This supplement contains the following items,

1. Original protocol, final protocol, summary of changes
2. Statistical analysis plan

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CLINICAL STUDY PROTOCOL

Protocol Title:	Phase 1 Study To Assess the Safety and Tolerability of Human Embryonic Stem Cell-Derived Midbrain Dopamine Neuron Cell Therapy (MSK-DA01) For Advanced Parkinson's Disease (STEM-Parkinsons)
Investigational Product:	MSK-DA01
Protocol Number:	MSK-DA01-101
Protocol Version:	BRT-US Version 1.0
Protocol Date:	01 February 2021
Sponsor:	BlueRock Therapeutics, Inc 1 Broadway Cambridge, MA 02142 USA Telephone: (857)-777-0501
Sponsor Contact:	[redacted] Neurology
Sponsor Physician:	[redacted]

Signature
02-Feb-2021 | 9:18:39 AM PST

Date

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without express written authorization of BlueRock Therapeutics.

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INVESTIGATOR'S AGREEMENT

I have received and read the protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

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1. SYNOPSIS

Name of Sponsor Company: BlueRock Therapeutics
Protocol Title: Study To Assess the Safety and Tolerability of Human Embryonic Stem Cell-Derived Midbrain Dopamine Neuron Cell Therapy (MSK-DA01) For Advanced Parkinson's Disease
Protocol Number: MSK-DA01-101
Version Number: BRT-US V1.0
Name of Investigational Product: MSK-DA01
Phase of Development: 1
Study Center(s): Multi-center (multi-site) study
Study Indication: Advanced Parkinson's Disease
Study Rationale: Cell-based therapies have the potential to deliver dopamine (DA) to the DA-depleted striatum in a more physiologic manner than is possible from medications. The Sponsor has derived authentic, engraftable midbrain dopamine (mDA) neurons from human embryonic stem cells (hESCs) using a novel, small molecule-based floor-plate differentiation strategy. These cells demonstrate excellent in vivo survival and function in animal models of Parkinson's disease (PD) with no evidence of tumor or excessive growth. The Sponsor will therefore implement an open-label, non-randomized study, with the primary objective of evaluating safety and tolerability of transplantation of 2 dose levels of MSK-DA01 cells in individuals with advanced PD at 1 year post transplant.
Accrual Period: Approximately 18 months
Study Duration: Subjects will be on study for up to 26 months. Projected study duration is 44 months.
Number of Subjects: 10 evaluable subjects
Study Population: Subjects with advanced PD, aged ≥60 to ≤76 years old, with motor symptoms inadequately relieved by standard treatments.
Objectives: *Primary:* The primary objective of the study is to assess the safety and tolerability of MSK-DA01 cell transplantation at 1 year post transplant. *Secondary:* The secondary objectives of the study are (i) to assess the evidence of transplanted cell survival and motor effects at 1 and 2 years post transplant; (ii) to evaluate continued safety and tolerability at 2 years; (iii) to assess feasibility of transplantation. *Exploratory:* The exploratory objectives of the study are (i) to determine the effects of MSK-DA01 transplantation upon motor and non-motor signs and symptoms of PD and upon accelerometry-based measures of motor function; (ii) to assess the subject's perception of their quality of life; (iii) to collect biosamples for anti-human leukocyte antigen testing; to obtain blood for storage for xenotransplantation-related future testing; and to store leftover samples for future studies of biomarkers of PD, DA function, inflammation, and immune response to engrafted cells.

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Endpoints:

Primary:

The primary endpoint of the study will be the incidence of serious adverse events (SAEs) at 1-year post transplant.

Secondary:

The secondary endpoints of the study will be (i) change in striatal fluorodopa (^{18}F-DOPA) uptake using positron emission tomography (PET) from baseline to 1 and 2 years; (ii) changes from baseline in the following measures at 2 years post transplant: International Parkinson and Movement Disorder Society (MDS)-Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore in the "off" state, number of waking hours in the "off" state, incidence of serious adverse events (SAEs) at 2 years post transplant, and incidence and type of adverse events (AEs) at 1 and 2 years post transplant; and (iii) feasibility, as defined by intra-operative delivery of at least 50% of the intended total number of deposits per brain in at least 6/10 subjects.

Exploratory:

The exploratory endpoints of the study will be as follows: (i) Changes in the following measures from baseline to 2 years in total MDS-UPDRS scores; MDS-UPDRS Part 1 scores; MDS-UPDRS Part 2 scores; MDS-UPDRS motor subscore in the "on" state; MDS-UPDRS Part 4 scores; 10-meter walking test; anti-PD medications (daily levodopa equivalent dose); Modified Schwab and England Activities of Daily Living; Unified Dyskinesia Rating Scale; neuropsychological testing; non-motor measures including Montreal Cognitive Assessment (MoCA), Beck Anxiety Inventory, Beck Depression Inventory, Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease (QUIP), and PD Non-Motor-Scale; Global Clinical Impression Scale; daily time in the "on," "on with dyskinesia," measured by the Hauser diary; daily time in the "on," "on with dyskinesia," "off" states measured by the Parkinson Kinetigraph; (ii) Quality of life as measured by Parkinson's Disease Questionnaire-39; and (iii) sample collection for biorepository, which does not have pre-specified endpoints.

Methodology: This is a multi-center, multi-site (Clinical Site, Surgical Site, PET Imaging Site), open-label, non-randomized, non-controlled study. Subjects will undergo a single session surgical transplantation of 1 of 2 different dose levels of MSK-DA01 cells to the post-commissural putamen bilaterally, and administration of a 1-year immunosuppression regimen. The first 5 subjects (Cohort A) will receive Dose A (0.9 million cells per putamen) and the second 5 (Cohort B) will receive Dose B (2.7 million cells per putamen). Safety and tolerability will be assessed at 1 year, along with evidence of cell survival and motor effects, and feasibility will be assessed at transplantation. Further safety and tolerability, with efficacy and exploratory assessments will take place at 2 years post transplant.

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Diagnosis and Eligibility Criteria:

Subject inclusion criteria include the following:

- Age ≥60 to ≤76 years old
- Idiopathic PD defined by the modified UK Parkinson's Disease Society Brain Bank criteria
- A minimum time of 5 years from time of PD diagnosis and a maximum time from PD diagnosis of 15 years
- Prior sufficient treatment comprising levodopa and at least 1 adjunct therapy, and additional appropriate therapy such as physical therapy
- Defined levodopa response of ≥40% improvement on the basis of MDS-UPDRS part 3
- Baseline Hoehn and Yahr score 0-2 "on" and 3-4 "off"
- Not eligible for deep brain stimulation or have refused deep brain stimulation after evaluation by an independent neurologist or neurosurgeon
- PD medications allowed: any approved oral, transdermal, and/or injectable PD medication and medications must be stable for ≥1 month prior to enrollment
- Abnormal Involuntary Movement Scale (AIMS) rating scale score of ≤2 for dyskinesia
- "Off" time of ≥2 hours daily
- MoCA score ≥26
- Hamilton Depression Scale (HAM-D) score ≤17
- Dysthymia allowed with single or 2 antidepressant medications if at stable dose for >6 months
- Normal endocrine, renal, and liver function as measured by standard laboratory testing unless clinically significant; no blood dyscrasias; no bleeding disorder; and no cardiovascular contraindications for surgery, except for stable and controlled conditions including diabetes type 2 and hypothyroidism
- All other concomitant disorders must be stable and well controlled, must not constitute a contraindication to general anesthesia or surgery, or interfere with scheduled study assessments
- Women of childbearing potential must agree to use a highly effective method of contraception from screening until at least 4 weeks after cessation of the oral immunosuppression medication regimen
- Able to participate in all study visits and evaluations, including brain magnetic resonance imaging (MRI)
- Able to give informed consent for study participation and sign the informed consent form
- Existence of a study participant partner who may act as potential surrogate over the long term for ongoing consent

Subject exclusion criteria include the following:

- Clinical features suggestive of a neurodegenerative diagnosis other than PD
- PD with only tremor-based symptoms
- Diagnosis of primary mitochondrial disorder, epilepsy, stroke, multiple sclerosis or other neurodegenerative diseases such as Alzheimer's disease
- Any current or relevant previous history of serious, severe, or unstable physical, neurological, or psychiatric illness that may make the subject unlikely to fully complete the study (including significant depression, psychosis, anxiety, cognitive impairment, or impulse control disorder)
- Receiving DA receptor-blocking agents, including typical neuroleptics, prochlorperazine, and metoclopramide at the time of screening or within 3 months prior to screening
- ^{18}F-DOPA PET imaging inconsistent with DA deficiency

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- Ongoing treatment with intrajejunal or subcutaneous infusion therapies for PD (Subjects who permanently discontinue these treatments are eligible to enroll after 2 months.)
- History of deep brain stimulation, lesion therapy, or gene therapy for PD
- Prior surgical or radiation therapy to the brain or spinal cord
- Per assessing clinician discretion, any abnormality on brain MRI that would preclude cell transplantation
- Significant concomitant medical disease limiting life expectancy to less than 24 months from study inclusion, or significant and serious concomitant medical disease that is poorly controlled
- Signs of active malignant disease or other clinically relevant abnormality on chest X-ray
- Clinically relevant abnormalities on standard safety laboratory tests, including blood count, partial thromboplastin time, blood chemistry (glucose, blood urea nitrogen, creatinine, electrolytes), and liver function tests (aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, total protein, bilirubin)
- Presence of a condition resulting in high risk of immunosuppressive drugs, including any active infectious disease of any nature, including clinically active viral infections (seropositive for human immunodeficiency virus, hepatitis C virus, hepatitis B virus, cytomegalovirus (CMV), and Venereal Disease Research Laboratory unless related to immunization or past CMV exposure, risk of tuberculosis
- Inability to temporarily stop anti-platelet agents or other anti-coagulants without significant risk
- Previous or currently active malignant disease within the past 5 years, except basal cell carcinoma or in situ uterine cervical carcinoma that have been definitively treated
- Use of immunosuppressive drugs including systemic steroids within the previous 3 months
- Severe obesity (>350 lb) or any condition that prevents use of PET/MRI
- Known substance abuse (recent history of abuse of alcohol or other drugs such as barbiturates, cannabinoids, and amphetamines) within last 5 years
- In the opinion of the investigator, presence of any cognitive, behavioral, or psychiatric symptoms that would be deemed contraindications to cell transplantation
- Pregnancy or breastfeeding
- Unable to cooperate or complete self-assessment scales and diaries
- Unable to provide and sign the informed consent form
- Receipt of another investigational agent or device within the 3 months prior to enrollment
- Contraindication to surgery or general anesthesia
- Contraindication to taking immunosuppressive drugs
- In the opinion of the investigator, any other condition regarded as making subject unsuitable for the trial

Study participant partner inclusion criteria is the ability to act as a potential surrogate over long term for the subject.

Study participant partner exclusion criteria is the inability to cooperate or complete questionnaires.

Investigational Product, Dosage and Mode of Administration:
Cell product: MSK-DA01 comprises cryopreserved DA neuron precursor cells derived from hESC line WA09 or 0062 (H9), that will be delivered as Dose A: 0.9 million cells per putamen, and Dose B: 2.7 million cells per putamen. Cells will be delivered in a single session of stereotactically guided surgical injection into the brain, bilaterally.

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Immunosuppressive regimen: Basiliximab 20 mg intravenously intraoperatively and post-operative day #4; methylprednisolone 500 mg intravenously prior to surgery, then taper to oral prednisone and continued at 5 mg daily for 1 year; tacrolimus 1 mg oral beginning on the day after surgery twice daily, then adjusted to target 4-7 ng/mL for a period of 1 year.

Duration of Treatment: Duration of participation, from time of first contact to time of completion of the 2-year scheduled evaluation, will be up to 26 months for an individual subject. Projected study duration is 44 months.

Reference Therapy, Dosage and Mode of Administration: Not applicable.

Criteria for evaluation:

Safety and Tolerability:

In order to determine safety and tolerability, incidence of transplant-related AEs and immunosuppressive drug-related AEs will be determined for up to 1 year, and clinically significant changes from baseline in physical examination, laboratory values and MRI of the brain from baseline to 2 years in addition to incidence of transplant-related AEs and of immunosuppressive drug-related AEs up to 2 years.

Statistical Methods:

One year:

A formal analysis of the primary endpoint will be performed when at least 1 year's worth of data is available for 10 evaluable subjects. At that time, a data cut will occur and the primary analyses to address safety and tolerability will be performed.

Analysis of secondary and exploratory aims is planned when 1 year's worth of data is available for all evaluable subjects.

Two years:

A formal analysis of secondary outcomes will be performed once at least 2 years' data is available for evaluable subjects. At that time, a data cut will occur and the secondary and exploratory analyses will be performed.

Statistical analyses will be primarily descriptive in nature. Descriptive statistics will include baseline characteristics of the cohort enrolled. Surgical delivery of MSK-DA01 cells will be described, including numbers of tracks, numbers of deposits, position of deposits, estimated cell numbers delivered per deposit, and percentage of target deposits delivered per putamen.

Incidence of SAEs will be tabulated at 1 year post transplant.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BAI-II	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory
BUN	blood urea nitrogen
CBC	complete blood count
CDRH	Center for Devices and Radiological Health
CMP	complete metabolic profile
CMV	cytomegalovirus
CNS	central nervous system
CRF	case report form
CRO	clinical research organization
CsA	cyclosporine A
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DA	dopamine
DBS	deep brain stimulation
DICOM®	Digital Imaging and Communications in Medicine
DNA	deoxyribonucleic acid
DSMC	data safety monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FIMR	Feinstein Institute for Medical Research

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Abbreviation or Specialist Term	Explanation
^{18}F-DOPA	fluorodopa F 18
fVM	fetal ventral mesencephalic
GCIS	Global Clinical Impression Scale
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GRE	gradient recalled echo
H&E	hematoxylin and eosin
HAM-D	Hamilton Depression Scale
HCV	hepatitis C virus
hESCs	human embryonic stem cells
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
hNA	human nuclear antigen antibody
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IHC	immunohistochemistry
IND	investigational new drug application
IRB	institutional review board
IS	immunosuppression monitoring visit
ISO	International Organization for Standardization
ISTA	International Safe Transit Association
IV	intravenous
LSO	Life Science Outsourcing
mDA	midbrain dopamine
MDS	International Parkinson and Movement Disorder Society
MMR	measles, mumps, rubella vaccine
MoCA	Montreal Cognitive Assessment
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
NACU	Neurosurgical Advanced Care Unit

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Abbreviation or Specialist Term	Explanation
NCI	National Cancer Institute
NHP	non-human primate
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NMSS	Non-Motor Symptoms Scale
6-OHDA	6-hydroxydopamine
PACU	Post-Operative Care Unit
PCR	polymerase chain reaction
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire-39
PET	positron emission tomography
PI	Principal Investigator
PKG	Parkinson Kinetigraph
PO	per os (orally)
PoOV	post-operative evaluation
PrOV	pre-operative evaluation
PT	prothrombin time
PTT	partial thromboplastin time
qPCR	quantitative polymerase chain reaction
QUIP	Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease
RBC	red blood cells
SAEs	serious adverse events
SAP	statistical analysis plan
SC	screening
spMRI	surgical planning magnetic resonance imaging
TH	tyrosine hydroxylase
TMT-A	Trial-Making Test A
TMT-B	Trial-Making Test B
TOPF	Test of Premorbid Functioning
UDysRS	Unified Dyskinesia Rating Scale
UK	United Kingdom
UPDRS	Unified Parkinson's Disease Rating Scale

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Abbreviation or Specialist Term	Explanation
US	United States
UTI	urinary tract infection
V	visit
VC	ventricular cannula
VDRL	Venereal Disease Research Laboratory
WA09 hESC	cell line 0062 in NIH registry
WBC	white blood cells

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4. INTRODUCTION

4.1. Disease Overview

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is estimated to affect 7 to 10 million subjects worldwide (Valente, 2012). PD is a progressive and disabling disease with cardinal clinical signs of bradykinesia, rigidity and resting tremor (Parkinson, 2002). These are attributed for the most part to progressive degeneration of dopaminergic input from the substantia nigra to the striatum. Oral medications that restore dopaminergic tone become less effective in advanced PD, and in particular lead to disabling motor complications. These complications of levodopa therapy include (1) motor fluctuations, in which levodopa duration of action is shortened and results in development of "off" periods in which PD symptoms are poorly controlled, and (2) presence of dyskinesia, that is, abnormal involuntary movements most commonly occurring at peak levodopa dose, that may limit therapy and become disabling. For patients with moderate-to-advanced PD in whom medications do not provide adequate control of symptoms, some are eligible for surgical intervention using deep brain stimulation (DBS), which has been Food and Drug Administration (FDA)-approved since 2002 for advanced PD and since 2016 for PD with motor complications and at least 4 years' disease duration. DBS involves surgical insertion of small electrodes that provide continuous high frequency electrical stimulation to a specific target, usually the subthalamic nucleus or the globus pallidus pars interna. These electrodes are connected to a battery/programming device, permanently located in the anterior chest wall of the patient. DBS surgery is a current standard of care in advanced PD, but limitations include the need for indwelling hardware in the brain, reliance on batteries implanted in the chest or abdomen, and the lack of any possibility to restore physiologic dopaminergic inputs. In clinical trials, surgical intervention providing bilateral DBS has resulted in reduced "off" periods (when medications are ineffective) of 70%, and reduction in dyskinesia by 60% to 70% at best. Other studies have found lower efficacy. Complications include hemorrhage, stroke, infection, seizures, and others. Moreover, DBS provides suboptimal relief of speech, gait, and balance difficulties in some individuals. Later stage symptoms, like dyskinesia (comprising random involuntary movements) are likely caused by the continuing degeneration of dopamine (DA) terminals in the striatum resulting in the increased pulsatility of DA receptor stimulation following levodopa therapy.

Cell-based therapies are therefore particularly attractive in that they have the potential to deliver DA in a more physiologic manner than is possible from medications and via synaptic integration, retain functionality of downstream striatal circuits required for long-term motor function. Several cell sources have now been tested in published clinical trials in PD, including fetal ventral mesencephalic (fVM) tissue (Barker, 2013). These studies are summarized briefly in Section 4.6, and provide valuable experience that has aided the trial design. The most extensive experience and most encouraging results derive from the numerous fVM transplant studies undertaken, and an ongoing study, named TRANSEURO, is currently underway (NCT01898390, University of Cambridge, United Kingdom [UK]) to further test fVM transplant in a more highly selected subject group. However, there are many advantages of a stem cell rather than fVM-based therapy, including improved homogeneity of cell type in the final product, scalability, and reproducibility, as well as routine, "off-the-shelf" access to a standardized cell source allowing for proper dosing studies. After extensive efforts in laboratories across the world, the Sponsor's team made a major discovery in 2011 (Gross, 2011) that enables the derivation of nearly

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unlimited numbers of authentic, engraftable DA neurons from human embryonic stem cells (hESCs). The Sponsor's team has extensive preclinical experience with this cell product and has further refined the production process since its last meetings with the FDA (pre-pre-Investigational New Drug Application [IND] 11 August 2014; pre-IND 23 May 2016). The scientific rationale for the therapy has been discussed in both the pre-pre-IND and the pre-IND documents and has been published by the Sponsor (Gross, 2011). Moreover, plans for clinical translation have been developed as part of an international consortium, GForce-PD, with key clinical translation considerations published in 2017 (Barker, 2017).

4.2. Study Interventions

4.2.1. Investigational Therapy: MSK-DA01

MSK-DA01 is an experimental cell product for the treatment of PD that is primarily composed of hESC-derived, midbrain dopamine (mDA) neurons. MSK-DA01 will be delivered using the ClearPoint Neuro SmartFlow® neuro ventricular cannula (510(k): K102101) in conjunction with the ClearPoint Neuro Navigation System (510(k): K100836 and K142505). The SmartFlow® cannula has been modified from the version with 510(k) approval; the modification has been approved for use this study. Thawed and resuspended cryopreserved cells will be delivered by stereotactically guided surgical injection into 9 sites along 3 tracks in the postcommissural putamen of each hemisphere. Subjects will receive 0.9 million cells per putamen (Cohort A) or 2.7 million cells per putamen (Cohort B).

MSK-DA01 was manufactured at Memorial Sloan Kettering's Michael G. Harris Cell Therapy and Cell Engineering Facility. Representatives from the Sponsor will be on site in the Surgical Site laboratory to assist with thawing and formulating the cells and to deliver the product to the operating room. Necessary clearance and training for all representatives will be obtained prior to the first patient enrolled.

MSK-DA01 was found to match pre-established release criteria for viability, identity, purity, microbiology, virology, and endotoxin levels. Vials of 8×10^6 cells per mL are frozen in cryopreservation media and stored in liquid nitrogen at the Good Manufacturing Practice (GMP) facility.

4.3. Immunosuppressive Regimen

An immunosuppressive regimen will be administered over the period of 1 year comprising drugs that are routinely used in solid organ transplant. Administration of the immunosuppression drug regimen, in addition to monitoring and dose adjustment, will be undertaken by the Immunosuppression Clinician.

The regimen comprises basiliximab, methylprednisolone followed by prednisone, and tacrolimus (see Section 8.3.6 for details of dose, route, and schedule of administration).

Alternative medications: Although it is anticipated that the regimen will be well-tolerated and that side effects can be managed with dose reductions, alternative or equivalent medications will be considered on an individual basis, as follows: daclizumab (alternative to basiliximab) and cyclosporine (alternative to tacrolimus).

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4.4. ^{18}F-DOPA Positron Emission Tomography (PET Imaging Site)

Fluorodopa (^{18}F-DOPA) is an FDA-approved imaging agent for PD and will be administered at the Positron Emission Tomography (PET) Imaging Site in the United States. The ^{18}F-DOPA PET protocol will be provided to the Clinical Site and filed in the Investigator Site File.

^{18}F-DOPA for injection will be manufactured at the PET Imaging Site. The proposed study involves administration of 5 mCi at baseline, 12 and 24 months, which is within the range of dosimetric safety data available for this agent and for other radiopharmaceuticals for brain imaging.

Patients are scanned after an overnight withdrawal from their PD medications. They are pretreated with 150 mg of carbidopa given orally approximately 60 minutes (but no more than 120 minutes) prior to the injection of ^{18}F-DOPA Injection. In the event of any unexpected delays with the production/delivery of ^{18}F-DOPA exceeding 120 minutes (post carbidopa administration), an additional 50 mg of carbidopa can be administered approximately 30 minutes prior to the injection.

4.5. Summary of Preclinical and Animal Data

MSK-DA01 is based on work published in Nature 2011 (Kriks, 2011), and validated in several follow-up studies including papers in Cell Stem Cell (2013) [Miller, 2013] and in Nature Biotechnology (2015) [Steinbeck, 2015].

