these risks, in Subsections (1) to (3):
(1) Dyskinesia, dystonia, and events of concern in dopamine replacement therapy
With respect to events related to dyskinesia (defined as adverse events coded to the standardised Medical Dictionary for Regulatory Activities [MedDRA] queries [SMQ] "Dyskinesia" [broad search]), dyskinesia occurred in 1 patient (PD0[redacted]). The severity was moderate, and the outcome was unrecovered; however, the event was assessed as unrelated to AMCHEPRY. Regarding events related to dystonia (defined as adverse events coded to the SMQ "Dystonia" [broad search]), dystonia occurred in 2 patients (PD01 and PD0[redacted]), and muscle tightness occurred in 1 patient (PD01). All events were mild in severity. The dystonia and muscle tightness observed in PD01 were both assessed as related to AMCHEPRY; such events were primarily observed during the ON state. Dystonia improved with treatment, and muscle tightness resolved without treatment; both events were manageable and reversible. The dystonia observed in PD0[redacted] resolved with treatment and was assessed as unrelated to AMCHEPRY. Dystonia and muscle tightness are occasionally observed during treatment with levodopa (*Ann Neurol* 1988;23:73-8). A clear association between AMCHEPRY and dystonia was not demonstrated.

The Unified Dyskinesia Rating Scale (UDysRS) during the ON state was used to evaluate dyskinesia. While 6 of 7 patients had a higher UDysRS total score at 24 months post-transplantation than at baseline, only 1 patient showed consistently higher scores than baseline at all post-transplantation time points; in the other patients, scores fluctuated above and below baseline without a consistent trend. Because dyskinesia observed in Study IACT16049-01 was mainly recorded during the ON state in patient-reported symptom diaries, it was suggested that these events were not graft-induced dyskinesia but rather drug-induced dyskinesia occurring during the ON state when anti-PD drugs were effective.

As psychiatric symptoms due to excessive dopamine secretion (defined as adverse events coded to the SMQ "Psychosis and psychotic disorders" [narrow search] and the preferred term (PT) "confusional state," "depressive symptom," "depressed mood," and "depression"), hallucination, olfactory occurred in 1 patient (PD0[redacted]). The event was mild in severity, and the event resolved without treatment. This event was assessed as unrelated to AMCHEPRY.

Among events of concern in dopamine replacement therapy, events related to neuroleptic malignant syndrome (defined as adverse events coded to the SMQ "Neuroleptic malignant syndrome" [broad search]) were dystonia in 2 patients (PD01 and PD0[redacted]), dyskinesia in 1 patient (PD0[redacted]), and pyrexia in 1 patient (PD0[redacted]). The pyrexia was mild in severity, resolved without treatment, and was assessed as unrelated to AMCHEPRY. No adverse event coded to the PT "neuroleptic malignant syndrome" occurred. The following other events of concern in dopamine replacement therapy were not observed, Sudden onset of sleep (PTs "sudden onset of sleep," "somnolence," "hypersomnia," "microsleep," "sleep disorder due to general medical condition, hypersomnia type," and "sleep attacks"), haemolytic

anaemia (PT “haemolytic anaemia”), thrombocytopenia (PT “platelet count decreased” and “thrombocytopenia”), malignant melanoma (SMQ “Non-haematological malignant tumours” [narrow search]), and angle closure glaucoma (PT “angle closure glaucoma” and “glaucoma”).

In conclusion, while dyskinesia, dystonia, and events of concern in dopamine replacement therapy were not identified as safety concerns in this clinical study, psychiatric symptoms due to excessive dopamine secretion may occur following transplantation of AMCHEPRY. The package insert and related materials will include precautions to ensure careful monitoring of patients’ conditions.

(2) Post-transplant graft overgrowth and tumorigenicity risk

Because the putamen, the site of transplantation, is anatomically adjacent to motor nerve fibers and compression due to graft overgrowth may cause neurological symptoms such as motor impairment, the volume of the transplanted tissue following transplantation of AMCHEPRY was evaluated by brain MRI in the 7 patients included in the safety analysis population. In the Study IACT16049-01 protocol, graft overgrowth was defined as a graft size exceeding 3 cm^3 on MRI at 24 months post-transplantation,[9)] and if the graft size did not exceed 3 cm^3, safety was considered to have been confirmed. Except for PD05, graft volume increased generally over time after transplantation in 6 patients, and while an increasing trend in graft volume was observed at 24 months post-transplantation, the rate of increase gradually attenuated [see Section 6.1.1.1, Table 16].

The primary reason for the time-dependent increase in graft volume is considered to be that the transplanted cells differentiated and matured into dopaminergic neurons, integrated with the host tissue within the putamen, and became more widely distributed beyond the transplantation site. In addition, elongation of neurites from dopaminergic neurons may have contributed to an increase in the overall volume occupied by the transplanted cells, including their processes. Graft volume in the brain showed an increasing trend over 24 months in Study IACT16049-01, but the mean fold increase in graft volume was 2.3-fold from 4 weeks to 12 months post-transplantation and 1.2-fold from 12 months to 24 months, indicating a decreasing trend of increase. Thus, the rate of graft enlargement beyond 24 months post-transplantation is expected to further decline. No graft enlargement exceeding 3 cm^3 was observed in any of the 7 patients.

Because the presence of undifferentiated cells or early neural cells in the transplanted cell population may be associated with tumor formation (*Stem Cells Dev*. 2016;25:815-25), tumorigenicity risk was also evaluated.

In the clinical study, no events related to tumor formation (defined as adverse events coded to the SMQ “Malignancies” [narrow search]) were observed.

In addition, PET using 3'-[18F]-fluoro-3'-deoxy-L-thymidine ([^{18}F]FLT[15)]) was performed to assess accumulation of [^{18}F]FLT at the transplantation site. No abnormal accumulation was observed in any patient at 6 months post-transplantation,[16)] suggesting no evidence of tumorigenicity of the graft.

In a biodistribution study of AMCHEPRY using 6-OHDA-induced PD model immunodeficient rats, the proportion of proliferative cells (Ki-67-positive cells, a marker of proliferating cells) within the intracerebral graft at 25 weeks post-transplantation was low (0.26% ± 0.29%) [see Section 4.1.2]. In a single-dose transplantation toxicity study in which AMCHEPRY was transplanted into the striatum of NOG mice, a subset of epithelial-like cells was Ki-67-positive (positive rate, 0.9% ± 1.23%); however, no findings indicative of tumorigenicity were observed up to the longest evaluation time point of 52 weeks in the tumorigenicity study of AMCHEPRY [see Section 5.2].

In the toxicity study in which AMCHEPRY was transplanted into NOG mice, epithelial-like cells and related structures considered to be choroid plexus epithelial cells were observed at the transplantation site in the AMCHEPRY group [see Sections 5.1 and 5.2]. Potential symptoms of adverse events caused by choroid plexus epithelial cells contained in AMCHEPRY may include neurological symptoms due to compression or damage to surrounding neural tissue; however, no corresponding adverse events were observed in Study IACT16049-01. Contamination with choroid plexus epithelial cells is not considered to pose safety concerns in humans.

Based on the results of the clinical study, no concerns regarding post-transplant graft overgrowth or tumorigenicity risk were identified. However, because AMCHEPRY is derived from iPS cells, the theoretical risk of graft overgrowth and tumor formation cannot be completely excluded. Accordingly, the package insert and related materials will state that AMCHEPRY should be used only in patients for whom transplantation is considered suitable, that appropriate monitoring such as periodic MRI should be performed after transplantation of AMCHEPRY, and that adequate measures should be taken if changes or symptoms occur.

(3) Allergic reactions (including transplant rejection)
As allergic reactions,[17)] eczema, nasopharyngitis, pyrexia, and chills occurred in 1 patient each; all events were mild in severity and were assessed as unrelated to AMCHEPRY.

Patients were assessed for neuroinflammation due to rejection after transplantation of AMCHEPRY, and PET using [^{18}F]GE180 was performed from 12 weeks post-transplantation, when acute rejection is generally expected to occur, to 16 months post-transplantation, corresponding to 1 month after completion of tacrolimus administration. As a result, no abnormal accumulation of [^{18}F]GE180 was observed in any patient after transplantation of AMCHEPRY, and no inflammatory findings suggestive

15) [^{18}F]FLT is a radiopharmaceutical consisting of an analogue of thymidine (component for DNA synthesis) labeled with fluorine-18 and was developed to evaluate cellular proliferative activity and nucleic acid synthesis. Because tumor cells exhibit higher proliferative capacity than normal cells, [^{18}F]FLT preferentially accumulates in tumor cells.
16) In the tumorigenicity study of AMCHEPRY, no tumor formation was observed at 39 weeks (9 months) or 52 weeks (12 months) post-transplantation [see Section 5.2]; therefore, PET was conducted at 6 months post-transplantation.
17) Events coded to the SMQ "Hypersensitivity" (narrow search) and the PTs "scratch," "swelling," "peripheral oedema," "pruritus," "acute respiratory failure," "bronchial obstruction," "chills," "flushing," "hypotension," "stridor," "throat tightness," "nasopharyngitis," "influenza like illness," "pyrexia," "hyperthermia," "autoimmune disorder," or "transplant rejection."

of rejection against the transplanted cells were identified. From 16 to 24 months post-transplantation, evaluation by MRI revealed no findings suggestive of rejection in any patient.

To evaluate the long-term safety of AMCHEPRY, of the 7 patients who received transplantation of AMCHEPRY, 6 are being assessed for safety beyond 2 years post-transplantation in an ongoing clinical research study. The remaining patient, PD0[redacted], died of aspiration pneumonia approximately 4 years and 3 months after transplantation of AMCHEPRY. As of October 31, 2025, the duration of time after transplantation of AMCHEPRY is >7 years in the first patient (PD01), >5 years in [redacted] patients (PD0[redacted], PD0[redacted], and PD0[redacted]), >4 years in [redacted] patient (PD0[redacted]), and >3 years in the seventh patient (PD0[redacted]). No serious adverse events related to AMCHEPRY, graft overgrowth, tumor formation, off-target cell proliferation, immune rejection, or other related findings have been reported.

Based on the above, the long-term safety profile of AMCHEPRY in patients with PD is considered acceptable.

PMDA's view:
In Study IACT16049-01, no deaths or serious adverse events were observed, and all adverse events considered related to the study treatment were mild in severity. Furthermore, evaluation of adverse events considered to require attention in association with transplantation of AMCHEPRY confirmed that no clinically significant concerns were identified. AMCHEPRY is considered tolerable provided that appropriate measures for transplantation of AMCHEPRY are taken by physicians with adequate knowledge and experience in stereotactic neurosurgery and use of AMCHEPRY, and that selection of eligible patients with PD and post-transplant management are undertaken by physicians with adequate knowledge and experience in the treatment of PD. However, because safety information on AMCHEPRY remains very limited, safety information should continue to be collected in the post-marketing setting and the obtained information should be appropriately provided to healthcare professionals.

6.R.3 Efficacy and safety of tacrolimus

In Study IACT16049-01, administration of tacrolimus as an immunosuppressant was specified [see Section 6.1.1.1].

The applicant's explanation about the clinical significance of immunosuppressants, the rationale for their selection, the basis for determining the dosage regimen in the clinical study, and the efficacy and safety of tacrolimus:

Clinical significance of immunosuppressants

Reports of experiments in non-human primates and clinical studies of cell transplantation using human fetal midbrain tissue have suggested that when cells with mismatched HLA are transplanted, rejection against the graft may occur (*Nat Commun*. 2017;8:385; *Ann Neurol*. 2003;54:403-14). Results of double-blind studies conducted in the US in human fetal ventral mesencephalic cell transplantation indicated that outcomes were unfavorable when immunosuppressants were not used or when the duration of administration was short (*N Engl J Med*. 2001;344:710-19; *Ann Neurol*. 2003;54:403-14). In addition, findings from human fetal ventral mesencephalic cell transplantation have indicated that

administration of immunosuppressants for ≥12 months is desirable (*Nat Rev Neurol*. 2015;11:492-503; *Cell Stem Cell*. 2017;21:569-73), and that after a certain period following transplantation, long-term graft survival may be achieved even without continued immunosuppressant therapy (*Arch Neurol*. 1999;56:179-87; *Nat Med*. 2008;14:507-9).

Based on the above, administration of an immunosuppressant from the day of transplantation of AMCHEPRY until 12 months post-transplantation was considered likely to suppress rejection and promote engraftment of AMCHEPRY.

Rationale for selecting tacrolimus as the immunosuppressant

In human fetal ventral mesencephalic cell transplantation, cyclosporine, azathioprine, and steroids were used in combination. Because such transplantation involves midbrain substantia nigra cells derived from multiple aborted fetuses, donors with multiple HLA types are presumed to be mixed. In contrast, AMCHEPRY is a cell product derived from a single donor and is thus considered to have lower immunogenicity than human fetal ventral mesencephalic cell transplantation. For this reason, tacrolimus, a calcineurin inhibitor with a mechanism of action similar to that of cyclosporine, was selected as monotherapy as the immunosuppressant to be used concomitantly with transplantation of AMCHEPRY.

Rationale for the dosage regimen of tacrolimus in the clinical study

Although distribution of tacrolimus into the brain is lower than into other tissues, it has been suggested that distribution may increase when the blood-brain barrier is disrupted. Therefore, in Study IACT16049-02, the dosage regimen of tacrolimus was determined with reference to the approved dosage and administration for suppression of rejection in organ transplantation, specifically the regimen for heart transplantation, which includes the lowest initial dose option. Tacrolimus was initiated and maintained at 0.03 to 0.15 mg/kg per dose, administered orally twice daily, with dose adjustments made as appropriate based on blood concentrations.

Efficacy and safety of tacrolimus

The efficacy and safety of tacrolimus were evaluated in Study IACT16049-02. All 7 patients in the safety analysis population received tacrolimus. Three patients were fully matched with AMCHEPRY with respect to HLA type, and 4 patients were partially matched [see Section 6.1.1.1, Table 14].

Efficacy data were analyzed in the 6 patients included in the efficacy analysis population, and the cumulative rejection suppression rate (non-occurrence rate) at 12 weeks and 12 months after transplantation of AMCHEPRY was 100% [see Section 6.1.1.2].

Safety data were analyzed, and adverse reactions to tacrolimus were observed in 3 of the 7 patients in the safety analysis population. All events were mild in severity [see Section 6.1.1.2].

There was no trend towards differences in efficacy or safety between patients who were fully matched and those who were partially matched with respect to HLA type of AMCHEPRY.

Based on the above, use of tacrolimus as the immunosuppressant in the transplantation of AMCHEPRY is considered appropriate.

PMDA's view:
Based on published literature, the applicant's explanation that administration of tacrolimus prior to transplantation of AMCHEPRY is expected to suppress rejection and promote engraftment of AMCHEPRY is understandable. In Study IACT16049-02, tacrolimus was administered orally from the morning of the day of transplantation of AMCHEPRY in all 6 patients in the efficacy analysis population; no rejection of AMCHEPRY was observed, and engraftment of AMCHEPRY was confirmed. Regarding safety, no particular concerns requiring special attention have been identified to date, and tacrolimus was considered tolerable. There are no clinical data directly comparing the efficacy and safety of AMCHEPRY with and without concomitant tacrolimus available, and the incidence of rejection in the absence of tacrolimus remains unknown. However, considering the potential risk of rejection if tacrolimus is not administered, administration of tacrolimus is recommended in the transplantation of AMCHEPRY.

6.R.4 Clinical positioning

The applicant's explanation about the expected clinical positioning of AMCHEPRY:
The intended population for AMCHEPRY comprises patients with PD who exhibit motor complications and whose motor symptoms are insufficiently controlled with conventional pharmacotherapy, including those who may be candidates for device-aided therapy, as well as patients with PD in whom frequent administration of levodopa or dose escalation of other anti-PD drugs is undertaken prior to consideration of device-aided therapy.

PD is a chronic and progressive neurodegenerative disorder caused by a deficiency of the neurotransmitter dopamine, and motor symptoms markedly impair activities of daily living. The mainstay of treatment is dopamine replacement therapy to supplement reduced dopaminergic function in the brain; however, this approach is symptomatic and does not suppress disease progression. As the disease progresses, pharmacotherapy becomes insufficient and device-aided therapy is considered; however, device-aided therapy is also symptomatic and does not modify the underlying disease process. In addition, maintenance of responsiveness to levodopa is essential for device-aided therapy to exert its effect, and diminished levodopa responsiveness is associated with reduced therapeutic benefit of device-aided therapy. DBS, one of the device-aided therapies, has been reported to potentially affect cognitive function. Furthermore, adverse reactions associated with the surgical procedure required for implantation of DBS must be taken into account when determining whether to use the therapy. Management of the implanted neurostimulation device is also required. For LCIG therapy and continuous subcutaneous levodopa infusion therapy, device management is necessary, and complications such as gastrostomy-related problems and infections at the infusion site have been reported.

AMCHEPRY is a cell-based product containing aggregates of dopaminergic progenitor cells derived from iPS cells generated from peripheral blood mononuclear cells of a healthy adult donor. Transplantation of AMCHEPRY is expected to exert a disease-modifying effect by replenishing

dopaminergic neurons and restoring dopaminergic function in the nigrostriatal pathway, thereby addressing the fundamental pathology of PD characterized by loss of dopaminergic neurons and consequent dopaminergic dysfunction, and potentially improving the progression of motor symptoms themselves. In contrast to device-aided therapy, AMCHEPRY does not require maintenance of an implanted device, and administration of immunosuppressants is likely to be completed after a defined period, thereby reducing the burden on patients, family members, and healthcare professionals.

Based on the above, AMCHEPRY is expected to provide a disease-modifying effect that improves the underlying motor symptom pathology, which is not achieved by conventional pharmacotherapy or device-aided therapy. In addition to restoring dopaminergic function, AMCHEPRY is expected to maintain or enhance the efficacy of conventional dopamine replacement therapy and to address treatment-related challenges associated with device-aided therapy, such as routine device management. Accordingly, AMCHEPRY is anticipated to represent a novel therapeutic option for patients with PD whose motor symptoms are inadequately controlled with conventional pharmacotherapy.

PMDA accepted the applicant's explanation described above.

6.R.5 Indication or performance

At the time of application, the "Indications or Performance" and "Precautions Concerning Indications or Performance" of AMCHEPRY were specified as follows.

Indication or Performance

Improvement of OFF-state motor symptoms in patients with advanced Parkinson's disease

Precautions Concerning Indication or Performance

1. AMCHEPRY should be used in patients who exhibit motor complications and have an inadequate response to conventional pharmacotherapy.
2. AMCHEPRY should be used in patients who have tolerability and therapeutic responsiveness to levodopa-containing drug products.
3. The Clinical Studies section, including the baseline characteristics of patients enrolled in the clinical studies, should be carefully reviewed, and AMCHEPRY should be used only if the expected therapeutic benefits outweigh the possible risks associated with treatment, based on a thorough understanding of the efficacy and safety of AMCHEPRY (see Section 17.1.1).

On the basis of reviews in Sections "6.R.1 Efficacy," "6.R.2 Safety," "6.R.4 Clinical positioning," and the review described below, PMDA concluded that the "Indications or Performance" and "Precautions Concerning Indications or Performance" for AMCHEPRY should be specified as follows.

Indication or Performance (Underline denotes additions and strikethrough denotes deletions.)

Improvement of ~~OFF-state~~ motor symptoms in patients with ~~advanced~~ Parkinson's disease who have an inadequate response to conventional pharmacotherapies, including levodopa-containing drug products

Precautions Concerning Indications or Performance (Underline denotes additions and strikethrough denotes deletions.)

1. ~~AMCHEPRY should be used in patients who exhibit motor complications and have an inadequate response to conventional pharmacotherapy.~~

~~2.~~ AMCHEPRY should be used in patients <u>with motor symptoms</u> who have tolerability and therapeutic responsiveness to levodopa-containing drug products.

~~3~~<u>2. Eligible patients should be selected</u> <u>by physicians with adequate knowledge of the "17.</u> ~~The~~ Clinical Studies" section, including the baseline characteristics of patients enrolled in the clinical studies, ~~should be carefully reviewed,~~ and ~~AMCHEPRY should be used only if the expected therapeutic benefits outweigh the possible risks associated with treatment, based on~~ a thorough understanding of the efficacy and safety of AMCHEPRY (see Section 17.1.1).

6.R.5.1 Patients with PD eligible for treatment with AMCHEPRY

The applicant's explanation:

Given the mechanism of action of AMCHEPRY, the most important prerequisite for expecting a therapeutic effect is responsiveness to levodopa. In Study IACT16049-01, 2 patients (PD05 and PD06) who were not classified as showing a marked response based on the OFF-state MDS-UPDRS Part III total score included 1 patient (PD05) who was older at the time of informed consent (69 years) than the other patient, and both patients had more advanced motor symptoms at baseline than the others. Severity of motor symptoms attributable to non-dopaminergic neurodegeneration associated with progression of disease pathology and aging are considered important factors influencing levodopa responsiveness.