In all the studies described here, and subsequently for the cell product to be used in subjects, the mDA neurons were derived from the WA09 hESC line (also referred to as cell line 0062 in the NIH registry), according to a protocol for the derivation of mDA neurons from hESCs. Using a step-wise differentiation of hESCs with small molecules and growth factors, large numbers of transplantable mDA cells could be generated by Day 16 of differentiation. **These steps do not include any genetic manipulation of the cells.** The mDA neurons were then tested in 3 animal models and the results are summarized herein.

In the original publication (Kriks, 2011), in **mouse**, 4.5-month survival assays were performed in adult, 6-hydroxydopamine (6-OHDA) lesioned ("Parkinsonian") animals (NOD-SCID IL2yR null). These studies included 6 animals and were performed with Day 25 cells at 150,000 cells/animal. At the time of sacrifice, the mice were analyzed for the presence of human cells using human neural cell adhesion molecule and mDA neurons using tyrosine hydroxylase (TH) and FOXA2 staining. Additionally, graft function after transplantation into the striatum of these mice was shown by measuring recovery of amphetamine-induced rotations at 4 months.

Additional, independent transplantation studies into parkinsonian mice were performed in 2 follow-up publications that further validated the results and demonstrated mechanism of action of those grafts using optogenetic strategies (Miller, 2013, Steinbeck, 2015).

More than 500 mice have been transplanted since to further optimize and validate the differentiation protocol including the definitive tumorigenicity, biodistribution, and toxicology studies detailed below.

Robust graft function was further confirmed in the 6-OHDA lesioned rat model. The rat model, unlike the mice, allows for more complex behavioral assays. Lesioned rodent models of PD remain the most robust and widely accepted in the field. The lesion is performed by

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stereotactically injecting 6-OHDA unilaterally in the striatum (in the mouse) or the median forebrain bundle (in the rat). The substance is retrogradely taken up by the axons of the DA neurons of the substantia nigra (SN), which project to the striatum. Once in the SN, 6-OHDA leads to selective DA neuron cell death and results in unilateral deficits referred to as hemiparkinsonism. The animals then start exhibiting stereotypical behavior, the most reliable being unilateral rotations, ipsilateral to the lesion, upon systemic injection with amphetamine. The rotations are quantitated: in general, a rat that exhibits >6 rotations per minute is considered parkinsonian (well lesioned) and is unlikely to experience any spontaneous recovery. Upon successful grafting, the rats start decreasing their rotations and eventually resume symmetric movements. This behavioral recovery, as well as a histological analysis of the grafted tissue, form the basis of the efficacy studies. Multiple sets of in vivo grafting have been performed using immunodeficient rats or Sprague-Dawley rats that received immunosuppression with cyclosporine A (CsA), thus allowing the evaluation of graft survival and function under immunosuppression. Published data with Sprague-Dawley rats (Kriks, 2011) show excellent graft survival, evidence of mDA fiber outgrowth and maintenance of midbrain-specific transcription factor expression confirming long-term survival of the hESC-derived neurons expressing authentic mDA neuron markers. Transplantation of mDA neurons derived from WA09 has been performed in >100 additional rats since the original report to optimize and validate the differentiation protocol and the cryopreservation method used.

The third pre-clinical model used to test the translational potential of the mDA neurons is the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned ("Parkinsonian") **rhesus** monkey. An initial set of studies was performed in 2 monkeys to test short-term (4-week) in vivo survival and maintenance of mDA neuron phenotype in the primate brain (Kriks, 2011). Day 25 mDA neurons derived from WA09 hESCs and from WA09-GFP hESCs (expression of GFP under control of EF1a promoter) were grafted into the striatum of adult MPTP lesioned rhesus monkeys (N=2, 1.25×10^6 cells/tract, 3 tracts/per putamen, 6 tracts in total, cell number of 3.75 million cells per putamen, in a volume of 30 µL). For both animals, 1 putamen each was grafted with unlabeled WA09-derived cells while the other putamen received cells derived from WA09-GFP cells. The animals received CsA for immunosuppression. Those studies showed robust survival of TH/FOXA2 positive mDA neurons and evidence of re-innervation of the host striatum. These findings were important and showed that grafting larger numbers of cells, similar to those ultimately required for future human grafting studies, is possible and results in robust mDA neuron survival.

Four batches of MSK-DA01 were manufactured in MSK's GMP facility and were used to qualify the differentiation process. All batches were tested for sterility, endotoxin, cell viability, markers for non-DA impurities, and markers for DA cells and passed release criteria. One lot was further tested for non-clinical safety and efficacy.

The following IND-enabling studies were conducted:

- Non-GLP study to assess the efficacy of MSK-DA01 in a rodent model of Parkinson's disease
- GLP study to assess biodistribution und toxicology of MSK-DA01
- GLP study to assess tumorigenicity of MSK-DA01

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- Non-GLP study to assess MR-guided implantation of MSK-DA01 in the nonhuman primate (NHP) brain

4.5.1. Study at MSK: Study to Assess the Efficacy of MSK-DA01 in a Rodent Model of Parkinson's Disease

An efficacy study was conducted under near Good Laboratory Practice (GLP) conditions. Twenty-seven 6-OHDA lesioned rats (male:female ratio ~1:1) received MSK-DA01 intrastriatal injections (400,000 cells) and 14 rats received vehicle-only injections.

There were no treatment-related effects on morbidity or mortality.

Blinded assessment of behavioral testing demonstrated significant improvement in the rotational behavior down to normal values in the animals grafted with MSK-DA01 while the vehicle-injected control animals maintained their abnormal behavior throughout the study period. Recovery of animal behavior in MSK-DA01 treated animals was statistically significant as demonstrated by improvement in rotation scores at 5 and 8 months post grafting, compared to sham controls ($p<0.05$ and $p<0.0001$, respectively).

MSK-DA01 graft survival was observed histologically in 100% of the animals. The grafts demonstrated the presence of DA neurons with normal morphology and good innervation of the striatum. Assessment of the surviving cell numbers showed an average of 45,741 DA neurons out of an average of 592,698 cells, ie, 12%. Remaining cells represented closely related or still immature midbrain lineages similar to the cell types expected to be present in developing human fetal mDA neuron grafts. No serotonin+ neurons, a cell type previously associated with the risk of graft-induced dyskinesia in human fetal grafts, were detected.

There were no tumors or evidence of overgrowth of neural tissue and the proliferation rate of surviving graft cells at terminal sacrifice was low.

4.5.2. Study C17399 at WuXi Apptec in St. Paul, Minnesota: GLP Study to Assess Biodistribution and Toxicology of MSK-DA01

To assess the biodistribution, toxicity, and persistence of the test article, MSK-DA01-002-051016 cells, at low and high doses, were injected unilaterally into the right striatum of NOD scid gamma (NSG; immunodeficient) mice. This is considered the most sensitive mouse model to detect tumor formation in a xenografting paradigm (Quintana, 2008).

Animals were observed for general health, mortality, and moribundity, clinical observations, body weights, and clinical chemistry. At terminal sacrifice, necropsies were performed and tissues collected for biodistribution/quantitative polymerase chain reaction (qPCR) or toxicology/histology. Four cases of early death occurred during the period covered by this study. All 4 cases of early death are unlikely to be related to the test article.

There were no treatment related deaths. There were no treatment related or clinically relevant effects on body weight, hematology, or clinical chemistry parameters.

Histologically, from Day 30 to Day 180, the injected cells transitioned from densely cellular clusters of small neural-progenitor-type cells to looser clusters of larger, more differentiated neuron-cell-body-like cells with much more abundant supporting neuropil that appeared more continuous with surrounding host neuropil. Growth of human-origin cell clusters from Day 30 to

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180 was apparently slow, with the largest clusters only about twice the size at 180 days than at 30 days after injection. These findings suggested maturation of injected human-origin dopaminergic cells into grey matter-like tissue, and incorporation into the host tissue over time. Immunohistochemistry analysis demonstrated that grafts were maturing neuronal cells with a low potential for proliferation.

The biodistribution as assessed by qPCR detection of MSK-DA01 genomes in major organs showed that at time point Day 30, the human cells remained primarily at the injection site in brain and did not extensively traffic outside that site. All samples in the negative control group tested below the limit of quantitation and were negative. All brain samples in the test article groups, low and high dose groups, tested positive except for the animal number C17-257 in the female low dose group, which tested negative. The positive results in the brain verify that the test article was injected in the target area of the brain. One negative incident could have been due to a mistake of sampling a wrong area of the brain or technical failure during cell injection.

4.5.3. Study C17400 at WuXi Apptec in St. Paul, Minnesota: GLP Study to Assess Tumorigenicity of MSK-DA01

To assess the tumorigenicity of human mDA neurons in immunodeficient mouse model, negative control (vehicle, Group 1), positive control (WA09 undifferentiated human ES cells, Group 2), Group 3 (mDA neurons + 0.1% WA09 undifferentiated human ES cells), Group 4 (mDA neurons + 0.01% WA09 undifferentiated human ES cells), and Group 5 (100%) cells were injected unilaterally into the right striatum of NSG mice.

Microscopic evaluation of individual animals in all groups was performed per protocol.

The negative control article, Reference I test article, Reference II test article, and MSK-DA01 were considered non-tumorigenic, as no animals in these groups developed a neoplastic mass at the injection site. However, the positive control article was considered tumorigenic, as 18/24 animals (75.0%) developed teratomas (ie, neoplasms that recapitulate multiple embryonic structures) at the injection site positive by immunohistochemistry (IHC) for human nuclear antigen antibody (hNA), consistent with origin from the WA09 cell line injected.

The majority of animals treated with Reference I test article, Reference II test article, and MSK-DA01 exhibited clusters of well-differentiated large neurons supported by neuropil with glial cells within the injection site or tract, positive by IHC for hNA. These findings were consistent with maturation into mature nervous tissue.

In the MSK-DA01 group, 3 out of 22 dosed male mice (13.6%) and 5 out of 22 dosed female mice (22.7%) died early or were euthanized. One male was euthanized early due to clinical signs associated with an unrelated spontaneous systemic lesion. Two male and 5 female animals died early due to unknown reasons, which the pathologist suggested might have been due to the mass effect of the large cluster of injected-cell-origin nervous tissue at the injection site within the brain. However, the grafts did not cause a midline shift and there was no evidence of herniation that would support a mass effect. Rather, the histological evidence supports the large cluster of cells are consistent with maturation of the injected MSK-DA01 cells into mature nervous tissue. Additionally, further IHC analysis demonstrated the cells were mature neuronal cells with a low potential for proliferation.

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4.5.4. MR-Guided Implantation of ES-Derived Dopaminergic Cells (MSK-DA01) in the Nonhuman (NHP) Brain (Study No. S17-10657) and Preclinical Histological Study Report UCSF (Study No. SC-003)

The objective of this study was to evaluate implantation conditions and survival of MSK-DA01 in the non-human primate (NHP). Eight Rhesus monkeys (*Macaca mulatta*) were assigned to 2 dose groups with different immunosuppressant regimens: Groups 1A-1B were treated with mycophenolate mofetil, tacrolimus, and prednisone; and Groups 2A-2B were treated with tacrolimus and prednisone. MSK-DA01 was administered bilaterally in small deposits into the putamen: 6×10^6 cells in 3 deposits of 20 µ/hemisphere within 8 hours of preparation. Acute intracerebral infusions were achieved using a modified 16-gauge VC (MRI Interventions Inc., Irvine CA [now ClearPoint Neuro, Inc.]) attached to a 100-µL Hamilton® syringe and a syringe pump. Infusion was performed by advancing the cannula 2 mm ventrally after every 6 to 7 µL of infusion at an infusion rate of 2 or 10 µL/minute. All animals were euthanized 2 months post-implantation and their brains processed for histopathological signs of toxicity, and immunohistological evaluation of survival and migration of MSK-DA01 cells. The in-life portion of the study was conducted at Valley Biosystems, Sacramento, California, and the post-mortem/histological analysis was conducted at Memorial Sloan Kettering Cancer Center.

Key findings with respect to the administration procedure were as follows:

- The intracerebral infusion procedure was well tolerated, and surgical recovery was uneventful.
- The derived volumes were effectively administered to target locations.
- Cells were observed settling in the syringe.
- Cellular occlusion of the cannula was observed in 1 instance.
- Cellular implants identified in some, but not all of the deposit sites were attributed to the gravitational settling of cells in the syringe, resulting in inconsistency in cell density between deposits. Because in this study, the entire volume of cell suspension required for a single hemisphere was loaded in a single syringe, the cells sat at room temperature for an extended period of time, which resulted in gravitational settling and unequal deposition of cells. As described in the Cell Preparation and Delivery Manual, cells loaded into the syringe will be held on ice until administration to the patient. This was shown to resolve gravitational settling.
- Gross necropsy findings were limited to adhesion of the dura to the cerebral surface and skull and the craniotomy site is a single monkey.
- No signs of hemorrhage or damage related to the implantation procedure were identified in any of the subjects. No major histopathological signs of toxicity were observed in the brain tissue.
- Mild neuro-inflammation was associated with both the administration procedure and implanted cells.

Key findings associated with the immunosuppression regimen were as follows:

- Mycophenolate mofetil may be negatively affecting cell survival.

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Key findings associated with engraftment of MSK-DA01 cells were as follows:

- The survival of the engrafted cells at 2 months post-implantation provides in vivo evidence that the cells were biocompatible with the ventricular cannula and lumen and that the 16-gauge cannula and Hamilton® syringe did not negatively affect cellular survival, for example by exerting excessive shear stress during administration.

4.6. Previous Experience with Cell Transplantation

Multiple cell sources have now been tested in published clinical trials in PD, including fVM tissue (Barker, 2013), adrenal medullary cells (Goetz, 1989), and most recently retinal pigmented epithelial cells (Gross, 2011). Of these, the best-studied reparative therapy in PD remains allotransplant of dopaminergic neuroblasts from fVM tissue, first performed in 1987 at Lund University, Sweden (Brundin, 1987; Brundin, 1988). These studies, carried out up until 2003, demonstrated graft survival as measured by neuroimaging modalities over a period of years. Moreover, analysis of tissue obtained at autopsy has demonstrated survival of engrafted tissue with dopaminergic neuron characteristics.

Recently, long-term data have confirmed that transplanted fVM tissue is capable of long-term survival in the host brain, although there is ongoing discussion as to how cell survival relates precisely to clinical effects (Kordower, 2017). Long-term symptomatic relief has been documented in 2 surviving subjects at 15 years and 18 years post transplant in 1 study (Kefalopoulou, 2014), and a recent report following autopsy demonstrated maintenance of DA transporter protein reflecting surviving engrafted tissue in 5 subjects from 4 to 14 years post transplant of fVM tissue (Hallett, 2014). An autopsy evaluation was performed in 5 individuals who had undergone bilateral putamen fVM tissue transplant in a sham surgery controlled clinical trial (Freed, 2001) 17 to 18 years previously. Clinical and neuroimaging results support (1) graft maintenance in each of 3 subjects undergoing neuroimaging, (2) evidence of graft activity based upon clinical signs, and (3) atypical outcomes with superior function to that expected, comparable with published data on long-term DBS outcomes, at up to 36 years of PD duration (Henchcliffe, 2016a; Henchcliffe, 2016b).

Data from these studies have been examined in detail to assist in clinical development planning (see Section 4.7 and Section 4.8), including development of inclusion and exclusion criteria, choice of study endpoints, study duration, and the use of an immunosuppression regimen. Of the fVM transplant studies, some studies found that subjects responded well while others have shown no or minimal improvements, but at least some of this heterogeneity may be due to different characteristics of the subjects enrolled, as well as choice of outcome measures, and various study durations. Data from 2 NIH-funded sham surgery controlled clinical trials have, in particular, provided valuable information based upon retrospective subgroup analyses in which younger subjects with better levodopa response and shorter disease duration experienced more benefit (Freed, 2001; Olanow, 2003). The studies also highlighted potential pitfalls. Some subjects experienced off-state graft-induced dyskinesias (Freed, 2001; Olanow, 2003; Hagell, 2001) that may be attributable in part to growth of non-dopaminergic, such as serotonergic neurons from grafted fetal tissue, but also possibly to irregular and patchy distribution of the surviving engrafted tissue and/or deficient innervation from graft to host. Finally, although some

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subjects reported benefit early after the transplantation procedure (Freed, 2001), some study participants have not demonstrated clinical improvement until later (Kefalopoulou, 2014).

To note, the potential risk of bilateral injections is due to hemorrhage following injections. There is a track record in the field for bilateral implantation of devices and for bilateral fetal grafts. The advantage of a single session is 1) the elimination of a second session of intubation and general anesthesia and 2) the elimination of a concern over repriming a patient with allograft material, which may be detrimental, despite immunosuppression, upon second administration of the same material. A repeat injection of graft material would also likely require reloading with immunosuppressants. In the current study, intraoperative magnetic resonance imaging (MRI) will be performed after the 3 tracks are placed in each putamen, to exclude the possibility of significant hemorrhage before proceeding to the other side.

At present, there are several studies ongoing internationally that aim to examine effects of intracerebral cell transplantation in PD. The open-label TRANSEURO study (NCT01898390, University of Cambridge UK) is underway. This study will re-examine the effects of bilateral putaminal engraftment of fVM cells in a target of 40 participants. The study design is optimized based upon prior experiences: Eligible individuals are aged 30 to 68 years old, with PD duration of 2 to 13 years. A study to examine safety and tolerability of human fVM transplant in 15 patients is ongoing in the CHA Bundang Medical Center, Republic of Korea (NCT01860794). A study of neural stem cell-derived neurons for 12 participants is reported as planned but not yet recruiting (NeuroGeneration, NCT03309514). Two studies using pluripotent stem cell-derived neural stem cells in 10 and 50 patients, respectively, are being conducted in China (NCT03815071 and NCT03119636). Another study in Melbourne, Australia is examining the safety of neural stem cell (not DA neurons) transplantation derived from parthenogenetic stem cells in individuals aged 30 to 70 years old with PD up to 13 years (NCT02452723). Finally, an open label study, using induced pluripotent stem cell derived dopaminergic neurons, has started in Japan (http://www.kuhp.kyoto-u.ac.jp/ips-pd.html).

4.7. Study Design Rationale

Cell–based therapies have the potential to deliver DA to the DA-depleted striatum in a more physiologic manner than is possible from medications. The Sponsor has derived authentic, engraftable mDA neurons from hESCs using a novel, small molecule-based floor-plate differentiation strategy. These cells demonstrate excellent in vivo survival and function in animal models of PD with no evidence of tumor or excessive growth (see Section 4.5). The Sponsor will therefore implement an open label, non-randomized study, with the primary objective of evaluating safety and tolerability of transplantation of 2 dose levels of MSK-DA01 cells in individuals with advanced PD at 1 year post transplant. The rationale for key design features is described in this section.

4.7.1. Rationale for the Study Population

Ascertainment of diagnosis will combine formal criteria and evaluation by a movement disorders neurologist. The minimum time of 5 years PD duration in the inclusion criteria will further enhance high diagnostic accuracy (88% based upon published autopsy data at >5 years versus 53% at <5 years) [Adler, 2014]. An upper limit of 15 years PD duration has been made to exclude subjects with the most advanced stages of PD, in whom more widespread pathology may

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impair ability of downstream neurons to respond to dopaminergic stimulation. The age range of ≥60 to ≤76 years at time of study entry has been chosen to balance (a) on the lower end, allowing enrollment of younger subjects who may stand to benefit more (Barker, 2013; Freed, 2001) and (b) on the upper end, maintaining ability to enroll subjects with typical age of onset of PD while avoiding the inclusion of older subjects who may be more likely to develop comorbidities and experience more risk during such a study.

Other inclusion-exclusion criteria are designed to ensure:

- response to dopaminergic medications, that will reflect integrity of the striatal receptors anticipated to be necessary to generate a graft response
- avoiding significant dyskinesia that might worsen based upon previous fVM studies
- avoiding significant load of non-motor symptoms that are predicted to be non-DA responsive and might possibly worsen with increased dopaminergic stimulation, such as hallucinations, cognitive decline, or impulse control disorders

Subjects also must be deemed able to tolerate immunosuppression, and not to be at undue risk of immunosuppression. Anatomic findings on MRI scans that could lead to a potentially higher risk of surgical adverse events (AEs), such as the presence of significant subdural collections, significant generalized or striatal atrophy, have also been included in the exclusion criteria.

4.7.2. Rationale for Use of ^{18}F-DOPA PET Scan

PET scans of the brain using ^{18}F-DOPA as a radiotracer will be performed at the PET Imaging Site. The ^{18}F-DOPA PET scan is widely used to evaluate presynaptic DA neuron integrity, due to uptake as ^{18}F-DOPA as a DA precursor in these neurons. This tracer binds to aromatic acid decarboxylase in the DA nerve terminals in the brain, and therefore has been extensively used in clinical trials as a measure of loss of DA neurons. It is a biomarker that reflects density of neuronal terminals that release DA into the striatum. Sensitivity and specificity for the diagnosis of PD are estimated to be 95% and 100% respectively, and it may therefore be used as a screening investigational tool that may correlate with graft survival and/or clinical progression. It has been used in multiple previous clinical trials of fVM tissue and cell transplantation in PD in order to detect increased uptake of DA precursors (specifically ^{18}F-DOPA) that is attributable to survival and differentiation of transplanted cells into dopaminergic neurons.

4.8. Dose Rationale

4.8.1. Rationale for Cell Dose

This is a first-in-human study of MSK-DA01 and therefore the optimal dose is not known in humans. However, the cell dose for injection was selected based upon target surviving cell dose, while knowing the cell survival rate of the same batch of cells nominated for clinical use from extensive preclinical studies. The target surviving cell doses are based upon:

(1) Knowledge of the number of cells lost in PD. Stereological counts of the substantia nigra indicate that a healthy individual has about 400,000 dopaminergic neurons per side (Rudow, 2008). It is estimated that >50% of DA neurons and about 80% of DA innervation to the striatum are lost by the time of diagnosis. In subjects with ongoing disease (average of 12 years), it was found that about 80% of DA neurons are lost (Rudow, 2008). This therefore provides an estimate

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of the number of cells that need to be replaced to approximate the threshold needed for DA function (cohort A: 100,000 surviving DA cells) or to more closely approximate physiological numbers of DA neurons (cohort B: 300,000 surviving DA cells). Albeit, these are minimum estimates since it is likely that not all surviving transplanted DA cells, when placed in the adult PD brain, will provide the same degree of innervation to as would the host's own native cells during development.

(2) Autopsy data from previous fVM studies. The doses (target 100,000 surviving cells per putamen, Cohort A; 300,000 surviving cells per putamen, Cohort B) are based upon the observation that clinical improvement in subjects requires the survival of at least 100,000 surviving DA cells per putamen (Hagell, 2001). While 1 study has demonstrated 33% improvement in a subject with only 37,000 cells per putamen at autopsy (Freed, 2001), this is an isolated finding and upon careful review of the literature represents an exception (Hagell, 2001).