Regarding age, improvement in the OFF-state UPDRS Part III total score after transplantation of human fetal midbrain substantia nigra cells was smaller in patients aged >60 years than in those aged ≤60 years (*N Engl J Med*. 2001;344:710-9; *Ann Neurol*. 2003;54:403-14). Based on the above reports, the insufficient efficacy observed in the oldest patient in Study IACT16049-01, and the fact that age may reflect severity of motor symptoms and disease progression in PD, age may be considered a predictive factor for attenuation of treatment effect. However, efficacy cannot be excluded in all elderly patients. Because eligibility for transplantation should be determined based on the individual patient's disease status, elderly patients should not be categorically excluded. In Study IACT16049-01, patients aged ≥70 years at the time of informed consent were excluded, and there is no clinical experience with transplantation in patients aged >70 years. A precaution should be provided in the package insert to that effect. For patients aged >70 years, AMCHEPRY should be used only if the anticipated benefits of transplantation outweigh the potential risks, taking into account the precaution in the package insert. PD commonly develops at ≥50 years of age but, given the mechanism of action of AMCHEPRY, restoration of dopaminergic function and improvement in motor symptoms following transplantation of AMCHEPRY may also be expected in patients with onset at <50 years of age. Patients aged <50 years should not be excluded from the indicated population.

With regard to the severity of motor symptoms, improvement in the OFF-state UPDRS Part III total score after transplantation of human fetal midbrain substantia nigra cells was smaller in patients with a baseline score ≥50 than in those with a baseline score ≤49 (*Ann Neurol*. 2003;54:403-14). However, in Study IACT16049-01, a patient with a baseline score of 71 (PD04) was judged to have shown a marked

response. Thus, a high baseline OFF-state MDS-UPDRS Part III total score does not preclude efficacy in all patients, and restriction of eligibility based solely on this score is considered unnecessary. Regarding H&Y stage, Study IACT16049-01 enrolled patients with advanced PD with an OFF-state H&Y stage ≥3 and levodopa responsiveness. However, some patients with OFF-state H&Y stage 2 may exhibit motor symptoms and motor complications comparable to those with stage 3. Furthermore, reports have suggested that patients with less severe motor symptoms may derive greater benefit from cell transplantation therapy (*Ann Neurol*. 2003;54:403-14; *Prog Brain Res*. 2012;200:169-98). This suggests that patients with OFF-state H&Y stage 2 may also be expected to benefit from transplantation of AMCHEPRY. Given that patients with OFF-state H&Y stage 1 have unilateral motor symptoms with no or only minimal impairment in daily living and transplantation of AMCHEPRY is an invasive procedure requiring concomitant use of immunosuppressants, such patients should not be considered candidates for transplantation, taking into account the balance of benefit and risk; this information will be provided in information materials.

PMDA's view:
Regarding the Indications or Performance, it is necessary to clarify that the target population comprises patients who have not responded adequately to conventional pharmacotherapy, including levodopa-containing drug products. In addition, because improvement was also observed both in the OFF-state and the ON-state MDS-UPDRS Part III total scores in Study IACT16049-01 [see Table 21 in Section 6.R.1.2.2], it is appropriate to delete wording that limits the indication to the OFF-state conditions.

Regarding age, the applicant's explanation that the association between age and severity of motor symptoms may vary among patients and eligibility should not be uniformly restricted based solely on age is understandable. A precaution should be provided in the package insert stating that there is no clinical experience in patients aged >70 years and that transplantation should be performed only if the anticipated therapeutic benefit outweighs the potential risks.

With regard to the severity of motor symptoms eligible for treatment with AMCHEPRY, progression of PD pathology may lead to attenuation of treatment effect due to non-dopaminergic neurodegeneration and associated non-motor symptoms. However, in Study IACT16049-01, improvements in the OFF-state MDS-UPDRS Part III total score and Bradykinesia subscale was observed through 24 months after transplantation even in patients with high baseline scores. The applicant's explanation that restriction based solely on the OFF-state MDS-UPDRS Part III total score is unnecessary is understandable. Although Study IACT16049-01 enrolled patients with OFF-state H&Y stage ≥3, patients with OFF-state H&Y stage 2 who exhibit motor symptoms inadequately controlled with conventional therapy receive similar treatments as those with H&Y stage ≥3. Therefore, the applicant's explanation that it is meaningful to consider patients with OFF-state H&Y stage 2 as candidates for AMCHEPRY is understandable.

Because transplantation of AMCHEPRY is an invasive procedure, careful patient selection and thorough consideration of the benefit-risk balance are essential. It is appropriate to provide detailed information regarding the target population in information materials. In addition, the target population should be re-evaluated based on the results of post-marketing clinical studies and use-results surveys.

6.R.6 Dosage and administration or method of use

The proposed "Dosage and Administration or Method of Use" of AMCHEPRY at the time of submission of an application was as follows.

Dosage and Administration or Method of Use

The usual adult dosage is approximately 5.4×10^6 dopaminergic neuronal progenitor cells derived from allogeneic iPS cells administered per hemisphere into the bilateral putamen (approximately 10.8×10^6 cells in total).

The applicant's explanation about the dose-response relationship for efficacy:

Qualitative assessment indicated accumulation of [^{18}F]FDOPA in all patients (2 in the low-dose group and 4 in the high-dose group). However, quantitative evaluation of [^{18}F]FDOPA uptake using Ki values demonstrated no marked change in the putamen transplanted with AMCHEPRY in the low-dose group, whereas an increasing trend was observed in the high-dose group. The Ki putamen/caudate ratio (bilateral mean) increased to a greater extent in the high-dose group compared with the low-dose group [see Table 17 in Section 6.R.1.2.1]. The above findings suggest that, compared with the low-dose group, a greater number of dopaminergic progenitor cells engrafted, differentiated, and matured at the transplantation site in the high-dose group, thereby exerting functional activity as dopaminergic neurons.

With respect to efficacy endpoints related to motor symptoms, no clear dose-response relationship was identified. However, for the OFF-state MDS-UPDRS Part III total score at 24 months after transplantation, decreases from baseline were observed in all 2 patients in the low-dose group and in 2 of 4 patients in the high-dose group; in 2 patients in the high-dose group, the magnitude of change was particularly marked. Of the 2 patients in the high-dose group who did not show a decrease from baseline at 24 months, 1 patient (PD06) exhibited improvements of −16 at Week 12, −9 at Month 6, −3 at Month 12, and −4 at Month 18, but worsened to +3 at Month 24. The result at Month 24 was considered attributable to disease progression. Since improvement had been maintained through 18 months after transplantation, these results demonstrated some efficacy in this patient as well, and the efficacy of AMCHEPRY at the high dose was be expected.

Based on the above, given that the mechanism of action of AMCHEPRY is to replenish lost dopaminergic neurons and restore dopaminergic function, it was considered that a greater number of transplanted cells would result in greater engraftment and functional expression of dopaminergic neurons, thereby leading to improved efficacy. Accordingly, the high-dose group in Study IACT16049-01 and the maximum feasible dose for transplantation under the specified surgical procedure, approximately 10.8×10^6 cells, were considered appropriate.

PMDA accepted the above explanation provided by the applicant.

PMDA considers that the description should be modified to specify the transplantation procedure for AMCHEPRY and administration of tacrolimus as an immunosuppressant at the time of transplantation should be stipulated as part of the Dosage and Administration or Method of Use of AMCHEPRY.

PMDA concluded that the "Dosage and Administration or Method of Use" of AMCHEPRY should be defined as specified in Study IACT16049-01, and described as follows.

Dosage and Administration or Method of Use (Underline denotes additions and strikethrough denotes deletions.)

1. Transplantation of AMCHEPRY

~~The usual~~ Usually, in adults, AMCHEPRY consisting of allogeneic iPS cell-derived dopaminergic progenitor cells is transplanted stereotactically using an invasive cranial fixation device for neurosurgical procedures ~~dosage is approximately 5.4×10^6 dopaminergic neuronal progenitor cells derived from allogeneic iPS cells administered per hemisphere~~ into the bilateral putamen ~~(approximately 10.8×10^6 cells in total)~~, with a target of 5.4×10^6 cells per hemisphere. The cells are administered through 3 injection tracts passing through a single burr hole in the skull, and approximately 1.8×10^6 cells per tract are transplanted into 6 to 9 sites at intervals of 1 to 2 mm. The infusion rate is approximately 0.1 μL/sec.

2. Administration of tacrolimus hydrate before and after transplantation of AMCHEPRY for the purpose of suppressing immune responses to AMCHEPRY

Usually, tacrolimus is initially administered orally at a dose of 0.03 to 0.15 mg/kg twice daily starting in the morning of the transplantation day. Thereafter, the dose should be adjusted to maintain the blood tacrolimus trough level in the range of 5 to 10 ng/mL while monitoring the blood trough level.

If rejection is observed, the trough blood tacrolimus level should be maintained in the range of 10 to 20 ng/mL.

As a general rule, approximately 1 year after the start of tacrolimus administration, the dose should be gradually tapered over the subsequent 12 weeks and then discontinued; however, the duration of administration may be extended as necessary.

7. Risk Analysis and Outline of the Review Conducted by PMDA

7.1 Post-marketing investigations

The applicant explained regarding the post-marketing clinical study and use-results survey to be conducted after marketing authorization, with the objectives of continuing to confirm the efficacy of AMCHEPRY and collecting additional safety information within a specified period as follows:

7.1.1 Post-marketing clinical study

Given the limitations of the efficacy evaluation based on Study IACT16049-01, which was conducted as an exploratory study, and the currently limited evaluation of the efficacy of AMCHEPRY, a post-marketing clinical study intended to evaluate in a verifiable manner the efficacy of AMCHEPRY was planned as outlined in Table 26.

Table 26. Outline of the post-marketing clinical study (draft)

Objective	Primary objective: To verify the efficacy of AMCHEPRY transplanted into the putamen in eligible patients aged ≤65 years in the main cohort. Secondary objectives: To evaluate the efficacy of AMCHEPRY transplanted into the putamen in eligible patients aged >65 years with PD in the sub-cohort. To evaluate the safety of AMCHEPRY transplanted into the putamen in eligible patients in both the main cohort and the sub-cohort.
Study design	Open-label, uncontrolled, multicenter study
Target population	Patients with PD who have an inadequate response to conventional pharmacotherapy, including levodopa-containing drug products
Observation period	96 weeks after transplantation of AMCHEPRY (with a separate 4-week baseline assessment period)
Target sample size	[Main cohort]: 30 patients aged ≤65 years Assuming an expected change from baseline in the OFF-state MDS-UPDRS Part III total score at 96 weeks after transplantation of −12 to −9[*1] based on Study IACT16049-01, and a standard deviation of 19 based on Study IACT16049-01 and the natural history of PD, the required sample size to detect the effect of AMCHEPRY by a one-sample t-test with two-sided significance level of 5% and 90% power, compared with a threshold[*2] of +4.0 points above that derived from the natural history of PD, was calculated to be 17 to 25 patients. Considering potential dropouts, the target sample size was 30 patients. [Sub-cohort]: 5 patients aged >65 years Assuming an expected change from baseline in the OFF-state MDS-UPDRS Part III total score at 96 weeks after transplantation of −5, which would be considered clinically meaningful, and a standard deviation of 16 based on the natural history of PD, the required sample size for which the probability that the expected mean would fall below the threshold[*2] of +2.5 points above that derived from the natural history of PD would be approximately 85% was calculated to be 5 patients. Accordingly, the target sample size was 5 patients.
Number of study sites	6-10 sites
Primary efficacy endpoint[*3]	Change from baseline in the OFF-state MDS-UPDRS Part III total score at 96 weeks after transplantation of AMCHEPRY
Statistical analysis of the primary endpoint	[Main cohort] Using MMRM assuming an unstructured covariance matrix, with evaluation time points (48 and 96 weeks after transplantation of AMCHEPRY) and the baseline OFF-state MDS-UPDRS Part III total score as covariates, the least-squares mean and its 95% CI at 96 weeks after transplantation will be calculated. If the upper limit of the 95% CI is below the threshold[*2] of +4.0 points above that derived from the natural history of PD, the efficacy of AMCHEPRY in patients aged ≤65 years will be considered demonstrated. [Sub-cohort] If the efficacy of AMCHEPRY is demonstrated in the main cohort, the mean change from baseline in the OFF-state MDS-UPDRS Part III total score at 96 weeks after transplantation of AMCHEPRY (with missing values imputed using LOCF) will be calculated. If the mean value is below the threshold[*2] of +2.5 points above that derived from the natural history of PD, the efficacy of AMCHEPRY in patients aged >65 years will be considered demonstrated.

Major secondary efficacy endpoints[*3,*4]	• OFF-state MDS-UPDRS Part III: Number and proportion of patients with treatment response or marked response - Number and proportion of patients with an improvement of ≥5 points from baseline in the total score at 96 weeks after transplantation of AMCHEPRY. In the main cohort, the proportion of responders will be compared with a threshold of 15% based on the natural history of PD. - Number and proportion of patients with an improvement of ≥10 points from baseline in the total score at 96 weeks after transplantation of AMCHEPRY. In the main cohort, the proportion of responders will be compared with a threshold of 10% based on the natural history of PD. • MDS-UPDRS Part III total score (ON-state and OFF-state) - Change and percent change from baseline at each evaluation time point [Main cohort only] - Number and proportion of patients with an improvement of ≥5 points from baseline at each time point - Number and proportion of patients with an improvement of ≥10 points from baseline at each time point - Number and proportion of patients with a worsening of ≥5 points from baseline at each time point - Number and proportion of patients with a worsening of ≥10 points from baseline at each time point • MDS-UPDRS Part II total score (ON-state) - Change from baseline in the total score at each evaluation time point • MDS-UPDRS Part I, II, and III (all ON-state) total scores, and MDS-UPDRS Part I and II (ON-state) and Part III (OFF-state) total scores - Change and percent change from baseline in the total score at each evaluation time point • MDS-UPDRS Part II and III (both ON-state) total scores, and MDS-UPDRS Part II (ON-state) and Part III (OFF-state) total scores - Change and percent change from baseline in the total score at each evaluation time point • MDS-UPDRS Part I (ON-state), Part II (ON-state), Part III (ON-state), Part III (OFF-state), and Part IV - Change from baseline in individual item scores at each evaluation time point • Bradykinesia subscale (OFF-state) - Change and percent change from baseline in the sum of the following items at each evaluation time point: 3.1 speech, 3.2 facial expression, 3.4 finger tapping, 3.5 hand movements, 3.8 leg agility, and 3.14 global spontaneity of movement (body bradykinesia) • H&Y stage (ON-state and OFF-state) - Change from baseline in the H&Y stage (ON-state and OFF-state) at each evaluation time point [Main cohort only] - Number and proportion of patients with an improvement of ≥1 stage from baseline at each time point - Number and proportion of patients with an improvement of ≥2 stages from baseline at each time point - Number and proportion of patients with a worsening of ≥1 stage from baseline at each time point - Number and proportion of patients with a worsening of ≥2 stages from baseline at each time point • Mean daily off time, good on time, and on time - Change from baseline in mean daily on time, good on time,[*5] and off time normalized to a standard waking hour of 16 hours per day • PDQ-39 - Changes from baseline in the PDQ-39 Summary Index score and domain scores at each evaluation time point • PGI and CGI - Changes from baseline in PGI-C, CGI-I, and CGI-S scores at each evaluation time point • [^{18}F]FDOPA uptake - Change from baseline in uptake at the transplantation site of AMCHEPRY (striatum, putamen, caudate nucleus) at each evaluation time point [Main cohort] - Number and proportion of patients judged to have uptake at the transplantation site of AMCHEPRY at each evaluation time point [Sub-cohort] - Presence or absence of uptake at the transplantation site of AMCHEPRY, and number and proportion of patients judged to have uptake at each evaluation time point
Other endpoints	• Status of anti-PD medications
Safety endpoints	• Adverse events and deficiencies • Presence or absence of graft overgrowth in the brain (≥3 cm^3) and graft size as assessed by brain MRI • UDysRS • 12-lead electrocardiogram, laboratory test values, immunological tests, vital signs, and body weight

*1 In the efficacy analysis population of 6 patients in Study IACT16049-01, the change from baseline in the OFF-state MDS-UPDRS Part III total score at Month 24 was −9.5 (13.79) (mean [SD]). Among these, in the 5 patients who were ≤65 years of age at baseline, the change from baseline in the OFF-state MDS-UPDRS Part III total score at Month 24 was −12.4 (13.22) (mean [SD]). Based on these results and the absence of reference values for patients aged <50 years in the main cohort, the expected value was given in a range.

*2 Based on the PPMI database, a large-scale global natural history observational study of PD, the mean change [95% CI] in the OFF-state MDS-UPDRS Part III total score at 2 years was +6.0 points [+4.0 to +8.1 points] in a population similar to the main cohort of the post-marketing clinical study and +4.5 points [+2.5 to +6.5 points] in a population similar to the sub-cohort. Accordingly, the lower bound of the 95% CI was used to define the threshold.

*3 OFF-state assessments for efficacy endpoints will be conducted in the practically defined off state, after withholding levodopa drug products for ≥12 hours and other anti-PD medications (including dopamine receptor agonists and monoamine oxidase B inhibitors) for the specified periods.

*4 Evaluation time points are as follows: MDS-UPDRS Part III (OFF-state), H&Y stage (OFF-state), and [^{18}F]FDOPA uptake at 48 and 96 weeks after transplantation of AMCHEPRY; MDS-UPDRS Part I, II, and III (ON-state), MDS-UPDRS Part IV, H&Y stage (ON-state), mean daily on time, good on time, off time, Parkinson's Disease Questionnaire-39 (PDQ-39), patient global impression of change (PGI-C), clinical global impression of improvement (CGI-I), and clinical global impression of severity (CGI-S) at 4, 12, 24, 48, 72, and 96 weeks after transplantation of AMCHEPRY. However, [^{18}F]FDOPA uptake at 48 weeks after transplantation of AMCHEPRY will be evaluated in patients in whom PET imaging can be performed within the specified period.

*5 Mean daily on time without troublesome dyskinesia that interferes with activities of daily living.

The rationale for the post-marketing clinical study plan is as follows.

Implementation as a post-marketing clinical study

One of the mechanisms of action of AMCHEPRY is an increase in endogenous dopamine produced and secreted by engrafted dopaminergic neurons. To evaluate this effect, assessment must be performed in the "practically defined off" state, after withholding levodopa drug products for ≥12 hours and other anti-PD medications (including dopamine receptor agonists and monoamine oxidase B inhibitors) for the specified periods. Evaluation in a state without anti-PD medications imposes a substantial burden on patients with PD and is difficult to conduct in routine clinical practice. In order to perform assessments in the "practically defined off" state, the efficacy of AMCHEPRY will be evaluated in a post-marketing clinical study.

Study design

For the following reasons, the study is designed as an uncontrolled, single-arm study without an internal control group:

- Establishing a sham surgery group as an internal control would raise concerns regarding risks associated with invasive procedures that are not intended for therapeutic benefit, as well as disease progression during the evaluation period.
- Establishing a standard-of-care group as an internal control would impose a substantial burden on patients, as efficacy assessments in the OFF state under periodic hospitalization over a long duration of 96 weeks would be required, potentially affecting willingness to participate in and continue the clinical study.
- The Parkinson's Progression Markers Initiative (PPMI) database, derived from a large-scale global natural history observational study of PD conducted mainly in Europe and the US, contains patient characteristics and OFF-state MDS-UPDRS Part III total scores and the information is available. By setting an appropriate threshold using the PPMI, it is considered possible to verify the efficacy of AMCHEPRY in a single-arm study.

Target population

The target population comprises all patients with PD who are eligible for AMCHEPRY [see Section 6.R.5.1].

Primary endpoint and statistical analysis

The primary endpoint is the change from baseline in the OFF-state MDS-UPDRS Part III total score, which was a key efficacy endpoint in Study IACT16049-01. The evaluation time point is 96 weeks after transplantation of AMCHEPRY, consistent with Study IACT16049-01.

In addition, considering the mechanism of action of AMCHEPRY, it is likely that adequate efficacy may not be achieved in patients whose motor symptoms are predominantly attributable to non-dopaminergic neurodegeneration. Given that age is a predictor of non-dopaminergic neurodegeneration, patients aged ≤65 years were defined as the main cohort to verify the efficacy of AMCHEPRY. On the other hand, efficacy of AMCHEPRY may also be expected in patients aged >65 years if non-dopaminergic neurodegeneration has not progressed or if motor symptoms attributable to non-dopaminergic neurodegeneration have not yet become manifest; accordingly, patients aged >65 years were defined as the sub-cohort. Because the manufacturing capacity of AMCHEPRY is limited, patient enrollment will first be conducted in the main cohort, in which efficacy is more strongly expected, to ensure the sample size required for hypothesis testing. After completion of enrollment in the main cohort, enrollment in the sub-cohort will begin. However, considering the time limit associated with the conditional and time-limited approval, the sub-cohort will enroll 5 patients from the perspective of feasibility, and efficacy will be evaluated based on comparison between the threshold and the point estimate.