One uncertainty when proposing a cell dose based in part upon previous fVM transplant for a human ES-based mDA neuron product is the functional equivalency of human ES versus fVM based mDA neurons. Detailed studies under the TransEURO effort (Rath, 2013) have established that in the rat model, the threshold for functional recovery in amphetamine-induced rotations using fVM tissue is 657 +/-199 neurons that immunostain positive for TH (TH+), that is, DA neurons. Recently, studies defining a functional threshold using hESC-derived mDA neurons by Parmar and colleagues show comparable cell numbers in the range of about 1,000 surviving TH+ neurons (Grealish, 2014). The Sponsor's own preliminary studies support a similar or slightly higher threshold of about a minimum of 1,000 to 2,000 surviving hESC-derived mDA neurons to achieve functional recovery in the 6-hydroxydopamine (6-OHDA) lesioned rat model. Therefore, existing evidence points to an approximate functional equivalency of fVM derived and human ESC derived mDA neurons.

The number of cells and volumes to be injected to achieve the desired surviving cell count is based upon the survival data in rodent studies, and the maximum concentration of 100,000 ± 10,000 cells/microliter. Volumes to be infused per putamen (10.5 and 33 µL for the low dose and high dose, respectively, ie, 3.5 and 11 µL per track, respectively) are expected to be feasible.

- Dose A: 0.9 million MSK-DA01 cells per putamen is estimated to provide the lower target of 100,000 surviving cells.
- Dose B: 2.7 million cells per putamen is estimated to provide the higher target of 300,000 surviving cells.

This dosing regimen takes into account safety and ethical considerations in the context of a clinical study. While the primary endpoint of the study is safety and tolerability, for a subject to undergo a surgical procedure that includes a 12-month immunosuppressive regimen, it is important to use a dose that is conservative but within the range of what might be expected to be therapeutic. It is acknowledged that fVM grafts have resulted in graft-induced dyskinesia in a subset of subjects, raising the concern that a high dose of MSK-DA01 could produce a similar effect. However, current evidence indicates that graft-induced dyskinesia is correlated to the extent of pre-existing L-Dopa-induced dyskinesia in grafted subjects, that it may be triggered in part by a non-mDA component (serotonergic neurons) [Politis, 2012] in the graft that are largely absent in the Sponsor's preparation as confirmed in the Sponsor's clinical batch, or that it could be due to uneven survival and reinnervation ("hotspot" hypothesis [Maries, 2006; Carlsson,

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2006]). In contrast, there is no well-established correlation of graft-induced dyskinesia with the number of surviving mDA neurons.

4.8.2. Rationale and Justification for Immunosuppression

Whether to provide immunosuppression for mDA neuron transplantation to improve graft survival remains an important question that has yet to be fully resolved. Some investigators have questioned the importance of a defined immunosuppression protocol for allogeneic cell transplantation into the central nervous system (CNS) [Freed, 1992]. Clinical, radiographic, and autopsy data have demonstrated maintenance of engrafted tissue to some degree in at least a subset of individuals without immunosuppression (Freed, 2001). However, fVM transplant recipients in this study had fewer surviving donor-derived DA neurons than expected when compared with other studies that had used a temporary immunosuppression regimen, raising the possibility that temporary immunosuppression might have provided benefit, although other factors than immunosuppression may have been responsible. Recent studies in monkey allografts of pluripotent-derived midbrain DA neuron showed lower DA neuron survival in allogenic versus isogenic hosts and showed that tacrolimus-based immunosuppression could significantly improve DA neurons survival in an allograft setting (Morizane, 2015). Furthermore, it is known that allografts to the brain are recognized by the immune system such that a peripheral challenge by injecting the same tissue peripherally can readily trigger graft rejection in the brain (Backes, 1990).

Therefore, there are now a number of lines of evidence that support judicious administration of a carefully monitored temporary immunosuppressive regimen.

a. Although the brain is traditionally considered an immunologically privileged site, such privilege is by no means absolute. Immune reaction to non-human leukocyte antigen (HLA) matched grafts of fetal neural and other allogeneic cells has been demonstrated in animals, with improvement with immunosuppression (Sayles, 2004).
b. Surgical intervention at the time of transplant compromises the blood-brain barrier (Kim, 2013), thus exposing the brain to circulating immune cells, and this structure is also abnormal in neurodegenerative conditions including PD (Cabezas, 2014).
c. Activated microglia and inflammatory responses have been documented at autopsy in recipients of allogeneic cell transplants into the CNS (Gross, 2011; Freed, 2001; Olanow, 2003; Lindvall, 1989). The risks of immunosuppression are well documented, with increased risk to the recipient of infection and (rarely) tumor formation.

Rationale for Duration of Immunosuppression

The majority of cell and tissue allograft transplantation trials involving the brain and spinal cord have incorporated a temporary phase of immunosuppression, but the duration has varied substantially. Most clinical trials have incorporated courses of immunosuppression ranging from 3 to 12 months after transplantation, although a minority have up to 2 to 4 years, particularly in early open-label studies. It has been suggested, although not proven, that worsened motor performance may have been related to withdrawal of immunosuppression at 6 months after fVM tissue transplants in PD (Barker, 2013; Olanow, 2003). This observation supports extending the length of immunosuppression to 12 months. The choice of 12 months is also consistent with the consensus of other investigations currently underway or planned in cell-based studies in PD

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(Barker, 2017; Kirkeby, 2017). Ultimately, the relatively immuno-privileged status of the CNS should optimize conditions for long-term cell engraftment after planned cessation of immunosuppression.

Rationale for Choice of Agents

Drugs administered in previous studies have typically comprised a calcineurin inhibitor, often combined with an anti-proliferative agent, and a steroid, based upon experience in solid organ transplants. For example the "Lund protocol" employed an immunosuppressive protocol comprising cyclosporine, azathioprine, and prednisolone for at least 12 to 24 months (Lindvall, 1989; Lindvall, 1990; Lindvall, 1992; Lindvall, 1994; Sawle, 1992), while in a sham surgery-controlled study, investigators elected to administer a single immunosuppressant, cyclosporine, over a 6-month period (Olanow, 2003). The question of immunosuppression and design of an appropriate regimen was discussed with a group of transplant experts. An immunosuppression clinician will be enrolled as an investigator to focus on the immunosuppressive component of the study.

All subjects who receive any amount of cell dose will undergo a 12-month course of immunosuppressive therapy with tacrolimus. Tacrolimus is a well-established drug for allogeneic solid organ transplantation, and is the leading immunosuppressive agent used in renal transplantation in North America (Smith, 2013). It has been shown to be successful in reducing the incidence of graft rejection in these cases by suppressing T-cell response and is generally well tolerated with known human safety profiles.

In addition, subjects will receive perioperative administration of intravenous (IV) basiliximab and IV methylprednisolone. The use of basiliximab and methylprednisone will provide an additional level of immunosuppression (via distinct immunological pathways) in the immediate post-operative period. This corresponds to the time of maximal disruption of the blood brain barrier secondary to the surgical transplant procedure, when the donor cells are potentially exposed to systemic immuno-surveillance.

Once subjects have undergone surgery, the steroid administered will be changed to oral prednisone, to be continued at a low dose together with tacrolimus. This and related oral glucocorticoids are used to prevent graft rejection in solid organ transplant protocols and, as noted above, have been incorporated with good tolerability into the postoperative regimens of many individuals with PD who have undergone fVM transplant.

The management of the immunosuppressive agents will be under the guidance of the Immunosuppression Clinician. In addition, the data safety monitoring committee (DSMC) will monitor the safety of the immunosuppression, and the regimen can be adjusted or discontinued if the subject is showing poor tolerance or AEs. The study will also monitor subjects following termination of the immunosuppression in order to assess any clinical change that might indicate cell rejection or complications thereof.

In summary, there is a strong rationale for using transient immunosuppression. On balance, it seems prudent to include temporary immunosuppression to enhance the possibility for cell survival and function, while carefully monitoring for the known risks of such a regimen.

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4.9. Benefit-Risk Assessment

The Sponsor cannot and does not guarantee that the subject will receive any benefits from this study. The primary goal of the study is to test the safety and tolerability of transplantation of MSK-DA01 cells into the bilateral putamen of each of the study subjects, and therefore such parameters will primarily be evaluated. However, both cell doses used are within a range that is anticipated to result in potential efficacy and therefore, data that might support potential improvement in subjects' conditions will also be collected. The possible benefits to the subject, if the cells survive and function as predicted by preclinical studies that led to this clinical trial, is that motor symptoms may improve. This may include improvement in movement and motor skills overall, less time spent in the "off" condition in which medication is not adequately controlling the symptoms, and it may lead to reduced need for anti-PD medications. However, these benefits may not be immediate, and could take months to years to become evident. Finally, other subjects with PD may benefit in the future from data collected in this research study.

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5. TRIAL OBJECTIVES AND ENDPOINTS

5.1. Objectives

This first-in-human Phase 1 study will have the primary focus of testing safety and tolerability of the intervention in an open label design. Additionally, data will also be collected on clinical and radiologic changes observed longitudinally that may be used as a basis for further studies in the development of this product. Exploratory aims will also be included that will support learning how other clinical, neurophysiological, biochemical and molecular measures may be helpful in future clinical trials of these and other cell products.

5.1.1. Primary Objective

The primary objective of the study is to assess the safety and tolerability of MSK-DA01 cell transplantation at 1 year post transplant.

5.1.2. Secondary Objectives

The secondary objectives of the study are as follows:

1. to assess the evidence of transplanted cell survival and motor effects at 1 and 2 years post transplant
2. to evaluate continued safety and tolerability at 2 years
3. to assess feasibility of transplantation

5.1.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

1. to determine the effects of MSK-DA01 transplantation upon motor and non-motor signs and symptoms of PD and upon accelerometry-based measures of motor function
2. to assess the subject's perception of their quality of life
3. to collect biosamples for anti-HLA testing; to obtain blood for storage for xenotransplantation-related future testing; and to store leftover samples for future studies of biomarkers of PD, DA function, inflammation, and immune response to engrafted cells

5.2. Endpoints

Descriptions of the measures to be used as listed below (primary, secondary, and exploratory endpoints) are contained in Appendix 2.

5.2.1. Primary Endpoint

The primary endpoint of the study will be the incidence of serious adverse events (SAEs) at 1 year post transplant. The analysis will be undertaken for each of the 2 cohorts separately. Safety will be defined as 2 or fewer of Cohort A or Cohort B developing 2 or more SAEs related to surgery, presence of transplanted cells, or immunosuppression; as 2 or fewer of Cohort A or Cohort B developing a tumor or abnormal tissue overgrowth related to presence of transplanted cells; as 2 or fewer of Cohort A or Cohort B developing an intracerebral hemorrhage that is deemed life-threatening; and as 1 or zero deaths for Cohort A or Cohort B. All data collected on any subject lost to follow up will be included in the assessment of safety.

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This safety definition is designed to allow for greater toxicity than many Phase 1 studies, due to combined known risks of 1) the surgical procedure that is similar to the standard of care for advanced PD (DBS) and 2) immunosuppression.

5.2.2. Secondary Endpoints

The secondary endpoints of the study will be

1. Change in striatal ^{18}F-DOPA uptake using PET from baseline to 1 and 2 years
2. Changes from baseline in the following measures at 2 years post transplant: International Parkinson and Movement Disorder Society (MDS)-Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore in the "off" state, number of waking hours in the "off" state, incidence of SAEs at 2 years post transplant, and incidence and type of AEs at 1 and 2 years post transplant
3. Feasibility, as defined by intra-operative delivery of at least 50% of the intended total number of deposits per brain in at least 6/10 subjects. The intended number of deposits is defined as the neurosurgeon's planned trajectories times the number of cellular deposits as determined during the procedure. For example, the surgeon may plan 3 trajectories through each putamen with 3 deposits in each trajectory; thus, a bilateral administration with a total of 18 cellular deposits would be made (ie, 3 trajectories × 3 cellular deposits × 2 putamina = 18). An individual subject's surgical procedure will be determined to be feasible if 9 of the 18 deposits are made in that subject. During the surgery, the surgeon may elect to alter the surgical plan (ie, number of cellular deposits) based on intra-operative imaging. For example, the number of trajectories may change from 3 trajectories to 2 trajectories with 3 deposits in each trajectory. In this case, the intended deposits would be 2 trajectories × 3 cellular deposits × 2 putamina = 12 total cellular deposits. The surgeon would then increase the volume delivered at each deposit so that the total dose will be delivered regardless of the number of deposits. The study procedure would be deemed feasible for this subject if the surgeon then successfully implants 6 or more of the intended total number of deposits.

5.2.3. Exploratory Endpoints

The exploratory endpoints of the study will be

1. Changes in the following measures from baseline to 2 years in: total MDS-UPDRS scores; MDS-UPDRS Part 1 scores; MDS-UPDRS Part 2 scores; MDS-UPDRS motor subscore in the "on" state; MDS-UPDRS Part 4 scores; 10 meter walking test; anti-PD medications (daily levodopa equivalent dose); Modified Schwab and England Activities of Daily Living; Unified Dyskinesia Rating Scale (UDysRS); neuropsychological testing; non-motor measures including Montreal Cognitive Assessment (MoCA), Beck Anxiety Inventory (BAI-II), Beck Depression Inventory (BDI-II), Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease (QUIP), PD Non-Motor Symptoms Scale (NMSS); Global Clinical Impression Scale; daily time in the "on," "on with dyskinesia," measured by the Hauser diary; daily time in the "on," "on with dyskinesia," "off" states measured by the Parkinson Kinetigraph (PKG)
2. Quality of life as measured by Parkinson's Disease Questionnaire-39 (PDQ-39)
3. Sample collection for biorepository does not have pre-specified endpoints.

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6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

6.1.1. Design

The study design is a multi-center, multi-site (Clinical Site, Surgical Site, PET Imaging Site), open label, non-randomized study to evaluate the safety, and tolerability of bilateral surgical implantation of 2 dose levels of MSK-DA01 into the post-commissural putamen, the site at which dopaminergic input from the substantia nigra is preferentially lost in PD.

- MSK-DA01 cells are GMP manufactured allogeneic, hESC (H9/WA09)-derived, cryopreserved mDA neuronal cells. This protocol is based upon data generated in rodent studies as detailed in Section 4.5, showing that transplantation of these cells is effective in treating standard animal models of PD.
- The intervention will comprise a single session of stereotactically guided, multi-deposit, surgical transplantation of MSK-DA01 cells to the post-commissural putamen bilaterally in 10 subjects with advanced PD. Subjects will then undergo a limited period of 12 months of immunosuppressive therapy.
- Two dose levels will be explored in cohorts of 5 subjects each. The first 5 subjects (Cohort A) will receive Dose A (0.9 million cells per putamen) and the second 5 (Cohort B) will receive Dose B (2.7 million cells per putamen).
- In order to determine safety and tolerability, incidence of transplant-related AEs and immunosuppressive drug-related AEs will be determined for up to 1 year, and clinically significant changes from baseline in physical examination, laboratory values, and MRI of the brain from baseline to 2 years in addition to incidence of transplant-related AEs and of immunosuppressive drug-related AEs will be determined up to 2 years.

While the primary objective is to demonstrate safety and tolerability, imaging and clinical data will also be collected to determine transplanted cell survival that may provide a signal as to whether the intervention at 1 or both of the 2 cell doses can lead to improvement in motor symptoms of PD. To accomplish the secondary aims, neuroimaging using ^{18}F-DOPA PET will provide evidence of graft survival and clinical data that include efficacy measures which will inform future studies, should the safety and tolerability profile of this product be deemed sufficient to proceed with further development of this product.

Long-term follow-up will also be done as part of an independent study for subjects enrolled into this trial. The study design is shown in Figure 1.

There will be 3 institutions with activities as follows:

- Recruitment, informed consent, and Screening (SC) will comprise clinical evaluations and MRI of the brain (Clinical Site).
- Pre-operative evaluation (PrOV) visit with Neurosurgery will include surgical consent, pre-operative clearance, MRI for surgical planning (Surgical Site).

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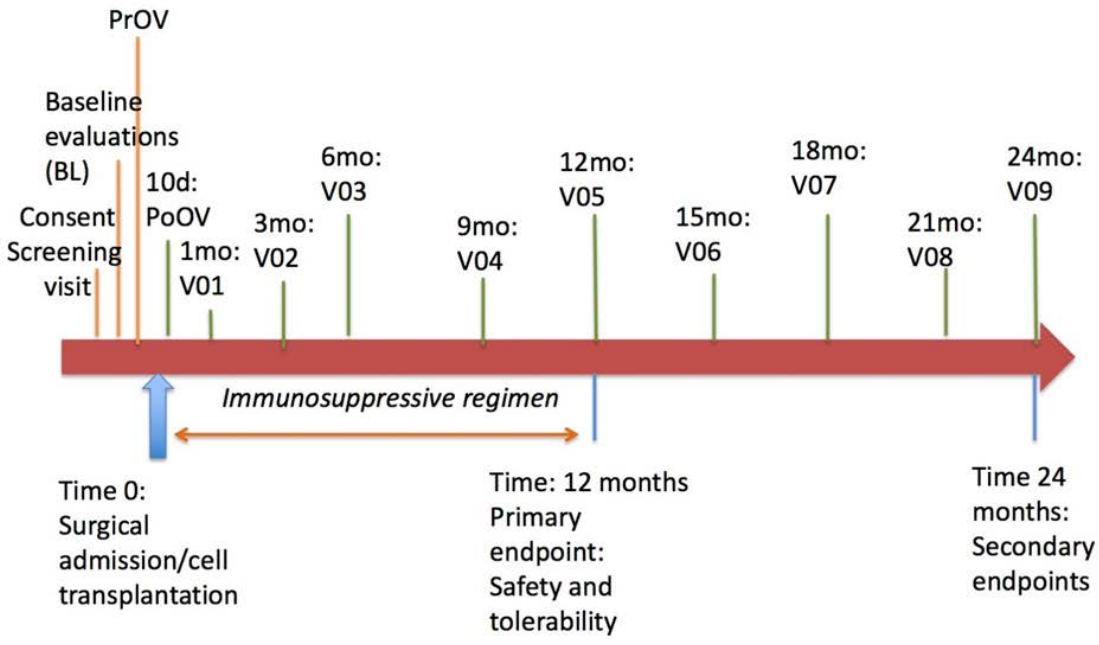
- Baseline visit (Clinical Site) will comprise clinical evaluations (Clinical Site), laboratory testing (Clinical Site), ^{18}F-DOPA PET consent and neuroimaging. (PET Imaging Site).
- Surgical admission: Subjects will be admitted by the Surgical Site on the day of surgery. Surgical transplantation of cells will occur under general anesthesia. Immunosuppressive regimen will begin on Day 0 intraoperatively. Subjects will be transferred to the Neurosurgical Advance Care Unit (Surgical Site). Subjects will then be discharged to home approximately 1 to 2 days post end of surgery.
- Post-operative evaluation (PoOV) and staple removal will occur approximately 10 days after the surgery (Surgical Site).
- Post-operative clinical evaluations will take place at the Clinical Site for visits V01 to V09 and IS01 to IS12. (Visits for immunosuppression monitoring alone are designated "IS," visits in which immunosuppression monitoring coincides with other study visits are designated "V.")
- MRI of the brain will be performed at the Clinical Site at V01, V02, V03, V05, V07, V09 (ie, at 1 month, 3 months, 6 months, then every 6 months for a total 24-month duration).
- ^{18}F-DOPA PET neuroimaging will take place at the PET Imaging Site as part of the baseline, V05, and V09 visits (ie, at baseline then every 12 months).

Figure 1: Study Design



Abbreviations: BL=baseline; d=day; mo=month; PoOV=post-operative evaluation – Neurology (Day 7)/Neurosurgery (Day 10); PrOV=pre-operative evaluation visit; V=visit.

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6.1.2. Intervention

The study intervention comprises 2 parts: surgical intracerebral transplantation of MSK-DA01 cells and administration of immunosuppressive drugs over the period of 1 year.

6.1.2.1. Surgical Intervention

In this study, subjects with PD who fulfill the eligibility criteria will undergo a surgical intervention that involves a single session stereotactic injection of DA neurons (MSK-DA01) in both putamen. The intervention is a surgical procedure that will be performed stereotactically under general anesthesia. Cells will be injected in 3 separate tracks through a single burr hole in the right frontal area, with 3 cell deposits per track. Once the injections are complete in the right putamen, the subject will undergo an MRI to exclude the possibility of hemorrhage due to the injections. The criteria for evaluation of the MRI are listed in Section 8.3.3.1. If the MRI passes the criteria, a second identical procedure will be performed on the left side of the brain, followed by MRI. At minimum, 2 MRIs will be performed, but more may be performed at the discretion of the investigator, if felt needed to assess safety of the patient. At the end of the procedure, the subject will be transferred to the recovery room, and subsequently, to an acute care unit, preferably the Neurosurgical Advanced Care Unit (NACU) at the Surgical Site. The trial will examine 2 cell dose levels, with 5 subjects per cohort. The first 5 subjects (Cohort A) will receive Dose A (0.9 million cells per putamen) and the second 5 (Cohort B) will receive Dose B (2.7 million cells per putamen).

Please see Section 4.8.1 for the rationale for choice of cell doses.

Please see Section 8.2 for a description of the Administration Device System.

6.1.2.2. Schedule of Surgical Interventions

The dates of surgery will be staggered between subjects at approximately 3 weeks (see Section 12.2.2).

6.1.2.3. Immunosuppression

The protocol comprises induction with IV basiliximab, IV methylprednisolone transitioning to oral prednisone, and tacrolimus. The latter 2 agents will be administered for 1 year following the transplant and will be under the supervision of the investigator with expertise in immunosuppression.

- Basiliximab 20 mg will be administered intravenously in the operating theater during surgery.
- Basiliximab 20 mg will be administered intravenously in the Clinical Site on post-operative Day 4.
- Methylprednisolone 500 mg will be administered intravenously 0 to 6 hours prior to surgery (Day 0), followed by an oral taper and chronic therapy as follows:
  - Day 1: 250 mg methylprednisolone administered intravenously in hospital prior to discharge
  - Day 2: 120 mg prednisone administered once orally (PO)

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  - Day 3: 60 mg prednisone administered once PO
  - Day 4: 40 mg prednisone administered once PO
  - Day 5: 20 mg prednisone administered once PO
  - Day 6: 10 mg prednisone administered once PO
  - Day 7 and continuing to 1 year: 5 mg prednisone daily PO
- Tacrolimus 1 mg taken orally twice daily will be started on the day after surgery (Day 1) and continued as outpatient with a target blood level of 4 to 7 ng/mL for the period of 1 year.
- In the rare circumstance where oral tacrolimus cannot be tolerated by the subject, the treating investigator must consult the Principal Investigator (PI) and obtain approval to administer tacrolimus intravenously, prior to administration.
- Medications related to immunosuppression protocol:
  - Sulfamethoxazole/trimethoprim (Bactrim) 400 mg/80 mg once daily PO will be started on Day 1 and continued to 6 months (see Section 8.3.5)
  - Omeprazole 20 mg once daily PO will be started on Day 1 and continued to 1 year

6.2. Number of Subjects

It is planned to recruit and consent 10 evaluable subjects at the Clinical Site. For the purposes of lessening patient burden, subjects will sign 1 consent document at the Clinical Site that includes the Surgical Site, Clinical Site, and PET Imaging Site consent components. Evaluable subjects are defined as those who provide informed consent, meet all inclusion criteria and no exclusion criteria, and successfully undergo surgical intervention to receive cell transplantation. Subjects may receive any amount of cells to be considered evaluable. For any subject who is enrolled and eligible to proceed but either chooses not to proceed or proceeds to the implantation procedure, receives the first dose of immunosuppression but does not receive cells, will be replaced by recruiting another subject, such that a total of 10 evaluable subjects are reached in this study. In the event that a subject proceeds to the implantation procedure and does not receive cells for any technical reason, if the subject wishes to remain in the study then screening and baseline studies will be repeated, prior to rescheduling the surgical admission. All efforts will be made to include women and minorities in recruitment for this study.