7.1.2 Use-results survey

A use-results survey was planned, as shown in Table 27, to evaluate the safety and efficacy of AMCHEPRY in clinical use in all patients who receive transplantation of AMCHEPRY (patients who receive transplantation of AMCHEPRY in the post-marketing clinical study will be registered after completion or discontinuation of evaluation in the post-marketing clinical study). Until completion of enrollment in the post-marketing clinical study, patient enrollment into the post-marketing clinical study will be prioritized.

Table 27. Outline of the use-results survey (draft)

Objective	Evaluation of the safety and efficacy of AMCHEPRY in clinical use
Target population	All patients who receive transplantation of AMCHEPRY (patients who receive transplantation of AMCHEPRY in the post-marketing clinical study will be registered after completion or discontinuation of evaluation in the post-marketing clinical study)
Registration and survey period	From the initiation of registration until the date on which a regulatory decision is made on an application for standard marketing approval to be submitted within the specified period of the conditional and time-limited approval
Observation period	From the date of transplantation of AMCHEPRY until the date on which a regulatory decision is made on an application for standard marketing approval to be submitted within the specified period of the conditional and time-limited approval
Planned sample size	All patients who receive transplantation of AMCHEPRY during the registration period (expected number of patients: 90-130)
Main survey items	Adverse events and deficiencies occurring from transplantation of AMCHEPRY up to 1 year after transplantation Serious adverse events and key survey items occurring ≥1 year after transplantation of AMCHEPRY Key survey items: Infections, tumorigenicity (including neurological deficits due to graft overgrowth), hypersensitivity (allergic reactions), rejection, and psychiatric symptoms due to excessive dopamine secretion Status of anti-PD medications, concomitant therapies for PD (non-pharmacological), overall improvement, H&Y stage (ON-state and OFF-state[*1]), mean daily on time, good on time, and off time

*1 A condition in which, despite taking anti-PD medications, the patient experiences symptoms such as sluggishness, bradykinesia, or tremor and feels that the medication does not provide adequate benefit.

7.R Outline of the review conducted by PMDA

PMDA's view on the post-marketing clinical study and the use-results survey plans submitted by the applicant:

Given that the current evaluation of the efficacy of AMCHEPRY is extremely limited, the applicant's policy to conduct a post-marketing clinical study to verify the efficacy of AMCHEPRY after the market launch is considered appropriate.

With respect to the design of the post-marketing clinical study, in an open-label setting, the possibility of bias in the results due to expectations of the patient or physician regarding AMCHEPRY cannot be excluded. To ensure objectivity of evaluation in the post-marketing clinical study, a randomized, double-blind, parallel-group design would in principle be appropriate. On the other hand, the applicant's explanation that it is difficult in Japan to establish a sham surgery group or a standard-of-care group as a control group in the post-marketing setting is understandable. Considering that disease progression would occur in the control group during the 96-week evaluation period and that periodic long-term OFF-state evaluations would impose a burden on patients, it is considered unavoidable to adopt a single-arm study design in which the efficacy of AMCHEPRY is verified by comparison between a predefined threshold and the change from baseline in the OFF-state MDS-UPDRS Part III total score.

Regarding efficacy evaluation of AMCHEPRY, the change from baseline in the MDS-UPDRS Part III total score (off-state) is widely used as a principal indicator for assessment of disease status in patients with PD (e.g., *Mov Disord*. 2008;23:2129-70; *N Engl J Med*. 2022;387:421-32). Use of the change from baseline in the OFF-state MDS-UPDRS Part III total score at 96 weeks after transplantation of AMCHEPRY as the primary endpoint is appropriate. PMDA considered it acceptable to establish the threshold based on PPMI, a database of a natural history observational study of PD, for the following reasons.

- The possibility of a placebo effect associated with surgical procedures for use of AMCHEPRY cannot be excluded, but reports indicate that placebo effects do not persist long in the absence of actual therapeutic benefit (*Arch Gen Psychiatry*. 2004;61:412-20; *Lancet Neurol*. 2011;10:509-19). This suggests that, at Week ≥96, the efficacy of AMCHEPRY is evaluable by comparison with a threshold established using the PPMI.
- There are few reports regarding placebo effects at Week 96. In a review article reporting a meta-analysis of sham surgery effects (*J Parkinsons Dis*. 2022;12:759-71), the weighted mean change [95% CI] from baseline in the OFF-state UPDRS Part III total score was −4.3 [−3.1 to −5.6], with a mean observation period [SD] of 11.3 [5.8] months. Because this differs from the evaluation period of AMCHEPRY, the appropriateness of adopting this value as a threshold is unclear.

In addition, considering that placebo effects associated with surgical procedures may remain to some extent together with the effects of cell transplantation, evaluation of the change from baseline on an individual-patient basis is also considered important. Thus, not only the primary endpoint but also the secondary endpoints, i.e., the number and proportion of patients with an improvement of ≥5 points (or ≥10 points) from baseline in the OFF-state MDS-UPDRS Part III total score at 96 weeks after transplantation of AMCHEPRY, are considered important for evaluation of the efficacy of AMCHEPRY.

An OFF-state MDS-UPDRS Part III total score is an indicator reflecting the mechanism of action of AMCHEPRY, but it does not represent daily motor symptoms. Efficacy should be evaluated comprehensively, taking into account not only the results of the primary endpoint (OFF-state MDS-UPDRS Part III total score) but also secondary endpoints, including on time, off time, and the impact on activities of daily living. Assessment of [^{18}F]FDOPA uptake, which is included as a secondary endpoint, provides useful information as a prerequisite for improvement of motor symptoms in patients with PD by AMCHEPRY; this assessment should be conducted in the post-marketing clinical study as in Study IACT16049-01.

Regarding the definition of patients aged ≤65 years as the main cohort and patients aged >65 years as the sub-cohort, and verification of efficacy in the main cohort, in principle, efficacy should be verified in the entire population of patients with PD who are eligible for AMCHEPRY. However, given limitations related to manufacturing capacity, stability, distribution, and requirements for study sites in the post-marketing clinical study, this approach is considered unavoidable. For patients aged >65 years, some efficacy is evaluable based on the plan presented by the applicant.

Furthermore, it is important to collect information on safety and efficacy in patients who are not included in the post-marketing clinical study, in patients whose evaluation in the post-marketing clinical study has been completed or discontinued, and in patients who receive transplantation of AMCHEPRY after completion of enrollment in the post-marketing clinical study. The applicant's policy to conduct a use-results survey targeting all patients who receive transplantation of AMCHEPRY is considered appropriate. The long-term safety and efficacy of AMCHEPRY should be evaluated in the use-results survey, and the planned safety and efficacy assessment items and survey period are considered acceptable.

Details of the post-marketing clinical study plan and the use-results survey plan will be finalized after taking into account discussions in the Expert Discussion regarding evaluation of the efficacy and safety of AMCHEPRY.

8. Results of Compliance Assessment Concerning the New Regenerative Medical Product Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The assessment is currently ongoing. Results and PMDA's conclusion will be reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The assessment is currently ongoing. Results and PMDA's conclusion will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of data submitted, PMDA has concluded that AMCHEPRY has some efficacy for "improvement of motor symptoms in patients with PD who have an inadequate response to conventional pharmacotherapy, including levodopa-containing drug products" and that AMCHEPRY has acceptable safety in view of its benefits. The available information on the efficacy and safety of AMCHEPRY is currently limited. Nevertheless, PMDA considers it meaningful to make AMCHEPRY available for use in clinical practice as a new therapeutic option for improvement of motor symptoms in patients with PD who have an inadequate response to conventional pharmacotherapy, including levodopa-containing drug products.

PMDA has concluded that if no particular concerns about the efficacy and safety of AMCHEPRY are raised by the Expert Discussion, AMCHEPRY may be approved with conditions and a time limit under Article 23-26 of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices, which will require continued efficacy assessment and safety data collection in a specified time period after marketing. The time limit as stipulated in this article will be determined in consideration of the plans for the post-marketing clinical study and post-marketing surveillance (including the preparation period for marketing, the patient enrollment period, the observation period for each patient, and the preparation period for the subsequent application), as well as discussions at the Expert Discussion.

Review Report (2)

February 10, 2026

Product Submitted for Approval

Brand Name	AMCHEPRY
Non-proprietary Name	Raguneprocel
Applicant	Sumitomo Pharma Co., Ltd.
Date of Application	August 5, 2025

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

On the basis of review in Section "6.R.1 Efficacy" of the Review Report (1), PMDA concluded that AMCHEPRY is expected to have some efficacy in improving motor symptoms in patients with PD who have an inadequate response to conventional pharmacotherapy, including levodopa-containing drug products. The efficacy of AMCHEPRY should be subject to further evaluation in the post-marketing setting because currently available information on such aspect is extremely limited.

The expert advisors at the Expert Discussion raised the following comments:

- There are limitations in the statistical interpretation of the results of Study IACT16049-01, which enrolled patients who had an inadequate response to conventional pharmacotherapy. However, the results, including those for the OFF-state MDS-UPDRS Part III total score, suggest the clinical efficacy of AMCHEPRY. Considering that there are many patients who have an inadequate response to conventional treatments, it is understandable to position AMCHEPRY, which has a novel mechanism of action, as one of the therapeutic options.
- Further investigation is warranted regarding the lack of correlation between the change from baseline in the OFF-state MDS-UPDRS Part III total score and [^{18}F]FDOPA uptake. In particular, patient PD05 had the most worsening OFF-state MDS-UPDRS Part III total score despite showing the greatest increase in [^{18}F]FDOPA uptake.

In light of the comments from the expert advisors at the Expert Discussion, PMDA requested the applicant to explain the lack of correlation between the change from baseline in [^{18}F]FDOPA uptake and the change from baseline in the OFF-state MDS-UPDRS Part III total score.

The applicant's response:
For the following reasons, the degree of improvement in OFF-state motor symptoms achieved with AMCHEPRY may vary depending not only on dopaminergic neuronal function but also on the complex pathophysiology of individual patients with PD, including progression of non-dopaminergic neurodegeneration. This suggests that, in some patients, the change in the Ki value, which reflects the function of AMCHEPRY, may not correlate with the change from baseline in the OFF-state MDS-UPDRS Part III total score, which most directly reflects improvement in motor symptoms:

- PD is a heterogeneous disorder, and the rate of progression of motor and other symptoms varies among individual patients.
- Motor symptoms in PD are affected not only by dopaminergic neurodegeneration but also by non-dopaminergic neurodegeneration associated with disease progression and aging (*Arch Neurol*. 2007;64:1242-6). Furthermore, the relative contributions of dopaminergic and non-dopaminergic neurodegeneration to motor symptoms differ among individual patients. AMCHEPRY is characterized by supplementation of dopaminergic neurons lost due to disease progression through transplantation, resulting in endogenous dopamine production from dopaminergic neurons at the transplantation site and restoration of dopaminergic neuronal function [see Section 3.R]. AMCHEPRY is not expected to have any effect on non-dopaminergic neurodegeneration.

PMDA's view:
The applicant's explanation about the results of the change in [^{18}F]FDOPA uptake is understandable in that the change in [^{18}F]FDOPA uptake does not necessarily translate into a change in the OFF-state MDS-UPDRS Part III total score. Accordingly, the absence of a correlation between the change in [^{18}F]FDOPA uptake and the change in the OFF-state MDS-UPDRS Part III total score is not considered to negate the efficacy of AMCHEPRY as suggested by the results of the OFF-state MDS-UPDRS Part III total score and other endpoints.

As noted by the expert advisors, in Study IACT16049-01, which enrolled patients who remained inadequately controlled despite receiving optimized conventional pharmacotherapy, the observed improvements in the OFF-state MDS-UPDRS Part III total score and related endpoints at 24 months post-transplantation were considered clinically meaningful. Accordingly, in light of the intent of the Conditional and Time-limited Approval System, PMDA has concluded that a conditional and time-limited approval should be granted to AMCHEPRY so that it is made available for use in clinical practice as a new therapeutic option for improvement of motor symptoms in patients with PD who have an inadequate response to conventional pharmacotherapy. The efficacy of AMCHEPRY should be evaluated in post-marketing surveillance, etc., based on predefined statistical success criteria, and a final decision should be made at the time of submission of an application for standard marketing approval that is supposed to occur within the specified period of the conditional and time-limited approval.

1.2 Safety

On the basis of the review described in Section "6.R.2 Safety" of the Review Report (1), PMDA concluded that AMCHEPRY is considered tolerable provided that appropriate measures for transplantation of AMCHEPRY are taken by physicians with adequate knowledge and experience in stereotactic neurosurgery and use of AMCHEPRY, and that selection of eligible patients with PD and post-transplant management are undertaken by physicians with adequate knowledge and experience in the treatment of PD. PMDA also concluded that long-term safety, including tumorigenicity, should continue to be evaluated in the post-marketing setting and that the information obtained should be appropriately provided to healthcare professionals.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning, indication or performance

On the basis of the review described in Section "6.R.5 Indication or performance" of the Review Report (1), PMDA concluded that the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections should be established as described in the corresponding section of the Review Report (1).

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.4 Dosage and administration or method of use

On the basis of the review described in Section "6.R.6 Dosage and administration or method of use" of the Review Report (1), PMDA concluded that the "Dosage and Administration or Method of Use" section for AMCHEPRY should be established as described in the corresponding section of the Review Report (1).

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion. The expert advisors also raised the following comment regarding medical devices used for stereotactic neurosurgery:

- In addition to an invasive neurosurgical head fixation device, it is acceptable to perform stereotactic neurosurgery using medical devices that enable transplantation of AMCHEPRY into the intended target region within an allowable margin of error.

In light of the comments from the expert advisors at the Expert Discussion, PMDA concluded as follows: Stereotactic neurosurgery may be performed using medical devices with confirmed precision, and it is not necessary to limit the medical device used for stereotactic neurosurgery to an invasive neurosurgical head fixation device in the "Dosage and Administration or Method of Use" section. PMDA determined that the "Dosage and Administration or Method of Use" section should be revised as shown below. It is appropriate to provide information, in relevant materials, on medical devices that may be used for stereotactic neurosurgery for transplantation of AMCHEPRY.

Dosage and Administration or Method of Use (Strikethrough denotes deletions from the Review Report [1].)

1. Transplantation of AMCHEPRY

Usually, in adults, AMCHEPRY consisting of allogeneic iPS cell-derived dopaminergic progenitor cells is transplanted stereotactically ~~using an invasive cranial fixation device for neurosurgical procedures~~ into the bilateral putamen, with a target of 5.4×10^6 cells per hemisphere. The cells are administered through 3 injection tracts passing through a single burr hole in the skull, and approximately 1.8×10^6 cells per tract are transplanted into 6 to 9 sites at intervals of 1 to 2 mm. The infusion rate is approximately 0.1 μL/sec.

2. Administration of tacrolimus hydrate before and after transplantation of AMCHEPRY for the purpose of suppressing immune responses to AMCHEPRY

Usually, tacrolimus is initially administered orally at a dose of 0.03 to 0.15 mg/kg twice daily starting in the morning of the transplantation day. Thereafter, the dose should be adjusted to maintain the blood tacrolimus trough level in the range of 5 to 10 ng/mL while monitoring the blood trough level.

If rejection is observed, the trough blood tacrolimus level should be maintained in the range of 10 to 20 ng/mL.

As a general rule, approximately 1 year after the start of tacrolimus administration, the dose should be gradually tapered over the subsequent 12 weeks and then discontinued; however, the duration of administration may be extended as necessary.

PMDA requested the applicant to specify the “Dosage and Administration or Method of Use” section as described above. The applicant responded to the request appropriately, and PMDA accepted the proposed revisions.

1.5 Plan for evaluation of post-marketing approval conditions (draft)

The applicant submitted a draft plan for a post-marketing clinical study and a use-results survey to further evaluate the efficacy and safety of AMCHEPRY in the post-marketing setting.

On the basis of the review described in Section “7. Risk Analysis and Outline of the Review Conducted by PMDA” of the Review Report (1), PMDA concluded the post-marketing clinical study shown in Table 26 should be conducted to verify the efficacy of AMCHEPRY in the post-marketing setting. Given that clinical experience with transplantation of AMCHEPRY remains extremely limited, PMDA also concluded that a use-results survey targeting all patients who receive transplantation of AMCHEPRY should be conducted, as shown in Table 27, to collect information and the obtained safety information should be promptly provided to healthcare professionals.

At the Expert Discussion, from the perspective that it is important to verify the efficacy of AMCHEPRY using a study design with the highest possible degree of objectivity, the expert advisors raised the following comments regarding the design of the post-marketing clinical study:

- Conducting the study as an external control study using an external control group derived from PPMI through propensity score matching would be appropriate. However, if such an externally controlled study is not feasible and the study is conducted as currently planned, i.e., a single-arm study with a predefined threshold, the following issues should be considered in the evaluation of efficacy:
  (1) Data from a standard-of-care group evaluated by the same evaluators at the institutions participating in the post-marketing clinical study should be collected to allow justification of the predefined threshold. In addition, a comparison using the standard-of-care group data as an external control should be performed.
  (2) Measures should be implemented to ensure the blinded assessment of efficacy endpoints by evaluators, such as having efficacy assessed by physicians not involved in transplantation of AMCHEPRY, or recording videos for efficacy assessment of a patient to conduct centralized blinded evaluations based on the recorded data.
  (3) The threshold was determined based on the data derived from 92 patients with available 2-year data among 200 patients in a population similar to that of the post-marketing clinical study extracted from PPMI. However, analyses that ignore missing data may introduce bias. The threshold should be determined taking into account the outcomes of patients without available 2-year data.
  (4) For the analysis of data from the post-marketing clinical study, the method for comparison with natural history is unclear; the estimand should be explicitly specified.

In light of the above comments from the expert advisors, PMDA requested additional explanations from the applicant and conducted the following review.

- Externally controlled study using a propensity score-matched external control group extracted from PPMI

The applicant's explanation:

Considering the following points, it is difficult to conduct an externally controlled study comparing AMCHEPRY with a propensity score-matched external control group derived from PPMI:

- Among the inclusion and exclusion criteria of the post-marketing clinical study shown in Table 28, certain criteria cannot be confirmed using data collected in PPMI, including inadequate control of motor symptoms of PD despite conventional pharmacotherapy and persistence of dyskinesia that interferes with activities of daily living despite conventional pharmacotherapy. Data extracted from PPMI using propensity scores may not ensure sufficient comparability with the post-marketing clinical study population.
- The potential covariates for estimating the propensity score would include age, disease duration, MDS-UPDRS Part III total score (OFF-state and ON-state), H&Y stage (OFF-state and ON-state), on time, and off time. However, as on time and off time are not available in PPMI, these variables cannot be used as covariates. Together with the above-mentioned absence of other clinically important prognostic factors that may influence treatment selection, even if an adjusted analysis using propensity scores were performed, residual confounding might not be adequately controlled.
- The feasibility of conducting an externally controlled study was examined under the assumption that propensity score matching would be performed using only covariates available in PPMI. Among patients expected to be enrolled in the post-marketing clinical study, those with OFF-state

H&Y stage 4 or 5 represent a relatively severe subgroup; however, only 3 such patients were available in PPMI. It is, therefore, highly likely that an adequate sample size for matching as an external control could not be secured, leading to reduced statistical power for hypothesis testing.

As an alternative to propensity score matching, the inverse probability of treatment weighting (IPTW) method, which allows inclusion of all patients in the analysis using the inverse of the propensity score as weights, was also considered. However, because propensity scores and inverse probability weights would provide extreme values, potentially resulting in unstable analyses, the applicant determined that the IPTW method would not be appropriate.