One study participant partner per subject will also be recruited and consented to this study.

Discussion Process

The consenting professionals at the Clinical Site will provide information on the study to any potential subject. That individual will be invited to an in-person meeting with the PI or an alternate consenting professional. The individual will be asked to bring a study participant partner of their choice (usually a relative or spouse), who will also be consented. During this visit at the Clinical Site, details of the study as contained in the informed consent form will be explained to the potential subject and study participant partner. Subjects along with their study participant partner will be given adequate time to consider participation in this trial. During this

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time, the PI, the consenting professional (if different than the PI), and the study research coordinator(s) will be available to answer questions by phone.

Informed Consent Procedure

Each subject will be required to sign 2 original informed consent forms. At this visit when consent is signed, they will be accompanied by the study participant partner. The study participant partner will also sign 2 original informed consent forms. The consenting process will occur at the Clinical Site only.

6.3. Duration of Study

Duration of participation, from time of first contact, to time of completion of the 2-year scheduled evaluation, will be up to 26 months for an individual subject. Projected study duration is 44 months.

6.4. Treatment Assignment

This is an open label, non-randomized study. Two dose levels will be explored in cohorts of 5 subjects each. The first 5 subjects (Cohort A) will receive Dose A (0.9 million cells per putamen), and the second 5 (Cohort B) will receive Dose B (2.7 million cells per putamen).

6.5. Criteria for Study Termination

Throughout the duration of the study, if there are any unexpected or unanticipated events that raise concerns about the safety risk of the subjects, the PI and/or the Institutional Review Board (IRB) has the authority to stop or temporarily suspend the study until further investigation and evaluation is completed. These decisions will be made in collaboration with all involved parties.

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7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Each patient must meet all the following inclusion criteria to be eligible for enrollment in the study:

- Age ≥60 to ≤76 years old
- Idiopathic PD defined by the modified UK Parkinson's Disease Society Brain Bank criteria
- A minimum time of 5 years from time of PD diagnosis and a maximum time from PD diagnosis of 15 years
- Prior sufficient treatment comprising levodopa and at least 1 adjunct therapy, and additional appropriate therapy such as physical therapy
- Defined levodopa response of ≥40% improvement on the basis of MDS-UPDRS part 3
- Baseline Hoehn and Yahr score 0 to 2 "on" and 3-4 "off"
- Not eligible for deep brain stimulation or have refused deep brain stimulation after evaluation by an independent neurologist or neurosurgeon
- PD medications allowed: any approved oral, transdermal, and/or injectable PD medication and medications must be stable for ≥1 month prior to enrollment
- Abnormal Involuntary Movement Scale (AIMS) rating scale score of ≤2 for dyskinesia
- "Off" time of ≥2 hours daily
- MoCA score ≥26
- Hamilton Depression Scale (HAM-D) score ≤17
- Dysthymia allowed with single or 2 antidepressant medications if at stable dose for >6 months
- Normal endocrine, renal, and liver function as measured by standard laboratory testing unless clinically significant; no blood dyscrasias; no bleeding disorder; and no cardiovascular contraindications for surgery, except for stable and controlled conditions including diabetes type 2 and hypothyroidism
- All other concomitant disorders must be stable and well controlled, must not constitute a contraindication to general anesthesia or surgery, or interfere with scheduled study assessments
- Women of childbearing potential must agree to use a highly effective method of contraception from screening until at least 4 weeks after cessation of the oral immunosuppression medication regimen
- Able to participate in all study visits and evaluations, including brain MRI

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- Able to give informed consent for study participation and sign the informed consent form
- Existence of a study participant partner who may act as potential surrogate over the long term for ongoing consent

7.2. Subject Exclusion Criteria

- Clinical features suggestive of a neurodegenerative diagnosis other than PD
- PD with only tremor-based symptoms
- Diagnosis of primary mitochondrial disorder, epilepsy, stroke, multiple sclerosis or other neurodegenerative diseases such as Alzheimer's disease
- Any current or relevant previous history of serious, severe, or unstable physical, neurological, or psychiatric illness that may make the subject unlikely to fully complete the study (including significant depression, psychosis, anxiety, cognitive impairment, or impulse control disorder)
- Receiving DA receptor-blocking agents, including typical neuroleptics, prochlorperazine, and metoclopramide at the time of screening or within 3 months prior to screening
- ^{18}F-DOPA PET imaging inconsistent with DA deficiency
- Ongoing treatment with intrajejunal or subcutaneous infusion therapies for PD (Subjects who permanently discontinue these treatments are eligible to enroll after 2 months.)
- History of DBS, lesion therapy, or gene therapy for PD
- Prior surgical or radiation therapy to the brain or spinal cord
- Per assessing clinician discretion, any abnormality on brain MRI that would preclude cell transplantation
- Significant concomitant medical disease limiting life expectancy to less than 24 months from study inclusion, or significant and serious concomitant medical disease that is poorly controlled
- Signs of active malignant disease or other clinically relevant abnormality on chest X-ray
- Clinically relevant abnormalities on standard safety laboratory tests, including blood count, partial thromboplastin time (PTT), blood chemistry (glucose, blood urea nitrogen (BUN), creatinine, electrolytes), and liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase, total protein, bilirubin)
- Presence of a condition resulting in high risk of immunosuppressive drugs, including any active infectious disease of any nature, including clinically active viral infections (seropositive for human immunodeficiency virus (HIV), hepatitis C virus, hepatitis B

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virus, cytomegalovirus (CMV), and Venereal Disease Research Laboratory (VDRL) unless related to immunization or past CMV exposure, risk of tuberculosis.

- Inability to temporarily stop anti-platelet agents or other anti-coagulants without significant risk
- Previous or currently active malignant disease within the past 5 years, except basal cell carcinoma or in situ uterine cervical carcinoma that have been definitively treated
- Use of immunosuppressive drugs including systemic steroids within the previous 3 months
- Severe obesity (>350 lb) or any condition that prevents use of PET/MRI
- Known substance abuse (recent history of abuse of alcohol or other drugs such as barbiturates, cannabinoids, and amphetamines) within last 5 years
- In the opinion of the investigator, presence of any cognitive, behavioral, or psychiatric symptoms that would be deemed contraindications to cell transplantation
- Pregnancy or breastfeeding
- Unable to cooperate or complete self-assessment scales and diaries
- Unable to provide and sign the informed consent form
- Receipt of another investigational agent or device within the 3 months prior to enrollment
- Contraindication to surgery or general anesthesia
- Contraindication to taking immunosuppressive drugs
- In the opinion of the investigator, any other condition regarded as making subject unsuitable for the trial

7.3. Study Participant Partner Inclusion Criteria

- Ability to act as potential surrogate over long term for the subject

7.4. Study Participant Partner Exclusion Criteria

- Inability to cooperate or complete questionnaires

7.5. Screen Failures

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

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7.6. Subject Withdrawal Criteria

7.6.1. Suspension of Study

Any of the following occurrences will result in suspension of further enrollment and transplantation procedure while the events are under investigation:

- Any death during the study
- Any subject developing Grade III-IV toxicity as a result of immunosuppressive drug administration
- Any subject experiencing a medically important event warranting further evaluation
- Any subject developing severe, sustained, clinically significant, and unexplained dyskinesias that do not respond to standard interventions and persist off levodopa treatment
- Any radiographic evidence of tumor in the brain
- Any occurrence of a malignancy
- Any clinical evidence of graft rejection or other serious immune-related event

In each of these situations, subjects who have already undergone cell transplantation surgery will continue to maintain the protocol schedule until the situation has been assessed and full recommendations are in place, and subjects who have already enrolled into the study but who have not yet undergone cell transplantation surgery will await recommendation with their procedures either postponed or cancelled.

In the event of study suspension, the DSMC (see Section 12.2.2.1) will review data relevant to the occurrence that triggered suspension, and will receive input from the Investigator before providing appropriate recommendations. Possible outcomes include: cessation of the study; restarting with a modified subject cohort based upon modified inclusion/exclusion criteria, a cessation or change in immunosuppressive drug dosing, restarting with a change in product preparation or in cell administration, or a change in the study monitoring plan.

The sponsor may terminate this study at any time after informing the investigators. In such a case, the sponsor will notify the investigators and appropriate regulatory authorities.

7.6.2. Withdrawal From Study

Time of Consent to End of Study

- Non-compliance with the screening evaluation procedures
- The subject may also withdraw consent
- Lost to follow up

Subject survival status will be followed until the end of the study, unless the patient withdraws consent for follow-up. In the event that a subject is lost to follow-up, the family of the subject will be asked for the subject's survival status and/or public record search.

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Investigational Treatment Stopping Prior to Completion

Investigational treatment may be aborted or stopped prior to completion under the following circumstances:

- Surgical complication: In the event that a severe complication from surgery occurs, such as significant hemorrhage, cell delivery will not be performed.
- Clinical deterioration during injection. This may be defined by the surgeon or anesthesiologist during surgery, and includes but is not limited to cardiovascular/hemodynamic or respiratory compromise during the operation.
- Recognition of significant intraparenchymal hemorrhage or occurrence of other events during surgery as discussed in Section 8.3.3.
- Deterioration in the subject's clinical condition immediately prior to the study
- Elective termination: A subject or family may decline further treatment at any point in the study.
- Loss to follow-up: The subject does not comply with follow-up mandated over the 24-month period post transplant.

The reason for interruption/termination will be documented.

Time of Surgical Transplantation

Once the study subject has undergone surgical implantation of MSK-DA01 cells, it is anticipated the cells may persist for the remainder of the subject's lifetime, and therefore it will not be technically possible to withdraw the intervention. The goal is therefore to retain subjects for all of the scheduled visits for the entire study, and extensive efforts will be made to ensure that this is the case. However, it is anticipated that circumstances including but not limited to severe, unexpected toxicities/side effects; recurrent, progressive, or new disease; subject non-compliance with the defined treatment plan; and the subject's right to withdraw consent for continued participation may lead to a subject withdrawing from the study.

7.6.3. Lost to Follow-up

The goal is to retain subjects for all of the scheduled visits for the entire study, and extensive efforts will be made to ensure that this is the case. However, due to unforeseeable circumstances, subjects may discontinue in-person follow-up. In this case, the Discontinuation of In-person Follow-up (DF) Visit will be conducted at the time the decision to stop in-person follow-up is made or as soon thereafter as possible (see Section 9.2.6.2).

For any subject who is unable to attend an in-person follow-up visit prior to Month 24, study staff will try to complete the visit activities that do not require face-to-face interaction by contacting the participant via telephone, telemedicine, email, or mail (see Section 9.2.6.3). Contact from the study staff will occur during the pre-established study visit windows.

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8. TREATMENT OF SUBJECTS

8.1. Description of Investigational Study Cells

MSK-DA01 is an experimental cell product for the treatment of PD that is primarily composed of hESC-derived, mDA neurons. It is formulated for transplantation as described in the Cell Preparation and Delivery Manual.

8.2. Description of Investigational Administration Device System

MSK-DA01 will be delivered using the ClearPoint Neuro SmartFlow® neuro ventricular cannula (510(k): K102101) in conjunction with the ClearPoint Neuro Navigation System (510(k): K100836 and K142505). The SmartFlow® cannula has been modified from the version with 510(k) approval; the modification has been approved for use this study. Thawed and re-suspended cryopreserved cells will be delivered by stereotactically guided surgical injection into 9 sites along 3 tracks in the postcommissural putamen of each hemisphere. Subjects will receive 0.9 million cells per putamen (Cohort A) or 2.7 million cells per putamen (Cohort B).

SmartFlow® Cannula (ClearPoint Neuro, Irvine, CA):

The SmartFlow® Neuro Ventricular Cannula is currently cleared for administration of cytarabine or removal of CSF from the ventricles during intracranial procedures (then called "SurgiVision, Inc.", 510(k) K102101, January 2011). The device will be used in accordance with the most recent version of the ClearPoint Neuro Instructions For Use document. The 510(k)-cleared cannula is modified by shortening the overall tubing length in order to reduce dead space. The SmartFlow® cannula packaging will be appropriately labeled to avoid confusion with the cleared device. As per 12 CFR 812.5, the investigational device package will bear a label with the following statement: "CAUTION- Investigational device. Limited by Federal (or United States) law to investigational use."

ClearPoint System (ClearPoint Neuro, Irvine, CA): This system is intended to provide stereotactic guidance and operation of instruments or devices during the planning and operation of neurosurgical procedures within the MRI environment and in conjunction with MR imaging. The ClearPoint System has been developed to accurately and precisely position the cannula to targeted anatomies in the brain utilizing MRI and surgical planning software in conjunction with a stereotactic apparatus. The ClearPoint System is intended as an integral part of procedures that have traditionally used stereotactic methodology. These procedures include biopsies, as well as catheter and electrode insertion. ClearPoint Neuro Navigation and all of its components are FDA cleared; 510(k) June 16, 2010 (k100836) and (K142505) in 2015. This 510(k)-cleared system is expected to be used consistent with its intended use (510(k) Number K171257).

Gastight 1700 Series Syringe (Hamilton Robotics Company, Reno, NV): The syringe has a 25 µL capacity (model 1702 LT, catalog #80201) with a borosilicate glass body and Luer connection, with a PTFE plunger seal and stainless steel plunger.

Aspiration needle (Hamilton Robotics Company): The needle used to draw the Drug Product into the syringe is an 18-gauge, Kel-F Hub NDL needle supplied by the Hamilton Company (catalog #7750-15 Kf718/0.385/pt2).

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8.3. Dose and Administration

The study intervention comprises 2 parts: surgical intracerebral transplantation of MSK-DA01 cells; and administration of immunosuppressive drugs over the period of 1 year. Assessments will take place over 2 years post transplant. All of the interventions and evaluations will be performed as related to this research study and will not be administered as standard of care.

For the purpose of this protocol, the day of surgery defines "Day 0."

8.3.1. Cell Preparation

MSK-DA01 is formulated for transplantation as described in the Cell Preparation and Delivery Manual. Briefly, on the day of surgery, the product will be thawed and aseptically prepared for injection. The product will be delivered cooled (on sterile ice) to the operating suite, where it will be aspirated into the syringe and loaded into the VC.

In the operating room, cell vials will be kept on sterile ice. Cells will be loaded into a Hamilton syringe, which will be then connected to the hub of the VC, which will be primed with the intended cell dose and the syringe kept on sterile ice until administration, as described below.

8.3.2. Surgical Intervention

8.3.2.1. Overall Treatment Plan

The subject will be admitted on the day of surgery. Each subject is planned to undergo stereotactic placement of cell grafts via the VC. The target area is the post-commissural putamen. The goal is to distribute the cell deposits relatively uniformly in the target area. Each subject will undergo a pre-operative non-contrast MRI for surgical planning (spMRI) within a week of the surgery date (see Section 9.1.2). Trajectories will be planned on the spMRI using the surgical navigation software, so that 3 separate cannula passes are performed through a single burr hole per putamen. Each track or cannula pass will be used to inject 3 cell deposits, the first one near the inferior aspect of the putamen as determined in the spMRI. The cannula is then withdrawn over ~3 to 5 mm and a second deposit is injected, followed by a third deposit after withdrawing the cannula for another ~3 to 5 mm. These distances are estimates and are expected to vary slightly across subjects, depending on their specific brain anatomy. The goal is to distribute the cells evenly in the putamen, along the needle track. Following the end of all injections in the right putamen (a total of 9 injections, in 3 tracks), the subject will undergo an MRI. This will consist of a T1 non-contrast and a gradient recalled echo (GRE) axial sequence to identify any hemorrhage. Stopping criteria will be applied, based on the MRI results (see Section 8.3.3.1). If the MRI passes the stop criteria, the exact same procedure will be performed again, ie, single burr hole, 3 tracks and 9 cell deposits, in the left putamen. This is followed by the same MRI, in order to identify any hemorrhage. The subject is then transferred to the recovery room, and subsequently, to the NACU under the care of the Neurosurgery department at the Surgical Site. In case of bed unavailability, the subject may remain in the recovery room or may be transferred to the intensive care unit (ICU) for overnight observation.

The procedure may be performed in the MRI-equipped operating room or in a diagnostic MRI equipped for sterile procedures. Both locations are referred to as "operating room" in this protocol.

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8.3.2.2. Surgical Procedure

Surgical planning of the trajectories is performed in the pre-operative setting, using the spMRI obtained within a week of surgery. On the day of surgery, the subject is brought into the operating room and general anesthesia with endotracheal intubation is induced. Antibiotic prophylaxis is administered, using a standard neurosurgical regimen (cefazolin, or vancomycin if penicillin-allergic), and redosed according to standard of care. Anesthesiology will require and place an arterial line for hemodynamic monitoring during surgery. The subject is positioned supine and the head is fixed in the frame. Bilateral entry sites that are preselected on a remote working station are marked on the scalp surface. An incision encompassing the entry points is designed for each putamen. The incision area is prepped and draped in a sterile fashion. A standard technique is then used to perform a burr hole at the desired site. The cortical surface is prepared using standard method. A guide frame is then adjusted to provide the appropriate trajectory of the first track into the pre-established target site within the putamen. The infusion cannula is then passed through the guide frame to the cortical surface. At this point, an optional MRI scan can be performed to confirm accurate trajectory and alignment of the infusion cannula. The cannula is connected to the Hamilton syringe containing the cells and injection is initiated, at 2 to 10 µL per minute. For the low dose, this will involve the injection of 3.5 µL per track over less than a minute, and for the high dose this will amount to 11 µL per track, which will require an infusion time of about 2 minutes. The cannula is retrieved after the first deposit by a distance determined by the pre-operative plan, and the second cell injection is performed at the same rate. The cannula is retrieved to the next deposit level and the third injection is completed. The cannula is left in place for an additional 5 minutes and then slowly withdrawn. The trajectory of the second track is then set in the software. The cannula is inserted along this trajectory into the predetermined second target site and 3 cell deposits are made in a similar manner as for the first track, followed by a 5-minute waiting time after the last deposit. An alignment scan may be required before each trajectory. The cannula is then retrieved and the system set to the third trajectory. A set of 3 cell deposits is then injected in a similar fashion to the first 2 tracks. At this point, the injections in the right putamen are considered complete.

Next, identical steps are performed in the contralateral putamen. In brief a contralateral burr hole is made, and the cannula is inserted along the trajectory of the first track towards the first putaminal target. A total of 3 cell deposits are made at pre-set intervals followed by a 5-minute waiting period. The cannula is withdrawn and the second set of deposits along the second trajectory is made and then followed by a third trajectory and 3 final sets of cell deposits. The cannula is withdrawn after 5 minutes. A bilateral procedure will likely require 5 to 6 hours, mostly due to the calculation of the multiple trajectories.

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Table 2: Low Dose (Dose A, 0.9 Million Cells per Putamen)

Putamen	Track	Number of Deposits	Volume per Track (µL) Dispensed[1]	Target Number of Cells per Track Delivered	Cells per Putamen
Right	1	3	3.5	300,000	0.9 million
	2	3	3.5	300,000	
	3	3	3.5	300,000	
Left	1	3	3.5	300,000	0.9 million
	2	3	3.5	300,000	
	3	3	3.5	300,000	

[1] Volumes required to achieve the target cell numbers will have to include an allowance for volume / cell loss during delivery. The low dose was experimentally determined to be 3.5 µL and the high dose will be 11 µL to deliver optimal cell dose targets of 300,000 and 0.9 million cells respectively.

Table 3: High Dose (Dose B, 2.7 Million Cells per Putamen)

Putamen	Track	Number of Deposits	Volume per Track (µL) Dispensed[1]	Target Number of Cells per Track Delivered	Cells per Putamen
Right	1	3	11	0.9 million	2.7 million
	2	3	11	0.9 million	
	3	3	11	0.9 million	
Left	1	3	11	0.9 million	2.7 million
	2	3	11	0.9 million	
	3	3	11	0.9 million	

[1] Volumes required to achieve the target cell numbers will have to include an allowance for volume / cell loss during delivery. The low dose was experimentally determined to be 3.5 µL and the high dose will be 11 µL to deliver optimal cell dose targets of 300,000 and 0.9 million cells respectively.

In each track, the volume will be divided between the deposits, as determined by the surgeon during surgery.

Figure 2 is a diagram depicting a needle track in each putamen, and 3 cell deposits, indicated by circles. Two additional tracks will be made on each side along the anteroposterior axis, targeting the remainder of the putamen.

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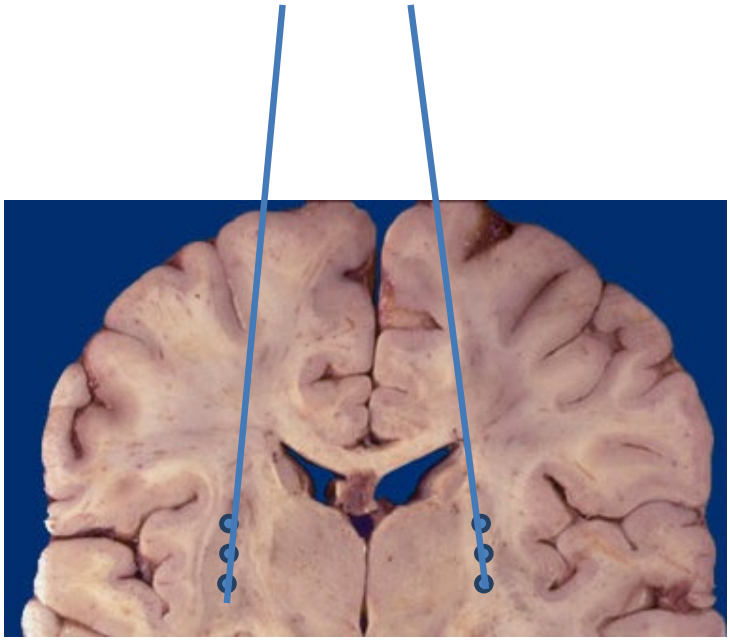
Figure 2: Depiction of Tracks of Administration



8.3.3. Interruption of Surgical Treatment

8.3.3.1. Stopping Rules for Injection of the Left Putamen

Cell injections will be performed sequentially, starting with the right putamen. Following the completion of injections in the right putamen, the subject will undergo MRI as a condition for resuming injections in the left putamen. If the MRI shows hemorrhage exceeding a total of 1.5 cm in diameter in any area of the brain, or multiple hemorrhages along the 3 tracks, or other significant surgical concerns, the surgical procedure may be aborted at the discretion of the surgeon, and the subject awakened from anesthesia.