Table 28. Main inclusion and exclusion criteria

Inclusion criteria	• Diagnosed with PD (clinically confirmed or clinically probable) according to the MDS clinical diagnostic criteria for PD (*Mov Disord*. 2015;30:1591-601) • Inadequate symptom control with conventional pharmacotherapy • Main cohort only: Aged ≥18 and ≤65 years at the time of informed consent • Sub-cohort only: Aged >65 years at the time of informed consent • Duration of PD ≥5 years • Presence of ON and OFF states (confirmed by MDS-UPDRS Part III and/or symptom diary assessments) • OFF-state H&Y stage ≥2 • OFF-state H&Y stage ≤3 • ≥30% responsiveness to L-dopa during withdrawal of anti-PD drugs • DAT scan showing a pattern of decreased uptake characteristic of PD in the basal ganglia region
Exclusion criteria	• Symptomatic organic lesions on brain MRI • Considered to have dementia or be at high risk for dementia • Persistent dyskinesia interfering with activities of daily living despite conventional pharmacological treatment • Presence of any of the following comorbidities: ➢ Malignant neoplasm ➢ Epilepsy ➢ Psychiatric disorders (including depression, bipolar disorder, and schizophrenia) ➢ Other serious comorbidities (including cerebrovascular disorder, cardiac disease, chronic respiratory disease, poorly controlled hypertension, or diabetes mellitus) • At the time of informed consent, the subject is receiving or has previously received globus pallidus surgery, thalamic surgery, deep brain stimulation surgery, or device-assisted continuous therapy with levodopa/carbidopa or foslevodopa/foscarbidopa • At clinical laboratory testing at screening, any of the following results applies: ➢ Neutrophils: <2,000/μL ➢ Platelets: $<5.0 \times 10^4/\mu L$ ➢ AST or ALT: >3.0 × upper limit of normal ➢ Total bilirubin: >1.5 × upper limit of normal ➢ eGFR: <60 mL/min/1.73 m²

PMDA's view:

The applicant explained that, because the information collected in PPMI is limited and covariates that should be used for estimating propensity scores cannot be obtained from PPMI, it would be difficult to conduct a comparative assessment ensuring sufficient comparability even if a comparison were performed with an external control group extracted from PPMI using propensity score matching. The above applicant's explanation is understandable. Therefore, the applicant's decision not to conduct an external control study comparing the results with data from an external control group derived from PPMI using propensity score matching to verify the post-marketing efficacy of AMCHEPRY is acceptable.

- Efficacy evaluation in a single-arm study with a prespecified threshold

The applicant's explanation about response to the issues (1) to (4) above:

(1) The study sites for the post-marketing clinical study must have the capability to evaluate the MDS-UPDRS Part III total score in the practically defined off state and to manufacture [^{18}F]FDOPA and perform PET imaging necessary for the evaluation of [^{18}F]FDOPA uptake; hence, the number of such sites is limited. Patients in the standard-of-care group also need to undergo evaluation in the practically defined off state after withdrawal of anti-PD drugs. Because the evaluation period, which is relatively long (96 weeks), would impose a substantial burden on patients, a large number of dropouts may occur during the study. It is considered difficult to prospectively collect a standard-of-care group at the sites conducting the post-marketing clinical study and to justify the validity of the threshold using data evaluated by the same evaluators.

(2) To ensure the blinding of evaluators, methods in which evaluation is performed by physicians not involved in transplantation of AMCHEPRY were investigated. Among the items of the MDS-UPDRS Part III total score, those related to rigidity require the evaluator to palpate the patient's resistance to passive movement. Therefore, the following two methods were considered: one in which physicians from other medical institutions not involved in transplantation of AMCHEPRY visit the post-marketing clinical study sites to perform evaluations, and the other in which patients visit medical institutions different from those where the transplantation surgery was performed to undergo evaluation. However, these approaches were difficult because of scheduling issues and the increased burden on patients. Selecting evaluators within the same institution would result in the situation where both physicians involved in transplantation and those not involved would present within the same institution, making it difficult to maintain blinding of the evaluators. In contrast, some clinical studies have been reported in which centralized evaluation of the MDS-UPDRS Part III total score using video recordings was adopted as an exploratory endpoint to ensure the objectivity of face-to-face assessments. Based on the above, centralized evaluation using video recordings will be conducted as a secondary endpoint in the post-marketing clinical study.

(3) In a population similar to that of the post-marketing clinical study, an analysis considering missing data was conducted using mixed-effects models for repeated measures (MMRM) with the baseline value of the OFF-state MDS-UPDRS Part III total score as a covariate. When missing values up to 5 years of follow-up were considered (153 patients in main cohort, 167 patients in sub-cohort), the least-squares mean change [95% CI] in the OFF-state MDS-UPDRS Part III total score at Year 2 was +5.5701 points [+3.6558 to +7.4844 points] in the population similar to the main cohort and +3.5450 points [+1.7407 to +5.3492 points] in the population similar to the sub-cohort. The lower limit of the 95% CI of each least-squares mean will be used to determine the threshold.

(4) The estimand for the analysis of data from the post-marketing clinical study is shown in Table 29, and the details will be described in the protocol of the post-marketing clinical study.

Table 29. Estimand for the analysis of the post-marketing clinical study

Treatment	Raguneprocel (AMCHEPRY)
Population	All patients with PD who were enrolled in the study and underwent transplantation of AMCHEPRY and who had inadequate response to conventional pharmacotherapy including levodopa-containing drug products
Variable (or endpoint)	Change from baseline in the OFF-state MDS-UPDRS Part III total score at 96weeks after transplantation of AMCHEPRY (evaluation in the practically defined off state)
Intercurrent events and their handling	Intercurrent events considered to affect the interpretation of the variable of interest include early discontinuation of the study for any reason and missing visits or assessments. These intercurrent events will be handled under a hypothetical strategy. Specifically, the treatment effect of interest will be defined as the outcome under a hypothetical situation in which all participants continued observation through Week 96. Efficacy data after study discontinuation will not be collected. These data will be predicted based on specific assumptions regarding how the data would have evolved after study discontinuation.
Population-based summary measure	It will be evaluated whether the upper limit of the 95% CI for the mean value of the variable of interest is below the prespecified threshold.

PMDA's view:

(1) Taking into account that efficacy evaluation in the OFF state imposes a substantial burden on patients, the applicant's explanation that it is difficult to prospectively collect a standard-of-care group after the market launch in Japan is understandable, and it is acceptable not to collect data from a standard-of-care group.

(2) The applicant's explanation that blinded evaluation is difficult is understandable, and it is acceptable to conduct centralized evaluation using video recordings as a secondary endpoint to enhance objectivity.

(3) and (4) The explanations provided by the applicant were accepted.

Based on the above, PMDA requested that the applicant present a post-marketing clinical study plan reflecting the above results. The applicant submitted an outline (draft) of the post-marketing clinical study shown in Table 30, and PMDA accepted it.

Table 30. Outline of the post-marketing clinical study (draft)
(the underlined texts are revised from Table 26)

Objective	Primary objective: To verify the efficacy of AMCHEPRY transplanted into the putamen in eligible patients aged ≤65 years in the main cohort. Secondary objectives: To evaluate the efficacy of AMCHEPRY transplanted into the putamen in eligible patients aged >65 years with PD in the sub-cohort. To evaluate the safety of AMCHEPRY transplanted into the putamen in eligible patients in both the main cohort and the sub-cohort.
Study design	Open-label, uncontrolled, multicenter study
Target population	Patients with PD who have an inadequate response to conventional pharmacotherapy, including levodopa-containing drug products
Observation period	96 weeks after transplantation of AMCHEPRY (with a separate 4-week baseline assessment period)
Target sample size	[Main cohort]: 30 patients aged ≤65 years Assuming an expected change from baseline in the OFF-state MDS-UPDRS Part III total score at 96 weeks after transplantation of −12 to −9[*1] based on Study IACT16049-01, and a standard deviation of 19 based on Study IACT16049-01 and the natural history of PD, the required sample size to detect the effect of AMCHEPRY by a one-sample t-test with two-sided significance level of 5% and 90% power, compared with a threshold[*2] of +3.6 points above that derived from the natural history of PD, was calculated to be 18 to 26 patients. Considering potential dropouts, the target sample size was 30 patients. [Sub-cohort]: 5 patients aged >65 years Assuming an expected change from baseline in the OFF-state MDS-UPDRS Part III total score at 96 weeks after transplantation of −5, which would be considered clinically meaningful, and a standard deviation of 16 based on the natural history of PD, the required sample size for which the probability that the expected mean would fall below the threshold[*2] of +1.7 points above that derived from the natural history of PD would be approximately 83% was calculated to be 5 patients. Accordingly, the target sample size was 5 patients.
Number of study sites	6-10 sites
Primary efficacy endpoint[*3]	Change from baseline in the OFF-state MDS-UPDRS Part III total score at 96 weeks after transplantation of AMCHEPRY (assessed by a physician at each study site)
Statistical analysis of the primary endpoint	[Main cohort] Using MMRM assuming an unstructured covariance matrix, with evaluation time points (48 and 96 weeks after transplantation of AMCHEPRY) and the baseline OFF-state MDS-UPDRS Part III total score as covariates, the least-squares mean and its 95% CI at 96 weeks after transplantation will be calculated. If the upper limit of the 95% CI is below the threshold[*2] of +3.6 points above that derived from the natural history of PD, the efficacy of AMCHEPRY in patients aged ≤65 years will be considered demonstrated. [Sub-cohort] If the efficacy of AMCHEPRY is demonstrated in the main cohort, the mean change from baseline in the OFF-state MDS-UPDRS Part III total score at 96 weeks after transplantation of AMCHEPRY (with missing values imputed using LOCF) will be calculated. If the mean value is below the threshold[*2] of +1.7 points above that derived from the natural history of PD, the efficacy of AMCHEPRY in patients aged >65 years will be considered demonstrated.

Major secondary efficacy endpoints[*3,*4]	• Video-based OFF-state MDS-UPDRS Part III total score (the assessment performed by physicians at each study site is recorded on video, and the evaluation is conducted by a central rater using the recorded video.) - Change from baseline in the total score (excluding item 3.3 rigidity) at Week 96 after transplantation of AMCHEPRY - Change from baseline in the total score (with item 3.3 rigidity supplemented by the physician assessment results obtained at each study site) at Week 96 after transplantation of AMCHEPRY • OFF-state MDS-UPDRS Part III: Number and proportion of patients with treatment response or marked response - Number and proportion of patients with an improvement of ≥5 points from baseline in the total score at 96 weeks after transplantation of AMCHEPRY. In the main cohort, the proportion of responders will be compared with a threshold of 15% based on the natural history of PD. - Number and proportion of patients with an improvement of ≥10 points from baseline in the total score at 96 weeks after transplantation of AMCHEPRY. In the main cohort, the proportion of responders will be compared with a threshold of 10% based on the natural history of PD. • MDS-UPDRS Part III total score (ON-state and OFF-state) - Change and percent change from baseline at each evaluation time point [Main cohort only] - Number and proportion of patients with an improvement of ≥5 points from baseline at each time point - Number and proportion of patients with an improvement of ≥10 points from baseline at each time point - Number and proportion of patients with a worsening of ≥5 points from baseline at each time point - Number and proportion of patients with a worsening of ≥10 points from baseline at each time point • MDS-UPDRS Part II total score (ON-state) - Change from baseline in the total score at each evaluation time point • MDS-UPDRS Part I, II, and III (all ON-state) total scores, and MDS-UPDRS Part I and II (ON-state) and Part III (OFF-state) total scores - Change and percent change from baseline in the total score at each evaluation time point • MDS-UPDRS Part II and III (both ON-state) total scores, and MDS-UPDRS Part II (ON-state) and Part III (OFF-state) total scores - Change and percent change from baseline in the total score at each evaluation time point • MDS-UPDRS Part I (ON-state), Part II (ON-state), Part III (ON-state), Part III (OFF-state), and Part IV - Change from baseline in individual item scores at each evaluation time point • Bradykinesia subscale (OFF-state) - Change and percent change from baseline in the sum of the following items at each evaluation time point: 3.1 speech, 3.2 facial expression, 3.4 finger tapping, 3.5 hand movements, 3.8 leg agility, and 3.14 global spontaneity of movement (body bradykinesia) • H&Y stage (ON-state and OFF-state) - Change from baseline in the H&Y stage (ON-state and OFF-state) at each evaluation time point [Main cohort only] - Number and proportion of patients with an improvement of ≥1 stage from baseline at each time point - Number and proportion of patients with an improvement of ≥2 stages from baseline at each time point - Number and proportion of patients with a worsening of ≥1 stage from baseline at each time point - Number and proportion of patients with a worsening of ≥2 stages from baseline at each time point • Mean daily off time, good on time, and on time - Changes from baseline in mean daily on time, good on time,[*5] and off time normalized to a standard waking hour of 16 hours per day • PDQ-39 - Changes from baseline in the PDQ-39 Summary Index score and domain scores at each evaluation time point • PGI and CGI - Changes from baseline in PGI-C, CGI-I, and CGI-S scores at each evaluation time point • [^{18}F]FDOPA uptake - Change from baseline in uptake at the transplantation site of AMCHEPRY (striatum, putamen, caudate nucleus) at each evaluation time point [Main cohort] - Number and proportion of patients judged to have uptake at the transplantation site of AMCHEPRY at each evaluation time point [Sub-cohort] - Presence or absence of uptake at the transplantation site of AMCHEPRY, and number and proportion of patients judged to have uptake at each evaluation time point
Other endpoints	• Status of anti-PD medications

Safety endpoints	• Adverse events and deficiencies • Presence or absence of graft overgrowth in the brain (≥3 cm^3) and graft size as assessed by brain MRI • UDysRS • 12-lead electrocardiogram, laboratory test values, immunological tests, vital signs, and body weight

*1 In the efficacy analysis population of 6 patients in Study IACT16049-01, the change from baseline in the OFF-state MDS-UPDRS Part III total score at Month 24 was −9.5 (13.79) (mean [SD]). Among these, in the 5 patients who were ≤65 years of age at baseline, the change from baseline in the OFF-state MDS-UPDRS Part III total score at Month 24 was −12.4 (13.22) (mean [SD]). Based on these results and the absence of reference values for patients aged <50 years in the main cohort, the expected value was given in a range.

*2 Based on the PPMI database, a large-scale global natural history observational study of PD, the mean change [95% CI] in the OFF-state MDS-UPDRS Part III total score at 2 years was +5.5701 points [+3.6558 to +7.4844 points] in a population similar to the main cohort of the post-marketing clinical study and +3.5450 points [+1.7407 to +5.3492 points] in a population similar to the sub-cohort. Accordingly, the lower bound of the 95% CI was used to define the threshold.

*3 OFF-state assessments for efficacy endpoints will be conducted in the practically defined off state, after withholding levodopa drug products for ≥12 hours and other anti-PD medications (including dopamine receptor agonists and monoamine oxidase B inhibitors) for the specified periods.

*4 Evaluation time points are as follows: MDS-UPDRS Part III (OFF-state), H&Y stage (OFF-state), and [^{18}F]FDOPA uptake at 48 and 96 weeks after transplantation of AMCHEPRY; MDS-UPDRS Part I, II, and III (ON-state), MDS-UPDRS Part IV, H&Y stage (ON-state), mean daily on time, good on time, off time, PDQ-39, PGI-C, CGI-I, and CGI-S at 4, 12, 24, 48, 72, and 96 weeks after transplantation of AMCHEPRY. However, [^{18}F]FDOPA uptake at 48 weeks after transplantation of AMCHEPRY will be evaluated in patients in whom PET imaging can be performed within the specified period.

*5 Mean daily on time without troublesome dyskinesia that interferes with activities of daily living.

1.6 Others

1.6.1 Designation of Designated Regenerative Medical Product

In accordance with the "Principles for Designation of Biological Products, Specified Biological Products, and Designated Regenerative Medical Products" [in Japanese] (PFSB/ELD Notifications No. 1105-1 and 1105-2 dated November 5, 2014, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare), AMCHEPRY is classified as a regenerative medical product using cells derived from allogeneic sources as its starting materials. Accordingly, PMDA has concluded that that AMCHEPRY should be designated as a Designated Regenerative Medical Product.

2. Results of Compliance Assessment Concerning the New Regenerative Medical Product Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new regenerative medical product application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new regenerative medical product application data (CTD 5.3.5.2-01, CTD 5.3.5.2-02) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication or performance and dosage and administration or method of use shown below, with the

following approval conditions, provided that a cautionary statement is included in the package insert and information on the proper use is disseminated appropriately in the post-marketing setting, and that specifically, a conditional and time-limited approval under Article 23-26 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices may be granted to the product. The time limit under the concerned article should be 7 years. The product should be designated as a Designated Regenerative Medical Product.

Indication or Performance

Improvement of motor symptoms in patients with Parkinson's disease who have an inadequate response to conventional pharmacotherapies, including levodopa-containing drug products

Dosage and Administration or Method of Use

1. Transplantation of AMCHEPRY

Usually, in adults, AMCHEPRY consisting of allogeneic iPS cell-derived dopaminergic progenitor cells is transplanted stereotactically into the bilateral putamen, with a target of 5.4×10^6 cells per hemisphere. The cells are administered through 3 injection tracts passing through a single burr hole in the skull, and approximately 1.8×10^6 cells per tract are transplanted into 6 to 9 sites at intervals of 1 to 2 mm. The infusion rate is approximately 0.1 μL/sec.

2. Administration of tacrolimus hydrate before and after transplantation of AMCHEPRY for the purpose of suppressing immune responses to AMCHEPRY

Usually, tacrolimus is initially administered orally at a dose of 0.03 to 0.15 mg/kg twice daily starting in the morning of the transplantation day. Thereafter, the dose should be adjusted to maintain the blood tacrolimus trough level in the range of 5 to 10 ng/mL while monitoring the blood trough level.

If rejection is observed, the trough blood tacrolimus level should be maintained in the range of 10 to 20 ng/mL.

As a general rule, approximately 1 year after the start of tacrolimus administration, the dose should be gradually tapered over the subsequent 12 weeks and then discontinued; however, the duration of administration may be extended as necessary.

Approval Conditions

1. The applicant is required to conduct a post-marketing approval condition assessment, for example through post-marketing surveillance covering all patients treated with the product, until the submission of an application for standard marketing approval of the product to which conditional and time-limited approval has been granted.
2. The applicant is required to take necessary measures, such as provision of seminars, to ensure that physicians with adequate knowledge and experience in the diagnosis and treatment of Parkinson's disease as well as in stereotactic neurosurgical procedures have a full understanding of relevant information, including the results of the clinical study of the product and adverse events reported, to use the product in compliance with the "Indication or Performance" and "Dosage and

Administration or Method of Use" at medical institutions with an established system for the treatment of Parkinson's disease.

List of Abbreviations

[^{18}F]FDA	6-[^{18}F]-fluoro-dopamine
[^{18}F]FDOPA	6-[^{18}F]-fluoro-L-dopa
[^{18}F]FLT	3'-[^{18}F]-fluoro-3'-deoxy-L-thymidine
6-OHDA	6-hydroxydopamine
ALT	alanine aminotransferase
AMCHEPRY	AMCHEPRY
Application	application for marketing approval
AST	aspartate aminotransferase
CAG	hybrid construct consisting of the CMV enhancer fused to the chicken beta-actin promoter
CGI-I	clinical global impression of improvement
CGI-S	clinical global impression of severity
CI	confidence interval
CiRA	Center for iPS Cell Research and Application
CMV	cytomegalovirus
CQA	critical quality attribute
DAT	dopamine transporter
DBS	deep brain stimulation
EBNA1	Epstein-Barr nuclear antigen 1
eGFR	estimated glomerular filtration rate
FIH study	first in human study
GCP	good clinical practice
GE180	flutriciclamide
H&Y staging	Hoehn and Yahr staging
HBV	hepatitis B virus
HCV	hepatitis C virus
HEK293	human embryonic kidney 293
HeLa cells	Human cervical cancer cells
HIV	human immunodeficiency virus
hKLF4	human kruppel like factor 4
HLA	human leukocyte antigen
hLIN28	human RNA-binding protein that acts as a posttranscriptional regulator
hL-MYC	human v-myc-1 proto-oncogene protein
HTLV	human T-cell leukemia virus
iPS cells	induced pluripotent stem cells
IPTW	inverse probability of treatment weighting

jRCT	Japan registry of clinical trials
[redacted]	
LCIG therapy	levodopa-carbidopa continuous infusion gel therapy
LEDD	levodopa equivalent daily dose
LOCF	last observation carried forward
MCB	master cell bank
[redacted]	
MDS	International Parkinson and Movement Disorder Society
MDS-UPDRS	MDS-Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities Japanese version
MMRM	mixed-effects models for repeated measures
mp53DD	mouse p53 carboxy-terminal dominant-negative fragment
MRC-5 cells	human fetal lung fibroblast cells
MRI	magnetic resonance imaging
[redacted]	
NOG mouse	NOD.Cg-*Prkdc*^{scid}*Il2rg*^{tm1Sug}/ShiJic
OCT3/4	POU class 5 homeobox 1
ParvoB19	parvovirus B19
[redacted]	
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire-39
[redacted]	
PET	positron emission tomograph
PGI-C	patient global impression of change
PMDA	Pharmaceuticals and Medical Devices Agency
[redacted]	
PPMI	Parkinson's Progression Markers Initiative
PT	preferred term
qPCR	quantitative polymerase chain reaction
[redacted]	
RT-PCR	reverse transcriptase polymerase chain reaction
SMQ	standardised MedDRA queries
SOC	system organ class
SOX	SRY-box transcription factor
[redacted]	
TTR	transthyretin
[redacted]	
UDysRS	Unified Dyskinesia Rating Scale
UPDRS	Unified Parkinson's Disease Rating Scale
Vero cells	African green monkey kidney epithelial cells
[redacted]	