8.3.3.2. General Conditions for Interrupting the Procedure

The surgical procedure may be aborted or paused under the following circumstances:

a. Surgical complication: In the event that a severe complication from surgery occurs, cell delivery will not be performed. Such complications include but are not limited to unusual bleeding at any time.
b. Clinical deterioration during the procedure: This may be identified by the surgeon or anesthesiologist during surgery, and includes but is not limited to cardiovascular/hemodynamic or respiratory compromise during the operation.

The reason for interruption of the procedure will be documented. If the subject receives any dose of cells, they will be considered evaluable, and continue on to receive the immunosuppressive regimen and all study activities.

If the subject does not receive any dose of cells, the subject will be considered not evaluable, and will need to be replaced with a future subject, if they do not wish to be rescreened. Subjects who

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do not receive any cell dose will be followed through Visit 01, which is 1 month after surgery. The decision regarding continuation of immunosuppression should the procedure be aborted, will be made on a case-by-case basis by the PI and co-investigators.

8.3.4. Post-operative Care Management Plan

The standard-of-care post-operative management plan for post-craniotomy surgery will be used at MSK. This includes the following:

- Patients are admitted to the Post-Operative Care Unit (PACU) and then to the NACU once cleared for transfer by a member of the anesthesia team.
- Neurological checks will be carried out per standard NACU protocol.
- Sequential compression devices will be used intra- and post-operatively.
- Regular home medications will be resumed as soon as safely possible post-operatively on the day of surgery.
- A computed tomography (CT) scan or MRI of the head will be performed on postoperative Day 1 to rule out delayed intracranial hemorrhage.
- Physical therapy/occupational therapy consults will be scheduled for subjects on post-operative Day 1, with plans for early mobilization and ambulation.
- Discharge will be planned to take place at approximately 24 hours post end of surgery, if the patient is deemed medically ready.
- Detailed written and verbal discharge instructions, including contact numbers at the sites, will be provided prior to discharge.

8.3.5. Supportive Care During Hospitalization

Following surgery, subjects will be monitored as follows:

- Subjects will be transported to the PACU at the Surgical Site immediately postoperatively.
- Antibiotics (cefazolin, or vancomycin if allergic), started at the onset of surgery, will continue to be administered according to routine post-surgical care protocol for a total of 24 hours.
- The subject's home medications will be continued unless not indicated in the immediate postoperative setting.
- Oral immunosuppressive drugs will be administered (see Section 6.1.2.3).
- Analgesics will be administered as clinically needed.
- When cleared by anesthesia, the subject will be transferred to the NACU at the Surgical Site or the ICU, if NACU beds are unavailable. Otherwise, they will remain in the recovery room.
- Diet will be advanced as tolerated.

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- Activity will be advanced as tolerated, in coordination with the Physical Therapy team who will evaluate the subject post-operatively and daily thereafter.
- The subject may be transferred to the Neurosurgery floor on the morning after surgery, if stable.
- Changes in neurological status or new abnormalities on neurological examination may be further evaluated by appropriate imaging (CT scan or MRI of the brain), and treated as clinically indicated.
- Laboratory studies, including complete blood count (CBC), full chemistry panel, and coagulation profile will be performed as deemed necessary by the clinical service, but at least once in the first 24 hours.
- Brain MRI (with contrast if deemed necessary in the opinion of the neurosurgeon and/or neurologist investigators) may be repeated prior to discharge, in the case of clinical concerns.

The subject will be discharged to home when deemed medically ready for discharge by the PI or co-investigators. A 24-hour stay is anticipated, but if extension of this time period is required in the opinion of the investigative or clinical team, the hospitalization may be longer.

8.3.6. Immunosuppressive Therapy

Immunosuppressive drugs will be administered intravenously and orally. The immunosuppressive protocol is planned to begin 0 to 6 hours prior to surgery, with basiliximab induction therapy, short-term methylprednisolone (4 days), then tacrolimus over 1 year, with standard monitoring and dose adjustments as per protocol.

- Basiliximab 20 mg will be administered intravenously in the operating theater on Day 0.
- Basiliximab 20 mg will be administered intravenously in the outpatient suite at the Clinical Site on post-operative Day 4 (Visit IS-0).
- Methylprednisolone 500 mg will be administered intravenously 0 to 6 hours prior to surgery (Day 0), followed by an oral taper and chronic therapy as follows:
  - Day 1: 250 mg methylprednisolone administered intravenously in hospital
  - Day 2: 120 mg prednisone administered once PO
  - Day 3: 60 mg prednisone administered once PO
  - Day 4: 40 mg prednisone administered once PO
  - Day 5: 20 mg prednisone administered once PO
  - Day 6: 10 mg prednisone administered once PO
  - Day 7 and continuing to 1 year: 5 mg prednisone daily PO
- Tacrolimus 1 mg taken orally twice daily will be started on the day after surgery (Day 1) and continued as outpatient to a target 4 to 7 ng/mL for the period of 1 year.

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  - In the rare circumstance where oral tacrolimus cannot be tolerated by the subject, the treating investigator must consult the PI and obtain approval to administer tacrolimus intravenously, prior to administration.

- Medications related to immunosuppression protocol:
  - Sulfamethoxazole/trimethoprim (Bactrim) 400 mg/80 mg once daily PO will be started on Day 1 and continued to 6 months (see Section 8.3.5)
  - Omeprazole 20 mg once daily PO will be started on Day 1 and continued to 1 year

Alternative medications to the specific antibiotics and proton-pump inhibitor listed here could be prescribed, at the discretion of the PI and the Transplant Immunosuppression team, in case of intolerance or other clinically relevant reason.

For any subject who receives only a partial cell dose or if adverse effects of the immunosuppression drugs occur, early termination of immunosuppression will be discussed with the subject by the PI and a clinical transplant specialist investigator. The threshold for advising termination of immunosuppression will depend upon a combination of the severity of the adverse effects of the immunosuppressive drugs experienced by that subject, in combination with the estimated percentage of the intended cell dose delivered.

For subjects who do not receive any cell dose, the decision regarding continuation of immunosuppression should the surgical procedure be aborted, will be made on a case-by-case basis by the PI and co-investigators.

Although the risks of stopping immunosuppressants is not known, there is a possibility that the transplant will not function as well without the immunosuppressant therapy. If the subject would like to withdraw, they will be advised that it is beneficial for them to continue with the protocol as long as it is safe to do so, and continue to receive immunosuppressants per protocol. If they do not agree and would like to no longer be a part of the study, the patient will be asked to come to clinic and for the Early Withdrawal Visit procedures.

Subjects will be advised not to receive vaccinations with live viruses (eg, measles, mumps, rubella [MMR], Varicella) while on immunosuppression therapy. Influenza vaccination with killed virus will be allowed prior to immunosuppression as directed by the Transplant Immunosuppression team. Expectant treatment for possible infections will be incorporated while subjects are receiving immunotherapy. The Transplant Immunosuppression team will monitor the study subjects for infection, including clinical monitoring for fungal and all other infections, and with blood (CMV polymerase chain reaction [PCR]) and urine tests (urinalysis) as detailed in Appendix 1.

8.3.7. Study Drug Preparation, Handling, and Storage

Study drug preparation, handling, and storage are described in the Cell Preparation and Delivery Manual.

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8.4. Concomitant Medications

There is no plan to adjust the medications according to a fixed paradigm. While the subjects are admitted on the Surgical Site for transplantation, the study neurologists may adjust their medications if needed. In addition, the study neurologists may make recommendations to the treating neurologists based upon information obtained from the study subjects. However, the study participants will be advised to follow up with their usual PD care with their own treating neurologist, who will be expected to make medication adjustments according to their own clinical judgment, and these changes will be captured at the scheduled (or any unscheduled) study visits. The study neurologists will be available for consultation to the subjects' own regular neurologists if required for questions or discussion.

8.5. Treatment Compliance

Compliance with immunosuppression drug regimen and prophylactic agents will be estimated via pill count at each visit.

8.6. Randomization and Blinding

This is an open-label study. There is no randomization procedure.

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9. STUDY ASSESSMENTS

Please refer to Appendix 1.

Details of all evaluations are provided in Appendix 2.

9.1. Screening/Baseline Assessments

Prior to the planned intervention, subjects will undergo a screening visit to ensure that each subject meets inclusion/exclusion criteria for the study (SC: Clinical Site), a pre-operative evaluation and visit with the neurosurgeon (PrOV: Surgical Site), and then a Baseline Visit (BL: Clinical Site, with the exception of ^{18}F-DOPA PET to be undertaken at the PET Imaging Site) for collection of all baseline data for the study. All of these visits must be completed within a 28-day period prior to the admission to the Surgical Site for surgical intervention. The following assessments will be administered at each time point:

9.1.1. Screening Visit (may be conducted over 1 to 2 days within 28 days prior to dosing surgery)

- Obtain written informed consent
- Review all inclusion/exclusion criteria
  - Evaluation of levodopa response will be made as follows. The MDS-UPDRS Part 3 will be administered to subjects in the "off" and "on" state, and the difference (improvement) will be calculated between these 2 scores. For "off" measures, subjects will come to the study visit in a "practically defined off" state, having withdrawn from anti-PD medications since their last dose of the day prior. For "on" state measures, subjects will be evaluated on their usual medication. If the subject reports an unexpected "off" at the time scheduled for "on" evaluation, then the evaluation will be delayed until the "off" resolves (either spontaneously or after the next medication dose).
- Obtain demographic information
- Obtain medical history, including smoking, alcohol, and caffeine information
- Obtain neurological history
- Review and document anti-Parkinson's medications
- Review and document concomitant medications
- Perform general medical examination with vital signs
- Perform general neurological examination
- Assess and document AEs
- Administer AIMS for the inclusion/exclusion (or other screening for dyskinesia)
- Provide Hauser diary with instruction for subject to self-complete immediately following the Screening Visit.
- Assess Modified Hoehn and Yahr Scale

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- Administer MDS-UPDRS
- Provide QUIP questionnaire to subject for self-administration
- Administer HAM-D for inclusion/exclusion criteria (or other screening for depression)
- Administer MoCA test
- Obtain blood for laboratory tests (See Appendix 1 and Appendix 2 for a list of tests to be performed and timing.)
- Urinalysis
- Neuroimaging
  - MRI with and without contrast

9.1.2. Pre-operative Evaluation (PrOV) [within 7 days prior to dosing surgery]

This visit will take place with the Surgical Site physicians who provide a routine presurgical testing service.

- Review of medical history
- Review of concomitant medications
- Perform general medical examination
- Electrocardiogram (ECG)
- Chest X-ray
- Obtain blood for laboratory tests (See Appendix 1 and Appendix 2 for a list of tests to be performed and timing.)
- Urinalysis
- Neuroimaging
  - Neuro Navigation (pre-operative) MRI (contrast scans may be performed if clinically indicated)
- Subjects older than 70 years are cleared by the Geriatrics service. At the discretion of the presurgical unit, cardiac or pulmonary clearance may be requested, depending on the subject's medical history.

9.1.3. Baseline Visit (may be conducted over 1-2 days within 28 days prior to dosing surgery)

- Re-review inclusion/exclusion criteria
- Review and update of medical and neurological history
- Review and update of concomitant medications
- Review and update of anti-PD medications

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- General medical exam with vital signs
- Neurological exam
- Assess and document AEs
- ECG
- Hauser Patient Diary
  - Diary will be supplied for completion at home within 1 week prior to Baseline Visit
- Assess Modified Hoehn and Yahr Scale
- Administer MDS-UPDRS
  - Part 3 will be administered in the "on medication" state only, and the exam will be video-recorded
- Assess Modified Schwab and England Activities of Daily Living
- Administer UDysRS
- Administer 10-Meter Walk Gait Speed Test
- Provide BDI-II, BAI-II, QUIP, and PDQ-39 questionnaires to subject for self-administration
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Administer Global Clinical Impression Scale (GCIS)
- Administer MoCA test
- Administer PD NMSS
- Laboratory tests (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Neuropsychological evaluation and testing (Table 6)

  A formal neuropsychological evaluation will be conducted to assess the subject's cognition and mood. This is based upon standard of care for subjects undergoing DBS (Defer, 1999), due to concerns that cognitive performance might be impacted by bilateral DBS (Xie, 2016). The cognitive evaluation will consist of a robust battery of standardized tests to measure brain functioning across a variety of cognitive domains, including overall cognition, attention/executive functioning, learning and memory, language, and visuospatial skills. Mood and neurobehavioral status will be examined with a combination of clinician rating scales and self-report measures. Neuropsychological findings can be useful in documenting baseline cognitive and emotional status as well as objectively quantifying the presence of post-operative changes and will be used to evaluate post-operative cognitive changes over time with annual evaluations over the course of the study. The following tests will supplement more frequent testing of non-motor functions as assessed by MoCA, BAI-II (Beck, 1993), BDI-II (Beck, 1996), and C-SSRS.

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- Neuroimaging
  - ^{18}F-DOPA PET (at the PET Imaging Site)
  - Women of childbearing potential will be subject to a stat urine pregnancy test on the day of the PET scan, if a pregnancy test was not performed within 30 days prior to the scan.
- Obtain blood for exploratory biomarkers and DNA. Whole blood will be collected for DNA isolation at baseline. No specified genetic testing is planned as part of the present clinical trial, but the samples will be stored in a biorepository for future research.
- Obtain blood for storage for xenotransplantation-related future testing
- PKG
  - A research coordinator will program the PKG device, instruct the subject on how to use it, and provide the PKG device for the subject to take home. The device will be worn for 7 days and then returned to the Clinical Site investigators in a prepaid, pre-addressed envelope provided per standard clinical protocol.
  - In the event that surgery is scheduled within 7 days of the baseline visit, the PKG may be provided prior to that visit.

9.1.4. Review of Subject Suitability for Study Participation

Once an individual has been deemed to meet inclusion and no exclusion criteria by the PI, the PI will make the enrollment decision. Prior to deciding to proceed, on an as-needed basis, the PI or consenting professional may consult with a member of the Steering Committee (see Section 12.2.2.2).

9.1.5. Research Participant Registration

Confirm eligibility as defined in Sections 7.1 and 7.2. Obtain informed consent by following procedures defined in Section 12.1.1. During the registration process, registering individuals will be required to complete a protocol-specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed.

9.2. Evaluation During Treatment/Intervention

9.2.1. Evaluation During Hospitalization

Following surgery, subjects will be evaluated as follows:

- Vital signs and neurological examinations per standard post-operative protocol
- Laboratory studies, including CBC, full chemistry panel, and coagulation profile will be performed as deemed necessary by the clinical service, but at least once in the first 24 hours.

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9.2.2. Outpatient Follow-Up

After hospital discharge, subject follow-up will be performed as follows:

- The subject will be followed 1 week post-operatively in the Neurology clinic for a neurological evaluation comprising vital signs, and collection of AEs (IS01).
- The subject will be seen approximately 10 days post-operatively in the Neurosurgery clinic for a postoperative evaluation including wound check, suture/staple removal and neurological examination (PoOV).

9.2.3. Study Evaluations Related to Transplantation: Outpatient

The following procedures and evaluations are to be performed at each visit (see Appendix 1 for descriptions). If subjects are unable to attend the clinic for blood draws, blood will be drawn at a local clinic and have results sent to the Clinical Site.

Subjects will be given a pill diary to record at home medication administration. The patient should bring the diary as well as medication bottles to each clinic visit (even if empty). The diary will be reviewed by the study doctor or nurse at each clinic visit.

9.2.3.1. Visit 01/Month 1: (Month 1 ± 2 days from the time of surgery)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure and heart rate)
- Perform general neurological examination
- Review and document PD medications and concomitant medications
- Assess and document AEs
- Pill diary and medication bottle review
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Assess Modified Hoehn and Yahr Scale
- Administer MDS-UPDRS
  - Part 3 will be administered in the “on medication” state only, and the exam will be video-recorded.
- Assess Modified Schwab and England Activities of Daily Living
- Administer UDysRS
- Administer C-SSRS
- Laboratory Blood Testing (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Tacrolimus level
- Urinalysis

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- Brain MRI (no contrast)
- Obtain blood for exploratory biomarkers
- Obtain blood for storage for xenotransplantation-related future testing

9.2.3.2. Visit 02 (Month 3 ± 1 week)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure, heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications
- Assess and document AEs
- Pill diary and medication bottle review
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Assess Modified Hoehn and Yahr Scale
- Administer MDS-UPDRS
  - Part 3 will be administered in the practically defined "off medication" state and in the "on medication" state, and the exam will be video-recorded in both states
- Assess Modified Schwab and England Activities of Daily Living
- Administer UDysRS
- Administer 10-meter Walk Gait Speed Test
- Provide BDI-II, BAI-II, QUIP, and PDQ-39 questionnaires to subject for self-administration.
- Administer C-SSRS
- Administer GCIS
- Administer MoCA test
- Administer PD NMSS
- Laboratory Blood Testing (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Tacrolimus level
- Urinalysis
- Brain MRI (no contrast)
- PKG

  A research coordinator will program the PKG device, instruct the subject on how to use it, and provide the PKG device for the subject to take home. The device will be

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worn for 7 days and then returned to the Clinical Site investigators in a prepaid, pre-addressed envelope provided per standard clinical protocol.

9.2.3.3. Visit 03 (Month 6 ± 1 week)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure and heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications.
- Assess and document AEs
- Pill diary and medication bottle review
- Hauser Patient Diary
- Diary will be supplied for completion at home 1 week prior
- Assess Modified Hoehn and Yahr Scale
- Administer MDS-UPDRS
- Part 3 will be administered in the practically defined "off medication" state and in the "on medication" state, and the exam will be video-recorded in both states
- Assess Modified Schwab and England Activities of Daily Living
- Administer UDysRS
- Administer 10-meter Walk Gait Speed Test
- Provide BDI-II, BAI-II, QUIP and PDQ-39 questionnaires to subject for self-administration.
- Administer C-SSRS
- Administer GCIS
- Administer MoCA test
- Administer PD NMSS
- Laboratory Blood Testing (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Tacrolimus level
- Urinalysis
- Brain MRI (no contrast)
- Obtain blood for exploratory biomarkers
- Obtain blood for storage for xenotransplantation-related future testing

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9.2.3.4. Visit 04 (Month 9 ± 1 week)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure and heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications.
- Assess and document AEs
- Pill diary and medication bottle review
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Assess Modified Hoehn and Yahr Scale
- Administer MDS-UPDRS
  - Part 3 will be administered in the practically defined "off medication" state and in the "on medication" state, and the exam will be video-recorded in both states
- Administer UDysRS
- Administer 10-meter Walk Gait Speed Test
- Administer C-SSRS
- Laboratory Blood Testing (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Tacrolimus level
- Urinalysis

9.2.3.5. Visit 05 (Month 12)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure and heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications
- Assess and document AEs
- ECG
- Pill diary and medication bottle review
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Assess Modified Hoehn and Yahr Scale
- Administer MDS-UPDRS

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  - Part 3 will be administered in the practically defined "off medication" state and in the "on medication" state, and the exam will be video-recorded in both states
- Assess Modified Schwab and England Activities of Daily Living
- Administer UDysRS
- Administer 10-meter Walk Gait Speed Test
- Provide BDI-II, BAI-II, QUIP and PDQ-39 questionnaires to subject for self-administration.
- Administer C-SSRS
- Administer GCIS
- Administer MoCA test
- Administer PD NMSS
- Perform neuropsychological testing
- Laboratory Blood Testing (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Tacrolimus level
- Urinalysis
- Brain MRI (no contrast)
- ^{18}F-DOPA PET (PET Imaging Site)
  - Women of childbearing potential will be subject to a urine pregnancy test on the day of the PET scan.
- Obtain blood for exploratory biomarkers
- Obtain blood for storage for xenotransplantation-related future testing
- PKG
  - A research coordinator will program the PKG device, instruct the subject on how to use it, and provide the PKG device for the subject to take home. The device will be worn for 7 days and then returned to the Clinical Site investigators in a prepaid, pre-addressed envelope provided per standard clinical protocol.

9.2.3.6. Visit 06 (Month 15 ± 1 week)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure and heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications
- Assess and document AEs

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- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Assess Modified Hoehn and Yahr Scale
- Administer MDS-UPDRS
  - Part 3 will be administered in the "on medication" state only, and the exam will be video-recorded
- Administer UDysRS
- Administer 10-meter Walk Gait Speed Test
- Administer C-SSRS
- Blood sample for exploratory biomarkers

9.2.3.7. Visit 07 (Month 18 ± 1 week)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure and heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications
- Assess and document AEs
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Assess Modified Hoehn and Yahr Scale
- Administer MDS-UPDRS
  - Part 3 will be administered in the practically defined "off medication" state and in the "on medication" state, and the exam will be video-recorded in both states
- Assess Modified Schwab and England Activities of Daily Living
- Administer UDysRS
- Administer 10-meter Walk Gait Speed Test
- Provide BDI-II, BAI-II, QUIP and PDQ-39 questionnaires to subject for self-administration.
- Administer C-SSRS
- Administer GCIS
- Administer MoCA test
- Administer PD NMSS
- Laboratory Blood Testing (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)

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- Brain MRI (no contrast)
- Blood sample for exploratory biomarkers

9.2.3.8. Visit 08 (Month 21 ± 1 week)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure, heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications
- Assess and document AEs
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Assess Modified Hoehn and Yahr Scale
- Administer MDS-UPDRS
  - Part 3 will be administered in the "on medication" state only, and the exam will be video-recorded
- Administer UDysRS
- Administer 10-Meter Walk Gait Speed Test
- Administer C-SSRS

9.2.3.9. Visit 09 (Month 24 ± 1 week)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure, heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications
- Assess and document AEs
- ECG
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Assess Modified Hoehn and Yahr Scale
- Administer MDS-UPDRS
  - Part 3 will be administered in the practically defined "off medication" state and in the "on medication" state, and the exam will be video-recorded in both states
- Assess Modified Schwab and England Activities of Daily Living
- Administer UDysRS

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- Administer 10-meter Walk Gait Speed Test
- Provide BDI-II, BAI-II, QUIP and PDQ-39 questionnaires to subject for self-administration.
- Administer C-SSRS
- Administer GCIS
- Administer MoCA test
- Administer PD NMSS
- Laboratory Blood Testing (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Perform neuropsychological testing
- Brain MRI (no contrast)
- ^{18}F-DOPA PET (PET Imaging Site)
  - Women of childbearing potential will be subject to a urine pregnancy test on the day of the PET scan.
- Obtain blood for exploratory biomarkers
- Obtain blood for storage for xenotransplantation-related future testing
- PKG
  - A research coordinator will program the PKG device, instruct the subject on how to use it, and provide the PKG device for the subject to take home. The device will be worn for 7 days and then returned to the Clinical Site investigators in a prepaid, pre-addressed envelope provided per standard clinical protocol.

9.2.4. Study Procedures Related to Immunosuppression Regimen: Outpatient

Procedures in this section will be carried out at the Clinical Site under the supervision of the Immunosuppression Clinician. Administration of the immunosuppression drug regimen and prophylactic agents, in addition to monitoring and dose adjustment, will be undertaken by the Transplant Immunosuppression team. The schedule of laboratory testing described below is a minimum follow-up. Testing and visits may be more frequent at the discretion of the Transplant Immunosuppression team.

Compliance will be estimated via pill count at each visit. AE recording will be made at each visit and will be reported to the PI and/or an Investigator within 24 hours.

Blood samples will be drawn by routine venipuncture at visits scheduled as detailed in Appendix 1 and Appendix 2.

9.2.5. Long Term Follow Up

At the end of this 2-year study, all subjects will be asked to enroll in a long term follow up study and will continue to have comprehensive visits, including neurological examination and MRI, with study neurologists every 6 months from Year 2 to Year 5, and annually from Year 6 to Year

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15, if their exams have been stable. The MRI scans will include fluid attenuated inversion recovery (FLAIR) sequences, which are sensitive to subtle changes in the brain parenchyma. In the event a patient exhibits unexpected neurological findings, or if the brain MRI shows abnormalities, patients will be monitored more closely with more frequent visits and imaging as clinically indicated.

Taken together, this will provide a total of 15 years of follow-up. At the end of the 15-year period, study participants will be asked to enroll into a registry that will allow future contact by the investigators. This will also be necessary to provide blood samples on a 5-yearly basis for potential xenotransplantation-related studies (of note: although cells are of human origin, MSK-DA01 cells are derived from a hESC line with a remote history of culture on murine feeder cells). This functions as a passive screening program, where appropriate clinical samples are obtained periodically and archived only for possible future testing.

9.2.6. Unscheduled and Other Visits

9.2.6.1. Unscheduled Visit

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the Investigator. The date and reason for the unscheduled visit will be recorded in the source documentation.

In most cases, an unscheduled visit will be warranted due to an AE, significantly abnormal laboratory values, and/or permanent discontinuation of study drug(s).

The following procedures and evaluations at a minimum are to be performed at an Unscheduled Visit:

- Review and document concomitant medications
- Assess and document AEs
- Update the pill diary as needed
- If the reason for the unscheduled visit is that the subject is permanently discontinuing any study medication at the visit, whether by choice, or for reasons concerning the health or well-being of the subject, the following additional procedures and evaluations should be completed:
  - Retrieve all previously dispensed study drug and calculate compliance.
  - Record last dosing on the pill diary.
  - Obtain weight and orthostatic vital signs (blood pressure and heart rate)

Obtain blood and/or urine for additional study chemistry or hematology tests, or other laboratory testing if warranted based on the Investigator's judgment.

9.2.6.2. Discontinuation of In-Person Follow-Up

The goal is to retain subjects for all of the scheduled visits for the entire study, and extensive efforts will be made to ensure that this is the case. However, due to unforeseeable circumstances, subjects may discontinue in-person follow-up. In this case, the Discontinuation of In-person

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Follow-up (DF) Visit will be conducted at the time the decision to stop in-person follow-up is made or as soon thereafter as possible.

The following procedures and evaluations are to be performed at the Discontinuation of In-person Follow-up Visit:

- Review and document concomitant medications
- Assess and document AEs
- Obtain weight and orthostatic vital signs (blood pressure and heart rate)
- Obtain blood for safety laboratory tests: serum urate, CHEM-7 panel, liver function tests, thyroid-stimulating hormone, lipids, CBC with differential
- Retrieve previously dispensed study drug/bottles and calculate compliance
- Record last dosing on Dose Management Log
- Administer MDS-UPDRS
  - Part 3 will be administered in the practically defined "off medication" state and in the "on medication" state, and the exam will be video-recorded in both states Provide MDS-UPDRS Parts IB and II, REM Sleep Behavior Disorder, and PDQ-39 questionnaires to subject for self-administration.
- Assess Modified Hoehn and Yahr Scale
- Assess Modified Schwab and England Activities of Daily Living
- Administer MoCA

Any AE that remains active at the Discontinuation of In-person Follow-up Visit for such a subject will be followed up for 28 days or until resolved or stabilized, whichever occurs first.

9.2.6.3. Alternative Participant Contact After Missed In-Person Follow-Up

For any subject who is unable to attend an in-person follow-up visit prior to Month 24, study staff will try to complete the visit activities that do not require face-to-face interaction by contacting the participant via telephone, telemedicine, email, or mail. Contact from the study staff will occur during the pre-established study visit windows.

The purpose of these telephone / telemedicine / email / mail visits will be to collect information such as:

- Review and record concomitant medications
- Review and record AEs
- Review study drug dosing
- Study Medication Adherence
- Complete other study activities that do not require face-to-face interaction:
  - Collection of the Hauser Diary
  - Assess Modified Schwab and England Activities of Daily Living

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- Administer UDysRS
- Provide BDI-II, BAI-II, QUIP and PDQ-39 questionnaires to subject for self-administration

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10. ASSESSMENT OF SAFETY

Please refer to Appendix 1 for details regarding the schedule of assessments.

10.1. Safety Parameters

10.1.1. Demographic/Medical History

Demographic information will be taken at the Screening Visit. Neurological history and PD medications will be taken at Screening and Baseline Visits. Medical history and concomitant medications will be taken at Screening, Baseline, and PrOV.

10.1.2. Vital Signs, Orthostatic Changes, Weight, and Height

Blood pressure and heart rate (supine and standing), and body weight will be measured at every visit. Height will be measured at the Baseline Visit only.

10.1.3. General Medical Examination

A general medical examination comprised of a skin examination, head/neck/lymphatic, eyes, ears/nose/throat, cardiovascular, lungs, abdomen, musculoskeletal, neurological and psychiatric systems will be taken at Screening, Baseline, and PrOV.

10.1.4. Electrocardiogram

A standard 12-lead ECG will be performed. Results will be based upon the Investigator's interpretation of standard machine readings and upon the reading by the Clinical Site cardiology laboratory service or the Clinical Site physician responsible for pre-surgical screening.

10.1.5. Laboratory Assessments

Refer to Appendix 2 for details regarding laboratory assessments. Refer to Appendix 1 for the time points at which each laboratory assessment is performed.

10.1.5.1. Blood Sample for Long-term Storage

To permit exploratory investigations and the application of novel approaches to bioanalysis that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action and/or efficacy of MSK-DA01, blood samples will be collected for long-term storage. These samples will be securely stored in a central biorepository for future testing.

Details regarding the collection, processing, storage, and shipping of samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by BlueRock Therapeutics or its designees.

All study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

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10.1.5.2. Pregnancy Testing

Pregnancy tests will be performed for women of childbearing potential only. Urine pregnancy testing (if applicable) will be performed on female subjects at Screening, PrOV, and Baseline Visit. Urine pregnancy tests will also be performed on the day of PET scan if a pregnancy test was not performed within 30 days prior to the scan.

10.2. Adverse and Serious Adverse Events

10.2.1. Definition of Adverse Events

10.2.1.1. Adverse Event

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of the drug (eg, off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Examples of AEs include the following:

- Any treatment-emergent signs and symptoms (events that are a change from the subject's baseline conditions, including an increase in frequency or severity)
- Clinically significant laboratory findings
- Disease-related (indication) signs and symptoms not present at baseline
- Reactions from the investigational treatment, including method of administration
- Injury or accidents
- Any other event or finding that the investigator feels is clinically significant

10.2.1.2. Serious Adverse Event

An AE is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening AE
- An AE that results in subject hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the subject or subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition

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Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

10.2.2. Severity of Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE) term (AE description) and grade: The descriptions and grading scales found in the revised National Cancer Institute (NCI) CTCAE version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program web site (http://ctep.cancer.gov).

10.2.3. Relationship to Study Intervention

The relationship of each AE to the study intervention must be assessed and classified by the PI according to the temporal relationship and their clinical judgment considering the following:

- Temporal association between the study treatments (eg, immunosuppression or surgery) and the event
- Cessation or re-challenge (eg, of a suspected concomitant medication)
- Compatibility with known effects of the study treatments
- Known effects of concomitant medications
- Pre-existing risk factors
- A plausible mechanism
- Intercurrent illness (eg, the flu)
- Underlying diagnosis

All AEs will be attributed to the VC, MSK-DA01 cells, ^{18}F-DOPA PET scan, and/or the immunosuppression regimen.

Categories of attribution:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

10.2.4. Recording Adverse Events

The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study subject presenting for scheduled study visits, medical care, or by communication between visits, and they will be continuously collected. Treatment-emergent AEs will start after the first dose of any immunosuppressive medication.

All AEs will be recorded on a subject specific AE log with information as follows: event term, onset date, resolution date if any, whether serious or not, severity level, action taken with study drug, outcome, investigator's opinion of the possible relationship between the AE and the device, injection, and the immunosuppression regimen or participation in the study.

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Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

All reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation will be recorded. At each study visit, the investigator will inquire about the occurrence of AE since the last visit. Events will be followed for outcome information until resolution or stabilization.

The AE log will be maintained by the research staff and kept in the subject's research chart.

10.2.5. Reporting Adverse Events

The investigators will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of AEs reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, X-rays, electrocardiographs, etc. When finalized test results will not be available prior to product release, the PI will electronically notify the IRB and the review division's Regulatory Project Manager at FDA, within 30 days, in the event acceptance criteria are not met.

Reporting: All AEs occurring on this study will be reported to the IRB according to the IRB policy.

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

10.2.5.1. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30 days after the participant's last dose of immunosuppression therapy, regardless of attribution to the VC, MSK-DA01 cells, ^{18}F-DOPA PET scan, and immunosuppression regimen. Any events that occur after the 30-day period and that are at least possibly related to any of the protocol treatments (the VC, MSK-DA01 cells, ^{18}F-DOPA PET scan, and immunosuppression regimen) must be reported.

SAE Reporting to the Clinical Research Organization

SAEs will be reported to the CRO. SAEs will be reported in writing within 24 hours of the investigator's knowledge of the event.

SAE reporting to ClearPoint Neuro

All SAEs related to the SmartFlow Cannula will be reported to ClearPoint Neuro. SAEs will be reported in writing within 24 hours of the investigator's knowledge of the event.

10.2.5.2. Sponsor Safety Reporting to Regulatory Authorities

The sponsor or its representative is required to report certain study events in an expedited manner to the US FDA.

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The following describes the safety reporting timeline requirements for suspected unexpected serious adverse reactions (SUSARs) and other reportable events:

Immediately and within 7 calendar days

- Any suspected adverse reaction that is associated with the use of the study cells, is unexpected, and is fatal or life-threatening. Follow-up information must be reported in the following 8 days.

Immediately and within 10 calendar days

- Evaluations of unanticipated adverse device effects and the results of such evaluations will be reported to the regulatory authorities and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as the health authority requests.
  - Any unanticipated adverse device effect
  - Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application)
  - Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

Immediately and within 15 calendar days

- Any suspected adverse reaction that is associated with the use of the study cells, is unexpected and serious, but is not fatal or life-threatening, and there is evidence to suggest a causal relationship between the study cells and the reaction
- Any finding from tests in laboratory animals that suggest a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity
- Any event in connection with the conduct of the study or the development of the study cells that may affect the safety of the trial patients

In addition, periodic safety reporting to regulatory authorities will be completed by the sponsor or its representative according to national and local regulations.

10.2.5.3. Pregnancy Reporting

If a female patient or the female partner of a male patient becomes pregnant during the study or through 90 days after the last dose of study cells, the investigator must report the pregnancy to the sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus.

The pregnancy should be followed by the investigator until completion. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death,

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or congenital anomaly, the investigator should follow the procedures for reporting an SAE as outlined in Section 10.2.5.1. Every infant will be followed for 2 months after delivery.

10.2.5.4. Overdose Reporting

An overdose is defined as any dose administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than specified in the protocol. It is the investigator's responsibility to decide whether a dose is to be considered an overdose, in consultation with the sponsor. Overdose must be recorded in the electronic case report form (eCRF).

All reports of overdose (with or without an AE) must be reported within 24 hours to the CRO.

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11. STATISTICS

A detailed statistical analysis plan (SAP) will be written after finalizing the protocol and before database lock. The SAP will detail the implementation of all the statistical analyses in accordance with the principal features stated in the protocol.

Subjects will comprise 10 evaluable subjects with advanced PD, who will undergo a single session surgical transplantation of MSK-DA01 cells to the bilateral post-commissural putamen, and with administration of a temporary (1 year) immunosuppression regimen. Two dose levels will be studied in cohorts of 5 subjects each. The first 5 subjects (Cohort A) will receive cell Dose A (0.9 million cells per putamen) and the second 5 (Cohort B) will receive cell Dose B (2.7 million cells per putamen). There is no expectation that incidence of AEs will differ by dose level and immunosuppression regimen is the same for both cohorts. Assessments for the primary, secondary, and exploratory endpoints of this study will take place over 2 years post transplant. At the end of this 2-year study, all subjects will be asked to enroll in a long-term follow-up study. This long-term follow-up study will be submitted as a separate protocol with yearly safety and clinical assessments conducted over a period of 3 years in person, followed by yearly assessments for a further 10 years that may be performed remotely, eg, by telephone or telemedicine. Taken together, this will provide a total 15 years of follow-up. At the end of the 15-year period, study participants will be asked enroll into a registry that will allow future contact by the investigators.

11.1. Determination of Sample Size

11.1.1.1. Sample Size Justification

The sample size of n=10 evaluable subjects has been chosen to allow 2 doses to be explored in a small number of subjects. If an enrolled subject is not considered a part of the evaluable population as described in Section 6.2, additional subjects will be enrolled to reach the 10 evaluable subjects. This size cohort allows surgical procedures to be staggered in order to mitigate risk.

11.2. Statistical Methodology

- One year:
  - A formal analysis of the primary endpoint will be performed once at least 1 year's worth of data is available for 10 evaluable subjects. At that time, a data cut will occur and the primary analyses to address safety and tolerability will be performed.
  - Analysis of secondary and exploratory aims is planned once 1 year's worth of data is available for all evaluable subjects.
- Two years:
  - A formal analysis of secondary outcomes will be performed once at least 2 years' data is available for evaluable subjects. At that time, a data cut will occur and the secondary and exploratory analyses will be performed.

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Statistical analyses will be primarily descriptive in nature. Descriptive statistics will include baseline characteristics of the cohort enrolled. Surgical delivery of MSK-DA01 cells will be described, including numbers of tracks, numbers of deposits, position of deposits, estimated cell numbers delivered per deposit, and percentage of target deposits delivered per putamen.

11.2.1. Populations to be Analyzed

Evaluable subjects are defined as those who provide informed consent, meet all inclusion criteria and no exclusion criteria, and successfully undergo surgical intervention to receive cell transplantation. Subjects may receive any amount of cells to be considered evaluable. Any subject who is enrolled and eligible to proceed but either chooses not to proceed or proceeds to the implantation procedure, receives the first dose of immunosuppression but does not receive cells, will be replaced by recruiting another subject, such that a total of 10 evaluable subjects are reached in this study. Although all of the subjects are expected to be able to be followed for the duration of the protocol, in the unlikely event that subjects are lost to follow-up, up to 2 subjects lost prior to the 1-year primary endpoint will be replaced. In the event that a subject proceeds to the implantation procedure and does not receive cells for any technical reason, if the subject wishes to remain in the study, then screening and baseline studies will be repeated prior to rescheduling the surgical admission.

11.2.2. Efficacy Analyses

No formal efficacy evaluations will be performed. However, the following information will be collected for preliminary descriptive analysis of any signals of efficacy using statistical measures such as median, mean, standard deviation, and range to describe:

- Change from baseline to 2 years post transplant in ^{18}F-DOPA PET uptake
- Change from baseline at 1 and 2 years post transplant in standardized measures of motor function: MDS-UPDRS Part 3 “off” state; hours of “off” time as recorded by Hauser diary

11.2.3. Safety Analyses

11.2.3.1. Primary Endpoint Analysis

Incidence of SAEs (as defined in Section 10.2.1.2) will be tabulated at 1-year post transplant.

11.2.3.2. Secondary Endpoint Analysis

Continued safety and tolerability will be evaluated at 1 and 2 years post transplant. Severity of AEs (as defined in Section 10.2.1.1 and Section 10.2.2) will be tabulated. All AEs will be attributed to device, cell product, ^{18}F-DOPA PET scan, or immunosuppressive regimen. All AEs will be summarized by time point, body system, dose Cohort, severity, and relationship to the administration of the study intervention. All SAEs will be categorized separately.

Number of evaluable subjects will be tabulated in whom at least 50% of the intended total number of deposits per brain are successfully intra-operatively delivered. If this is 6 or more patients of 10, MSK-DA01 cell transplantation will be deemed feasible.

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11.2.3.3. Exploratory Endpoint Analysis

Exploratory outcomes (motor and non-motor signs, symptoms, and quality of life) will stem from various assessments given at baseline, 1 year, and 2 years post transplant.

In general, descriptive statistics including mean, standard deviation, median, minimum, and maximum will be presented for continuous parameters. Categorical parameters will be displayed using counts and percentages. Various exploratory statistical tests may be applied to data generated from this study to generate hypotheses to be tested in subsequent trials. Longitudinal changes in designated outcome measures will be compared, and correlations between these measures will be examined.

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12. Study Administration

12.1. Ethics and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable government laws, regulations, and guidances where the study is being conducted including policies with foundations in the World Medical Association Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and all other applicable medical privacy laws and regulations.

12.1.1. Written Informed Consent

Consent will be obtained for all patients at the Clinical Site, using a consent with combined elements from the Clinical, Surgical, and PET Imaging Sites. Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB-approved consent form indicating their consent to participate. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, subjects will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of subject privacy concerning research specific information. In addition to signing the IRB Informed Consent, all subjects must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

12.1.2. Ethics Review

This study will be conducted in accordance with the Good Clinical Practice (GCP) guidelines promulgated by the ICH and any applicable national and local regulations.

Information regarding risks of study participation, possible benefits, in addition to known toxicities and side effects will be provided to potential study participants and will be described in the informed consent document. Potential participants will be informed that an alternative is not to participate in this clinical trial, and that participation is voluntary.

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Clinical information and study data will not be released without written permission of the subject, except as necessary for monitoring by the IRB, the health authorities, or the Sponsor. The PI will assure that the privacy of subjects, including their personal identity and personal medical information, will be maintained at all times, including following local privacy obligations to study subjects.

Subjects will be identified by code numbers on all case report forms (CRFs) and other documents.

12.1.3. Discontinuation of the Clinical Study

The study as represented by this protocol may be modified or discontinued at any time, with approval of the IRB as warranted, and/or the FDA Office for Human Research Protections, or other government agencies as part of their duties to ensure that research subjects are protected. If the study is prematurely terminated or suspended, the PI will promptly inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB will be informed promptly and provided the reason(s) for the termination or suspension by the PI or by the Site Investigator/institution, as specified by the applicable regulatory requirement(s). Through timely notification of Site Investigators, the PI will encourage prompt notification of research subjects with instructions for study drug discontinuation and activities completion to ensure their health and well-being.

12.2. Data Quality Control and Quality Assurance

12.2.1. Data Handling

Subject information and all data collected during pre-enrollment assessment and during the course of the study will be entered onto source document worksheets that correspond to the eCRF. The worksheets will serve as source documents for the eCRFs in a study-specific database. An eCRF will be completed for each subject screened or enrolled according to the subject's source data on a per-visit basis. Authorized study personnel will each be granted access to the electronic data capture tool via provision of a unique password-protected user-ID that will limit access to enter and view data specifically for subjects enrolled. The database has been created by the CRO for this study.

12.2.2. Study Monitoring

12.2.2.1. Data Safety Monitoring Committee

This study will be monitored by a DSMC. Membership of the DSMC will include clinicians with expertise in Neurosurgical Medicine and PD.

The DSMC will meet at least quarterly. It will examine in particular risks to which subjects are exposed, progress of the study, adequacy of data storage, and whether sufficient data is being entered into the eCRF.

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12.2.2.2. Steering Committee

The Steering Committee, comprised of the PI, selected investigators and individuals with clinical expertise in neurology, neurosurgery, and ethics, will serve in an advisory capacity to the PI. Meetings will convene on an as-needed basis.

12.2.2.3. Monthly Investigator Teleconferences

Monthly teleconferences will be held with the PI, investigators, and the sponsor to review study activities, including subject accrual, subject retention, study activities, AEs, and timeliness of activities.

12.3. Quality Assurance

The PI will be responsible for ensuring that data entries on the CRFs and in the database are proper and complete. Once the data are entered to the eCRF, they are accessible for review, and the cycle of electronic data entry, review, query identification/resolution, and correction will occur over the course of the study period until all subjects have completed the study.

The Sponsor will conduct standard required processes for quality control and assurance. Monitoring will be performed by the Sponsor or designee. Monitoring will include confirmation of subject eligibility, review of records to confirm that informed consent is properly obtained and procedures are performed according to study protocol, and monitoring of subject accrual. The patient's Electronic Medical Record will be used to compare to the eCRFs to ensure accuracy. Written and verbal feedback will be provided to investigators following all monitoring visits.

Clinical study documentation binders for the clinical protocol will be maintained for each study subject in a privacy-compliant manner. Documentation binders will be made available to the IRB and other regulatory bodies at any point during the study. Records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medical inventory records, will be retained by the PI in accordance with local health authority regulations. Data will be reported to the IRB at each continuing review, as required by IRB Approval.

The PI will review the study data from all visits at the Monthly Investigator Teleconferences. The PI is responsible for monitoring the clinical data and its accuracy, assuring protocol compliance, and conducting the safety reviews for reporting to health authorities.

12.4. Audits and Inspections

The study may be inspected by regulatory agencies, such as the FDA. These inspections may take place at any time during or after the study.

Periodically, the sponsor or its authorized representatives will audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted and whether data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. Details concerning sponsor or its authorized representative's audit and inspections are included in the clinical trial agreement for this study.

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A regulatory authority or an IRB may visit the site to perform audits or inspections, including source data verification. The investigator should contact the sponsor or designee immediately if contacted by a regulatory agency about an inspection.

12.5. Study Records Retention

Records and documents pertaining to the conduct of this study and the distribution of investigational drug will be retained by the PI for a duration of time in accordance with applicable local regulations.

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14. APPENDICES

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APPENDIX 1. SCHEDULES OF ASSESSMENTS

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Table 4: SOA Part 1: Pre-treatment Assessments, and Surgical Intervention and Follow up

Assessments	**Visit**	**SC**	**BL**	**PrOV[a]**	**Surgical admission[b]**	**Post Op**	**PoOV[c]**
	Week						**1.5**
	Day				**Day 0 is surgery**		**Day 10 (post surgery)**
Window		**-28 days of surgery**	**-28 days of surgery**	**-7 days of surgery**		**Day 1 post surgery**	**±2 days**
Written informed consent		X					
Review inclusion/exclusion criteria		X	X				
Demographic information		X					
Medical history		X	X	X			
Neurological history		X	X				
Concomitant medications		X	X	X			
Parkinson's medications		X	X				
General medical exam		X	X	X			
Neurological exam		X	X		X	X	X
Vital Signs		X	X				
ECG			X	X			
Adverse events[d]		X	X				
Surgical admission (PACU and NACU)					X		
Surgery and MSK-DA01 administration					X		
Use of SCDs					X		
Antibiotics					X		

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Assessments	**Visit**	**SC**	**BL**	**PrOV[a]**	**Surgical admission[b]**	**Post Op**	**PoOV[c]**
	Week						**1.5**
	Day				**Day 0 is surgery**		**Day 10 (post surgery)**
Immunosuppression regimen					X	X	
Physical therapy/occupational therapy consult						X	
Surgical discharge						X	
Staple removal and wound check							X
PD Motor evaluations							
AIMS		X					
Hauser Patient Diary		X	X				
Modified Hoehn and Yahr Scale		X	X				
MDS-UPDRS with video recording		X	X				
Modified Schwab and England			X				
UDysRS			X				
10-Meter Walk Gait Speed Test			X				
PD Non-motor evaluations							
BAI-II			X				
BDI-II			X				
C-SSRS			X				
GCIS			X				
HAM-D		X					
MoCA		X	X				

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Assessments	**Visit**	**SC**	**BL**	**PrOV[a]**	**Surgical admission[b]**	**Post Op**	**PoOV[c]**
	Week						**1.5**
	Day				**Day 0 is surgery**		**Day 10 (post surgery)**
PD Non-motor scale			X				
PDQ-39			X				
QUIP		X	X				
Laboratory testing[e]							
HbA1c		X					
CBC with differential		X		X	X	X	
CMP		X	X	X	X	X	
CMV		X	X				
HIV		X					
HCV		X					
Hepatitis B profile (HBcAb, HBsAb, HBsAg)		X					
QuantiFERON-TB gold Plus		X					
Lipid Profile		X					
Mg/Phos		X	X	X			
Pregnancy test (if applicable)[f]		X					
PT/PTT		X		X	X	X	
RPR (VDRL)		X					
Tacrolimus level							
Type and Screen				X			

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Assessments	**Visit**	**SC**	**BL**	**PrOV[a]**	**Surgical admission[b]**	**Post Op**	**PoOV[c]**
	Week						**1.5**
	Day				**Day 0 is surgery**		**Day 10 (post surgery)**
Uric acid		X	X				
Urinalysis		X		X			
Imaging							
CXR				X			
MRI (or CT if applicable)		X			X	X	
Neuro Navigation MRI				X			
Intraoperative MRI					X		
^{18}F-DOPA PET			X				
Exploratory motor and laboratory testing							
Blood sample for exploratory biomarkers			X				
Blood sample for xenotransplantation assays			X				
Blood sample (DNA)			X				
PKG			X				
Neuropsychological evaluation[g]							
Neuropsychological evaluation			X				

[a] This visit will be carried out either by Geriatrics or Internal Medicine services.
[b] See Section 8.3.2.1 and Section 6.1 for surgical evaluation and admission
[c] IS01 will be done 7 days post-surgery. The PoOV is 8-12 days post-surgery. The neurological exam will occur at the PoOV, not IS01.
[d] Continuous monitoring of AEs will be performed. At visits marked with "X" subjects will be questioned on AEs during the scheduled study visits.
[e] Blood for all laboratory testing for SC, BL, and V01-V09 will be collected by routine venipuncture at the Clinical Site and sent for designated tests. Blood for all laboratory testing for IS01-IS12 will be collected by routine venipuncture and sent for designated tests. Blood tests required for immunosuppression

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monitoring will be drawn at the Clinical Site during study visits V01-V05 and results will be available to the Immunosuppression Clinician for immunosuppression monitoring.

[f] Pregnancy testing will be performed per local standard of care procedures, at the location of where the pregnancy test will be performed.

[g] See Appendix2 and Section 9.1 and Section 10 for full list of Neuropsychological evaluations

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BAI-II=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory; BL=baseline; CBC=complete blood count; CXR=chest X-ray; CMP=complete metabolic profile; CMV=cytomegalovirus antibody (IgG, IgM); C-SSRS=Columbia Suicide Severity Rating Scale; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ^{18}F-DOPA PET=fluorodopa F 18 positron emission tomography; GCIS=Global Clinical Impression Scale; HAM-D=Hamilton Depression Scale; HbA1c=hemoglobin A1c; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HCV=hepatitis C antibody; HIV=human immunodeficiency virus -1 and -2 antibody enzyme linked immunosorbent assay; MDS-UPDRS=Unified Parkinson's Disease Rating Scale Parts I-V; Mg=magnesium; MRI=magnetic resonance imaging; MoCA=Montreal Cognitive Assessment; MRI=magnetic resonance imaging; NACU=Neurosurgical Advanced Care Unit; PACU= Post-Operative Care Unit; PD=Parkinson's disease; PDQ-39=Parkinson's Disease Questionnaire-39; Phos=phosphorus; PKG=Parkinson Kinetigraph; PoOV=post-operative evaluation – Neurology (Day 7)/Neurosurgery (Day 10); Post Op=post operation; PrOV=pre-operative evaluation visit; PT=prothrombin time; PTT=partial thromboplastin time; QUIP=Questionnaire for Impulsive Compulsive Disorders in PD; RPR=rapid plasma reagin; SC=screening visit (Clinical Site); SCD=sequential compression device; UDysRS=Unified Dyskinesia Rating Scale; VDRL=Venereal Disease Reference Laboratory.

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Table 5: SOA Part 2: Immunosuppression Monitoring and Other Study Visits

Assessments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal Visit	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
Concomitant medications						X				X			X			X			X	X	X	X	X	X	X
Parkinson's medications						X				X			X			X			X	X	X	X	X		
General medical exam			X			X				X			X			X			X	X	X	X	X	X	
Neurological exam			X			X				X			X			X			X	X	X	X	X		
Vital Signs			X			X				X			X			X			X	X	X	X	X	X	X
Weight						X				X			X			X			X	X	X	X	X		X
ECG																			X				X		
Adverse events[c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immuno-suppression regimen		X																							

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Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal Visit	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
Pill diary and medication review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						X
PD Motor evaluations																									
Hauser Patient Diary						X				X			X			X			X	X	X	X	X		
Modified Hoehn and Yahr Scale						X				X			X			X			X	X	X	X	X	X	
MDS-UPDRS with video recording						X				X			X			X			X	X	X	X	X	X	
Modified Schwab and England						X				X			X						X		X		X	X	
UDysRS						X				X			X			X			X	X	X	X	X		
10-Meter Walk Gait Speed Test										X			X			X			X	X	X	X	X		

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Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal Visit	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
PD Non-motor evaluations																									
BAI-II										X			X						X		X		X		
BDI-II										X			X						X		X		X		
C-SSRS						X				X			X			X			X	X	X	X	X		
GCIS										X			X						X		X		X		
HAM-D																									
MoCA										X			X						X		X		X	X	
PD Non-motor scale										X			X						X		X		X		
PDQ-39										X			X						X		X		X		
QUIP										X			X						X		X		X		
Laboratory testing[d]																									
HbA1c													X						X						
CBC with differential			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	
CMP			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	

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Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal Visit	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
CMV						X				X			X			X			X						
Lipid Profile																								X	
Mg/Phos										X			X			X			X						
Tacrolimus level			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Uric acid										X			X			X			X						
Urinalysis						X		X		X	X	X	X	X	X	X	X	X	X						
Imaging																									
MRI						X				X			X						X		X		X		
^{18}F-DOPA PET																			X				X		
Exploratory motor and laboratory testing																									
Blood sample for exploratory biomarkers						X							X						X	X	X		X		

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Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal Visit	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
Blood sample for xenotransplantation assays						X							X						X				X		
Blood sample (DNA)																									
PKG										X									X				X		
Neuropsychological evaluation[e]																									
Neuropsychological evaluation																			X				X		

[a] See Section 6.1 for IS-0 visit for administration of IV basiliximab for induction phase of immunosuppression
[b] Additional testing may be warranted based on the Investigator's judgment
[c] Continuous monitoring of AEs will be performed. At visits marked with "X" subjects will be questioned on AEs during the scheduled study visits.
[d] Blood for all laboratory testing for SC, BL, and V01-V09 will be collected by routine venipuncture at the Clinical Site and sent for designated tests. Blood for all laboratory testing for IS01-IS12 will be collected by routine venipuncture and sent for designated tests. Blood tests required for immunosuppression monitoring will be drawn at the Clinical Site during study visits V01-V05 and results will be available to the Immunosuppression Clinician for immunosuppression monitoring.
[e] See Appendix 1 and Section 9.1 and Section 10 for full list of Neuropsychological evaluations
Abbreviations: BAI-II=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory; BL=baseline; CBC=complete blood count; CMP=complete metabolic profile; CMV=cytomegalovirus antibody (IgG, IgM); C-SSRS=Columbia Suicide Severity Rating Scale; D/d=day; DNA=deoxyribonucleic acid;

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ECG=electrocardiogram; ^{18}F-DOPA PET=fluorodopa F 18 positron emission tomography; GCIS=Global Clinical Impression Scale; HAM-D=Hamilton Depression Scale; HbA1c=Hemoglobin A1c; IS=immunosuppression monitoring visit; MDS-UPDRS=MDS-Unified Parkinson's Disease Rating Scale Parts I-V; Mg=magnesium; MRI=magnetic resonance imaging; MoCA=Montreal Cognitive Assessment; PD=Parkinson's disease; PDQ-39=Parkinson's Disease Questionnaire-39; Phos=phosphorus; PKG=Parkinson Kinetigraph; QUIP=Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease; SC=screening visit (Clinical Site); V=visit; wk=week.

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APPENDIX 2. DESCRIPTION OF CLINICAL EVALUATIONS AND RATING SCALES, LABORATORY TESTS AND NEUROIMAGING PROCEDURES

Clinical Evaluations and Rating Scales

10-Meter Walk Gait Speed Test (National Institute of Neurological Disorders and Stroke [NINDS] Common Data Element)

The 10-meter Walk Gait Speed Test assesses walking speed in meters per second over a short duration. The subject will be instructed to walk a set distance of 10 meters 3 times. The time will be measured while the individual walks the set distance. The average time of the 3 attempts will be calculated.

Abnormal Involuntary Movement Scale (AIMS) [ECDEU, 1976]

The AIMS is a 12-item clinician-rated scale to assess severity of dyskinesias (specifically, orofacial movements and extremity and truncal movements) in patients taking neuroleptic medications. Additional items assess the overall severity, incapacitation, and the patient's level of awareness of the movements and distress associated with them.

Beck Anxiety Inventory (BAI-II) [Beck, 1993]

This is a 21-question multiple-choice self-report inventory that is used for measuring the severity of anxiety in children and adults. The questions used in this measure ask about common symptoms of anxiety that the subject has had during the past week.

Beck Depression Inventory (BDI-II) [Beck, 1996]

This is a 21-question multiple-choice self-report inventory. This test is used for measuring the severity of depression.

Chest X-ray

A standard chest X-ray will be performed at PrOV prior to surgery.

Columbia Suicide Severity Rating Scale (C-SSRS) [Posner, 2011]

The C-SSRS is a questionnaire used for suicide assessment developed by multiple institutions. The scale is evidence-supported and is part of a national and international public health initiative involving the assessment of suicidality. A trained professional administers the scale.

Electrocardiogram (ECG)

A standard 12-lead ECG will be performed. Results will be based upon the Investigator's interpretation of standard machine readings and upon the reading by the Clinical Site cardiology laboratory service, or the Clinical Site physician responsible for pre-surgical screening.

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Global Clinical Impression Scale (GCIS) [Busner, 2007]

The GCIS is a scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's experience with patients who have the same diagnosis.

Hamilton Depression Rating Scale (HAM-D) [Hamilton, 1960]

The HAM-D scale contains 17 items (HDRS17) pertaining to symptoms of depression experienced over the past week. The scale was designed for completion by the examiner after an unstructured clinical interview with the subject.

Hauser Patient Diary (Hauser, 2000)

The Hauser patient diary will be given out to subjects to be completed at home. Subjects will be given instructions on how to fill out the diary prior to each time they will be asked to fill it out. The home diary that includes the categories: ASLEEP, OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, and ON with troublesome dyskinesia. Patients are instructed to indicate their state based on those categories over the course of 3 days.

Modified Hoehn and Yahr Scale (Goetz, 2004)

The Modified Hoehn and Yahr Scale is an 8-level Parkinson's disease (PD) staging instrument. Stage 0 is "no signs of disease" and the highest stage (5) is "wheelchair bound or bedridden unless aided." This joint subject/ Investigator assessment will be conducted periodically at SC1, BL, V01 to V03, and V05 to V09. The same Investigator will assess all subjects at all study visits.

Montreal Cognitive Assessment (MoCA) [Nasreddine, 2005]

The MoCA is a rapid screening instrument like the MMSE, but was developed to be more sensitive to patients presenting with mild cognitive complaints. It is designated as a NINDS CDE for PD. The MoCA assesses short term and working memory, visual-spatial abilities, executive function, attention, concentration, language and orientation. The total score ranges from 0 to 30 (highest function).

Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS) [Goetz, 2008a]

The same investigator will make every attempt to assess all subjects at all study visits.

The MDS-UPDRS has 4 parts:

- Part I (non-motor experiences of daily living), comprising:
  - Part IA concerning behaviors that are assessed by the investigator with all pertinent information from patients
  - Part IB that is completed by the patient, independently of the investigator.
- Part II (motor experiences of daily living), designed to be a self-administered questionnaire like Part IB, but will be reviewed by the investigator to ensure completeness and clarity.

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- Part III (motor examination) has instructions for the rater to give or demonstrate to the patient; it is completed by the investigator. The patient will be video-recorded.
- Part IV (motor complications) with instructions for the rater and also instructions to be read to the patient. This integrates patient-derived information with the rater's clinical observations and judgments and is completed by the rater.

Neurological Exam

A neurological examination, including examination of cranial nerves, motor strength, reflexes, coordination, sensation, and gait and balance will be performed and recorded.

Neuropsychological Evaluation

A formal neuropsychological evaluation will be conducted to assess each participant's cognition and mood. The cognitive evaluation will consist of a robust battery of standardized tests to measure a variety of cognitive domains, including overall cognitive function, attention/executive functioning, learning/memory, language, visuospatial, and constructional skills. Mood and neurobehavioral status will be examined with a combination of clinician rating scales and self-report measures in order to document baseline cognitive and emotional status as well as objectively establish the presence of postoperative changes. Analysis of cognitive and emotional variables will used to evaluate post-operative cognitive changes over time with annual evaluations over the course of the study. These tests will supplement more frequent testing of non-motor functions as assessed by MoCA, BAI-II (Beck, 1993), BDI-II (Beck, 1996), and C-SSRS.

Table 6: Neuropsychological Evaluation and Testing

Domain Assessed	Measures
Overall cognitive function (baseline only)	Test of Premorbid Functioning (TOPF) [Pearson, 2009]
Multiple domains (including learning and memory, visuospatial skills, attention, executive function, language)	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [Randolph, 1998]
Attention/executive function	Trail-Making Test A and B (TMT-A and TMT-B) [Reitan, 1985] Stroop Color Word Test (Golden version) [Golden, 1978] Frontal Systems Behavior Scale (FrSBe) [Stout, 2003]
Language	Verbal Fluency: Oral Word Association Test (Spreen, 1969)
Mood and neurobehavioral features	Neuropsychiatric Inventory - Questionnaire (NPI-Q) [Cummings, 1997]

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- Test of Premorbid Functioning (TOPF) [Pearson, 2009]
  - The TOPF was designed to estimate subjects' cognitive and memory functioning prior to the onset of illness or disease. The test asks participants to read a list comprised of 70 words, in order of increasing difficulty, that feature irregular relationships between words' pronunciations as compared to the words' spellings (ie, words with irregular grapheme-to-phoneme translation). The ability to read and pronounce previously learned words of this type seems less affected by the cognitive dysfunction introduced by illness or disease than other measures of intellectual and memory functioning; because of this, the TOPF provides a robust estimate of individuals' premorbid cognitive functioning with vocabulary level serving as a correlate to IQ. Test of Premorbid Functioning estimates an individual's pre-morbid cognitive and memory functioning. It is a revised and updated version of the Wechsler Test of Adult Reading™, and helps predict pre-injury IQ and memory abilities.
- The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [Randolph, 1998]
  - The RBANS is a reliable and valid measure of multiple cognitive domains including attention, visuospatial abilities, language, as well as both immediate and delayed memory, and it has been used extensively in a variety of patient populations. A major advantage of the RBANS is that it has the benefit of providing subscales scores for each of the domains assessed, as well as 1 total standard score that summarizes the individual's overall neurocognitive status. This instrument yields a concise set of summary scores that can promote efficient data analysis and interpretation.
- Trail-Making Test A and B (TMT-A and TMT-B) [Reitan, 1985]
  - TMT-A requires an individual to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper. Task requirements are similar for TMT-B except the subject will be asked to alternate between numbers and letters (eg, 1, A, 2, B, 3, C, etc.). The score on each part represents the amount of time required to complete the task.
- Stroop Color Word Test (Golden, 1978)
  - The Stroop Task is a test measuring executive function. It involves participants reading a list of words for colors, such as blue, red, or green, but the words are printed in a color different to the word itself. The goal of the task is to name the color of the ink the words are printed in.
- Frontal Systems Behavior Scale (FrSBe) [Stout, 2003; Batistuzzo, 2009]
  - The FrSBe provides a brief, reliable, and valid measure of 3 frontal systems behavioral syndromes: apathy, disinhibition, and executive dysfunction. It also quantifies behavioral changes over time by including both baseline (retrospective) and current assessments of behavior.
- Verbal Fluency: Oral Word Association Test (Spreen, 1969)

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  - The Verbal Fluency Test involves asking the participant to name words beginning with a letter, excluding proper nouns, for 1 minute and this procedure is repeated 3 times. The most commons letters used are F, A, S because of their frequency in the English language.

- Neuropsychiatric Inventory- Questionnaire (NPI-Q) [Cummings, 1997]
  - The NPI-Q was developed to assess psychopathology and evaluates 12 neuropsychiatric disturbances in terms of severity and frequency: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behavior disturbances, and appetite and eating abnormalities. It is administered to the study participant partner.

Parkinson's Disease Questionnaire (PDQ-39) [Peto, 1995]

The PDQ-39 is PD specific health status questionnaire comprising 39 items. Respondents are requested to pick 1 of 5 ordered response categories according to how often, due to their PD, they have experienced the problem defined by each item. Items are grouped into 8 scales that are scored by expressing summed item scores as a percentage score ranging between 0 and 100.

Parkinson's Kinetigraph (Griffiths, 2012) [PKG; Global Kinetics Corporation]

This FDA-approved wearable device objectively measures bradykinesia and dyskinesia in PD. It is worn as a wristband. Measurements are based upon accelerometry, with a novel algorithm allowing collection of a bradykinesia score and dyskinesia score every 2 minutes over a standard 6-day period. It is in clinical use in a number of institutions, including the Clinical Site. Participants will be asked to wear this device continuously for 7 days. Research assistants will verbally instruct them at the baseline visit, with refresher instructions at each subsequent visit. After the 7 days, the study participant will mail in the device to the study center using a pre-paid pre-addressed envelope. The data is uploaded to a cloud-based platform with results then provided to the PI by Global Kinetics. No identifying information, no clinical data, and no data collected other than that on the PKG device is uploaded nor supplied by any means to the Global Kinetics platform, nor Global Kinetics personnel.

PD Non-Motor Symptoms Scale (NMSS) [Chaudhuri, 2004]

The PD NMSS is a questionnaire administered by the investigator, aimed to assess non-motor symptoms in individuals with PD.

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) [Weintraub, 2012]

The QUIP is a self-administered rating scale is designed to measure severity of symptoms and support a diagnosis of impulse control disorders and related disorders in PD.

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General Medical Exam

A general medical examination will be comprised of a skin examination, head/neck/lymphatic, eyes, ears/nose/throat, cardiovascular, lungs, abdomen, musculoskeletal, neurological, and psychiatric systems.

Modified Schwab and England Activities of Daily Living Scale (McRae, 2002)

The Schwab and England scale is an Investigator and subject assessment of the subject's level of independence. The subject will be scored on a percentage scale reflective of his/her ability to perform acts of daily living. Printed scores with associated descriptors range from 100% to 0% in increments of 10%, where 100% is "subject has full ability and is completely independent; essentially normal" and 0% is "vegetative functions such as swallowing, bladder and bowel functions are not functioning; bedridden." Scores should be coded in increments of 5 (ie, 90%, 80%).

Unified Dyskinesia Rating Scale (UDysRS) [Goetz, 2008b]

The UDysRS is developed to evaluate involuntary movements often associated with treated PD. The scale has 2 parts: Historical and Objective. The scale provides measurements for "on-dyskinesia" and "off-dyskinesia."

Vital Signs, Orthostatic Changes, Weight, and Height

Blood pressure and heart rate (supine and standing), and body weight will be measured at every visit. Height will be measured at the Baseline Visit only.

Clinical Laboratory Assessments

- Blood tests performed as indicated in Appendix 1 include the following:
  - Hepatitis C antibody
  - Hepatitis B profile
  - Human immunodeficiency virus (HIV; HIV-1 and -2 antibody ELISA)
  - Lipid profile
  - Rapid plasma reagin (VDRL)
  - QuantiFERON-TB gold Plus
  - Type and screen
  - Prothrombin time
  - Partial thromboplastin time
  - Complete metabolic profile (CMP): The CMP is a made up of 14 tests – glucose, calcium, sodium, potassium, CO_2, chloride, blood urea nitrogen, creatinine, albumin, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and bilirubin.

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  - CBC with differential (hematocrit, hemoglobin, platelet count, RBC indices, total RBC, total WBC, and WBC and differential)
  - Magnesium/phosphorus
- Hemoglobin A1c
- Uric acid
- The following blood tests for immunosuppression monitoring will be obtained:
  - CMP
  - CBC with differential
  - CMV (IgG, IgM) serum antibody screening
  - Tacrolimus level
  - Exploratory biomarkers. Please see details outlined in "Additional blood samples for archiving and exploratory endpoints" section of this document.
- Blood samples for storage as recommended in the case of xenotransplantation will be collected in accordance with Appendix 1 and cryopreserved.
- Urine pregnancy testing will be performed on female subjects of childbearing potential in accordance with Appendix 1.
- Urinalysis will be performed in accordance with Appendix 1.

Samples obtained at the Clinical Site will be analyzed at a local laboratory, except for blood for exploratory biomarkers and xenotransplantation.

Samples obtained at the Surgical Site will be analyzed at a local laboratory.

The investigators may order additional testing, if needed, to further assess an adverse event (AE), or if there is any suspicion that a subject may be pregnant, throughout the course of the study.

Neuroimaging Procedures

Brain Magnetic Resonance Imaging (MRI)

Location: the Clinical Site

Brain MRI will additionally be performed at intervals during the study (see Appendix 1) in order to evaluate structural changes associated with engrafted cells, edema or inflammation, and importantly to monitor for cellular overgrowth, and development of structural abnormalities such as cysts, or development of potential tumors.

Sequences will be performed as follows:

Gadolinium contrast will be administered at the baseline MRI scan, for imaging with and without contrast. If subsequent MRI scans reveals abnormal signal that could reflect potential AEs, such as cell overgrowth, tumor formation, or edema, then after discussion of the radiologist with the investigators, a repeat brain MRI may be implemented with and without gadolinium contrast.

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Pre-operative planning MRI: Brain MRI for surgical planning will be performed within 1 week of surgical admission at the Clinical Site.

^{18}F-DOPA positron emission tomography (PET) study (Luxen, 1990; Dhawan, 2002)

^{18}F-DOPA PET scanning will be performed at the PET Imaging Site.

^{18}F-DOPA PET scanning will be performed at Baseline, V05, and V09 (see Appendix 1).

^{18}F-DOPA is produced on-site in the cyclotron/radiochemistry facility at the Feinstein Institute for Medical Research (FIMR) as reported elsewhere. All participants will receive nothing orally (except water) 4 hours prior to scanning and must stop antiparkinsonian medication 12 hours prior to scanning. Participants will be pretreated with 150 mg of carbidopa given orally within 120 minutes prior to the injection of ^{18}F-DOPA. (Carbidopa pre-administration is to prevent AAAD decarboxylation of ^{18}F-DOPA and thereby to increase the bioavailability of the drug substance in the brain. There are no known side effects for carbidopa when used alone.) Participants are injected intravenously with 5.0 mCi of ^{18}F-DOPA with a lower limit of 3.0 mCi in the event that production yield is lower than expected. Subjects are encouraged to void 30 to 60 minutes post injection in order to reduce radiation exposure to the bladder. A 9-second CT attenuation correction scan will be acquired followed by the acquisition of 3-dimensional PET images about 80 to 100 minutes (4 × 5 minute frames) post injection using a new high resolution/sensitivity PET tomograph (GE Discovery IQ-5 ring PET/CT scanner, General Electric Medical Systems, Milwaukee, WI: FWHM=5 mm, axial FOV=26 cm, slice thickness=3.3 mm, 79 slices) at FIMR. At the end of the scanning procedure, the patient is to void again to reduce bladder wall radiation. All women will be screened for pregnancy prior to scanning. Women of childbearing potential will be subject to a urine pregnancy test within 30 days prior to each PET scan.

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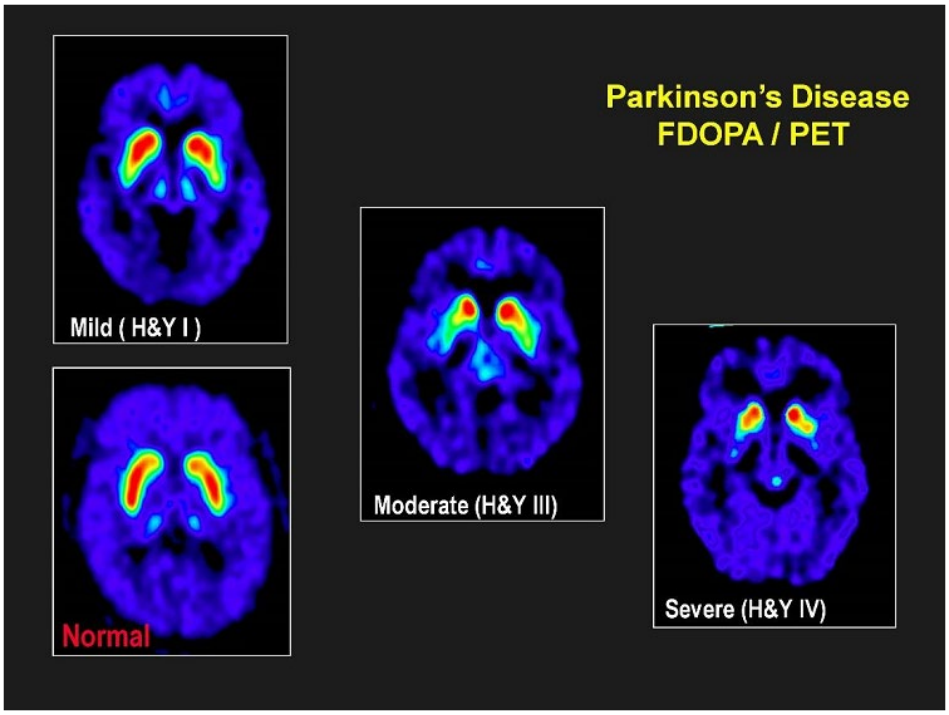
Figure 3: Representative PET scan with ^{18}F-DOPA



Abbreviations: ^{18}F-DOPA=fluorodopa F 18; H&Y=Hoehn and Yahr; PET=positron emission tomography.

Figure 3 is an image of a representative PET scan with ^{18}F-DOPA at the PET Imaging Site demonstrating feasibility to perform PET scans at that site. Previous studies indicate that the signal of ^{18}F-DOPA uptake in the posterior putamen is reduced by approximately 40% compared to normal control values in PD patients. The Feinstein Institute has performed numerous previous studies using human ^{18}F-DOPA PET imaging.

Image Archival/Transfer

All PET scans will be stored as DICOM® (Digital Imaging and Communications in Medicine) files after removing any protected health information that may identify the subject. An electronic version of PET worksheet will also be created containing specifics such as subject weight, dose administered and time of injection. These files will be saved on a password-protected computer server at the PET Imaging Site for further analysis or transfer to the sponsor. An online ftp site will be set up locally or at the sponsor site to facilitate secure electronic transfer of PET images and PET worksheet along with 1 high-resolution structural MRI scan acquired at the enrolling site (the latter is needed to define anatomical regions of interest in the striatum).

Image Analysis

^{18}F-DOPA PET images will be analyzed to calculate ^{18}F-DOPA uptake in the striatum. Definition of striatal subregions in each subject will be defined by using high-resolution anatomical MRI scan acquired separately during neurosurgery. Anatomic structures of caudate nucleus and putamen will be first segmented in MRI scan using an automated processing routine. The regions of anterior and posterior putamen will then be segmented using a semi-automated

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procedure involving realignment of anterior commissure - posterior commissure (AC-PC) planes on each scan.

Multiple ^{18}F-DOPA PET images will be re-aligned with each other and then registered to the MRI scan (Table 7). Time activity curve will be computed automatically in each region of interest, including caudate nucleus, anterior and posterior putamen, and occipital cortex (16-mm diameter sphere in each hemisphere). ^{18}F-DOPA uptake will then be calculated (regional ^{18}F-DOPA counts / occipital counts – 1) in each frame. ^{18}F-DOPA uptake is expected to reach the maximum at the end of the study. The values in the last 2 frames of 10 minutes' duration between 90 to 100 minutes post-injection will be averaged to provide striatal DA function in each subject.

Table 7: Brain Imaging Parameters for the Clinical Trial of Stem Cell Therapy in Patients with PD

Subject: ID Number	Structure Volume (µL)		^{18}F-DOPA Uptake Baseline		^{18}F-DOPA Uptake Post	
	Left	Right	Left	Right	Left	Right
Caudate Nucleus						
Anterior Putamen						
Posterior Putamen						

Abbreviations: ^{18}F-DOPA=fluorodopa F 18; ID=identification number; PD=Parkinson's disease.

Additional Blood Samples for Archiving and Exploratory Endpoints

(i) At Month 1, Month 6, Month 12, Month 15, Month 18, and Month 24 approximately 12 mL of whole blood will be collected in two 6 mL heparin tubes, processed to separate out plasma, and aliquoted for storage at -80°C. These samples will be used for inflammation assays.

ii) At Month 1, Month 6, Month 12, and Month 24, approximately 12 mL of whole blood (one 6 mL ethylene diamine tetra-acetic acid tube and one 6 mL heparin tube) will be collected and processed for storage at -80°C. These samples will be used for potential future study of latent viruses or pathogens.

(iii) At Baseline, 8.5 mL of whole blood will be collected for preparation of DNA by standard venipuncture into a PAXgene collection tube and processed for DNA biobanking and testing of the genetic signature of PD.

(iv) At Month 1, Month 6, Month 12, Month 15, Month 18, and Month 24 approximately 5 mL of whole blood (5 mL standard serum tube) will be collected, processed to separate out serum, and aliquoted for storage at -80°C. These samples will be used for assessment of donor cell allo-recognition by anti-human leukocyte antigen screen and potential biomarkers for PD.

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CLINICAL STUDY PROTOCOL

Protocol Title:	Phase 1 Study To Assess the Safety and Tolerability of Human Embryonic Stem Cell-Derived Midbrain Dopamine Neuron Cell Therapy (MSK-DA01) For Advanced Parkinson's Disease (STEM-Parkinsons)
Investigational Product:	MSK-DA01
Protocol Number:	MSK-DA01-101
Protocol Version:	Version 5.0
Protocol Date:	08 November 2022
Sponsor:	BlueRock Therapeutics LP 238 Main Street, 3rd Floor Cambridge, MA 02142 USA Telephone: +1 857 777 0501
Sponsor Physician:	[redacted] Clinical Development DocuSigned by: [redacted] Signing Reason: I approve this document Signing Time: 17-Nov-2022 | 4:11:18 PM EST ACD00DD8EA9F498A8421135C4814B58C Signature 17-Nov-2022 Date

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without express written authorization of BlueRock Therapeutics LP.

INVESTIGATOR'S AGREEMENT

I have received and read the protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

1. SYNOPSIS

Name of Sponsor Company: BlueRock Therapeutics LP
Protocol Title: Phase 1 Study To Assess the Safety and Tolerability of Human Embryonic Stem Cell-Derived Midbrain Dopamine Neuron Cell Therapy (MSK-DA01) For Advanced Parkinson's Disease (STEM-Parkinsons)
Protocol Number: MSK-DA01-101
Version Number: 5.0
Name of Investigational Product: MSK-DA01
Phase of Development: 1
Study Center(s): Multi-center (multi-site) study
Study Indication: Advanced Parkinson's Disease
Study Rationale: Cell-based therapies have the potential to deliver dopamine (DA) to the DA-depleted striatum in a more physiologic manner than is possible from medications. The Sponsor has derived authentic, engraftable midbrain dopamine (mDA) neurons from human embryonic stem cells (hESCs) using a novel, small molecule-based floor-plate differentiation strategy. These cells demonstrate excellent in vivo survival and function in animal models of Parkinson's disease (PD) with no evidence of tumor or excessive growth. The Sponsor will therefore implement an open-label, non-randomized study, with the primary objective of evaluating safety and tolerability of transplantation of 2 dose levels of MSK-DA01 cells in individuals with advanced PD at 1 year post transplant.
Accrual Period: Approximately 18 months
Study Duration: Subjects will be on study for up to 26 months. Projected study duration is 44 months.
Number of Subjects: Approximately 12 evaluable subjects
Study Population: Subjects with advanced PD, aged ≥50 to ≤78 years old (Canada) or ≥60 to ≤78 years old (US), with motor symptoms inadequately relieved by standard treatments.
Objectives: *Primary:* The primary objective of the study is to assess the safety and tolerability of MSK-DA01 cell transplantation at 1-year post transplant. *Secondary:* The secondary objectives of the study are (i) to assess the evidence of transplanted cell survival and motor effects through 2 years post-transplant; (ii) to evaluate continued safety and tolerability at 2 years; (iii) to assess feasibility of transplantation. *Exploratory:* The exploratory objectives of the study are (i) to determine the effects of MSK-DA01 transplantation upon motor and non-motor signs and symptoms of PD and upon accelerometry-based measures of motor function; (ii) to assess the subject's perception of their quality of life; (iii) to collect biosamples for anti-human leukocyte antigen testing; to obtain blood for storage for xenotransplantation-related future testing; and to store leftover samples for future studies of biomarkers of PD, DA function, inflammation, and immune response to engrafted cells.

Endpoints:

Primary:

The primary endpoint of the study will be the incidence of serious adverse events (SAEs) at 1-year post transplant.

Secondary:

The secondary endpoints of the study will be (i) change in striatal fluorodopa (^{18}F-DOPA) uptake using positron emission tomography (PET) from baseline through 2 years; (ii) changes from baseline in the following measures at 2 years post transplant: International Parkinson and Movement Disorder Society (MDS)-Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore in the "off" medication state, number of hours in the "on" state without troublesome dyskinesia, incidence of serious adverse events (SAEs) at 2 years post transplant, and incidence and type of adverse events (AEs) at 1 and 2 years post transplant; and (iii) feasibility, as defined by intra-operative delivery of at least 50% of the intended total number of deposits per brain in >50% of subjects.

Exploratory:

The exploratory endpoints of the study will be as follows: (i) changes in the following measures from baseline to 2 years in total MDS-UPDRS scores; MDS-UPDRS Part 1 scores; MDS-UPDRS Part 2 scores; MDS-UPDRS motor subscore in the "on" state; MDS-UPDRS Part 4 scores; 10-meter walking test; anti-PD medications (daily levodopa equivalent dose); Modified Schwab and England Activities of Daily Living; Unified Dyskinesia Rating Scale (UDysRS); neuropsychological testing; non-motor measures including Montreal Cognitive Assessment (MoCA), Beck Anxiety Inventory (BAI-II), Beck Depression Inventory (BDI-II), Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease (QUIP), and PD Non-Motor Symptoms Scale (NMSS); Clinical Global Impression-Severity (CGI-S); daily time in the "off," "on without dyskinesia," "on with non-troublesome dyskinesia," and "on with troublesome dyskinesia" states as measured by the Hauser diary; daily time in the "on," "on with dyskinesia," and "off" states measured by the Personal KinetiGraph; (ii) quality of life as measured by Parkinson's Disease Questionnaire-39; and (iii) sample collection for biorepository, which does not have pre-specified endpoints.

Methodology: This is a multi-center, multi-site (Clinical Site, Surgical Site, PET Imaging Site), open-label, non-randomized, non-controlled study. Approximately 12 subjects will undergo a single session surgical transplantation of 1 of 2 different dose levels of MSK-DA01 cells to the post-commissural putamen bilaterally, and administration of a 1-year immunosuppression regimen. The first 5 subjects (Cohort A) will receive Dose A (0.9 million cells per putamen) and subsequent subjects (Cohort B) will receive Dose B (2.7 million cells per putamen). Safety and tolerability will be assessed at 1 year, along with evidence of cell survival and motor effects, and feasibility will be assessed at transplantation. Further safety and tolerability, with efficacy and exploratory assessments, will take place at 2 years post transplant.

Diagnosis and Eligibility Criteria:

Subject inclusion criteria include the following:

- Age:
  - Canada: ≥50 to ≤78 years old
  - US: ≥60 to ≤78 years old
- Idiopathic PD defined by the modified UK Parkinson's Disease Society Brain Bank criteria
- A minimum time of 3 years from time of PD diagnosis and a maximum time from PD diagnosis of 20 years
- Prior sufficient treatment comprising levodopa and at least 1 adjunct therapy, and additional appropriate therapy such as physical therapy
- Defined levodopa response of ≥30% improvement on the basis of MDS-UPDRS Part 3
- Hoehn and Yahr score:
  - Canada: 0 to 3 "on"
  - US: 0 to 2 "on" and 3 to 4 "off"
- For US only: Not eligible for deep brain stimulation or have refused deep brain stimulation after evaluation by an independent neurologist or neurosurgeon
- PD medications allowed: any approved oral, transdermal, and/or injectable PD medication and medications must be stable for ≥1 month prior to enrollment
- Abnormal Involuntary Movement Scale (AIMS) rating scale score of ≤2 for dyskinesia on each of Sections 1 to 10 of the 12-item AIMS
- "Off" time of ≥2 hours daily
- MoCA score ≥26, or ≥22 if no significant cognitive impairment by neuropsychological testing per assessing clinical discretion
- Hamilton Depression Scale (HAM-D) score ≤17
- Dysthymia allowed with single or 2 antidepressant medications if at stable dose for >6 months
- Normal endocrine, renal, and liver function as measured by standard laboratory testing unless abnormality is not clinically significant; no blood dyscrasias; no bleeding disorder; and no cardiovascular contraindications for surgery, except for stable and controlled conditions including diabetes type 2 and hypothyroidism
- All other concomitant disorders must be stable and well controlled, must not constitute a contraindication to general anesthesia or surgery, or interfere with scheduled study assessments
- Women of childbearing potential must agree to use a highly effective method of contraception from screening until at least 4 weeks after cessation of the oral immunosuppression medication regimen
- Able to participate in all study visits and evaluations, including brain magnetic resonance imaging (MRI)
- Able to give informed consent for study participation and sign the informed consent form
- Existence of a study participant partner who may act as potential surrogate over the long term for ongoing consent

Subject exclusion criteria include the following:

- Clinical features suggestive of a neurodegenerative diagnosis other than PD
- PD with only tremor-based symptoms
- Diagnosis of primary mitochondrial disorder, epilepsy, stroke, multiple sclerosis or other neurodegenerative diseases such as Alzheimer's disease

- Any current or relevant previous history of serious, severe, or unstable physical, neurological, or psychiatric illness that may make the subject unlikely to fully complete the study (including significant depression, psychosis, anxiety, cognitive impairment, or impulse control disorder)
- Receiving DA receptor-blocking agents, including typical neuroleptics, prochlorperazine, and metoclopramide at the time of screening or within 3 months prior to screening
- ^{18}F-DOPA PET imaging inconsistent with DA deficiency
- Ongoing treatment with intrajejunal or subcutaneous infusion therapies for PD (Subjects who permanently discontinue these treatments are eligible to enroll after 2 months.)
- History of deep brain stimulation, lesion therapy, or gene therapy for PD
- Prior surgical or radiation therapy to the brain or spinal cord
- Per assessing clinician discretion, any abnormality on brain MRI that would preclude cell transplantation
- Significant concomitant medical disease limiting life expectancy to less than 24 months from study inclusion, or significant and serious concomitant medical disease that is poorly controlled
- Signs of active malignant disease or other clinically relevant abnormality on chest X-ray
- Clinically relevant abnormalities on standard safety laboratory tests, including blood count, partial thromboplastin time, blood chemistry (glucose, blood urea nitrogen, creatinine, electrolytes), and liver function tests (aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, total protein, bilirubin)
- Presence of a condition resulting in high risk of immunosuppressive drugs, including any active infectious disease of any nature, including clinically active viral infections (seropositive for human immunodeficiency virus, hepatitis C virus, hepatitis B virus, cytomegalovirus (CMV), and Venereal Disease Research Laboratory unless related to immunization or past CMV exposure, or positive QuantiFERON-TB gold Plus)
- Inability to temporarily stop anti-platelet agents or other anti-coagulants without significant risk
- Previous or currently active malignant disease within the past 5 years, except basal cell carcinoma or in situ uterine cervical carcinoma that have been definitively treated
- Use of immunosuppressive drugs including systemic steroids within the previous 3 months
- Severe obesity (>350 lb [159 kg]) or any condition that prevents use of PET/MRI
- Known substance abuse (recent history of abuse of alcohol or other drugs such as barbiturates, cannabinoids, and amphetamines) within last 5 years
- In the opinion of the investigator, presence of any cognitive, behavioral, or psychiatric symptoms that would be deemed contraindications to cell transplantation
- Pregnancy or breastfeeding
- Unable to cooperate or complete self-assessment scales and diaries
- Unable to provide and sign the informed consent form
- Receipt of another investigational agent or device within the 3 months prior to enrollment
- Contraindication to surgery or general anesthesia
- Contraindication to taking immunosuppressive drugs
- In the opinion of the investigator, any other condition regarded as making subject unsuitable for the trial

Study participant partner inclusion criteria is the ability to act as a potential surrogate over long term for the subject.

Study participant partner exclusion criteria is the inability to cooperate or complete questionnaires.
Investigational Product, Dosage and Mode of Administration: **Cell product:** MSK-DA01 comprises cryopreserved DA neuron precursor cells derived from hESC line WA09 or 0062 (H9), that will be delivered as Dose A: 0.9 million cells per putamen, and Dose B: 2.7 million cells per putamen. Cells will be delivered in a single session of stereotactically guided surgical injection into the brain, bilaterally. **Immunosuppressive regimen:** Basiliximab 20 mg intravenously intraoperatively and post-operative day #4; methylprednisolone 500 mg intravenously prior to surgery, then tapered to oral prednisone and continued at 5 mg daily for 1 year; tacrolimus taken orally twice daily (BID) (recommended starting dose of 0.05 mg/kg BID [3 to 3.5 mg BID for a 70-kg person]) beginning on the day after surgery (Day 1), then adjusted to a target trough blood level of 4 to 7 ng/mL for a period of 1 year.
Duration of Treatment: Duration of participation, from time of first contact to time of completion of the 2-year scheduled evaluation, will be up to 26 months for an individual subject. Projected study duration is 44 months.
Reference Therapy, Dosage and Mode of Administration: Not applicable.
Criteria for evaluation: **Safety and Tolerability:** In order to determine safety and tolerability, incidence of transplant-related AEs and immunosuppressive drug-related AEs will be determined for up to 1 year, and clinically significant changes from baseline in physical examination, laboratory values and MRI of the brain from baseline to 2 years in addition to incidence of transplant-related AEs and of immunosuppressive drug-related AEs up to 2 years.
Statistical Methods: One year: A formal analysis of the primary endpoint will be performed when all subjects dosed have reached Year 1 or discontinued from the study. At that time, a data cut will occur and the primary analyses to address safety and tolerability will be performed. Analysis of secondary and exploratory aims is planned when all subjects dosed have reached Year 1 or discontinued from the study. Two years: A formal analysis of secondary outcomes will be performed when all subjects dosed have reached Year 2 or discontinued from the study. At that time, a data cut will occur and the secondary and exploratory analyses will be performed. Statistical analyses will be primarily descriptive in nature. Descriptive statistics will include baseline characteristics of the cohort enrolled. Surgical delivery of MSK-DA01 cells will be described, including numbers of tracks, numbers of deposits, position of deposits, estimated cell numbers delivered per deposit, and percentage of target deposits delivered per putamen.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BAI-II	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory
BID	twice daily
BUN	blood urea nitrogen
CBC	complete blood count
CDRH	Center for Devices and Radiological Health
CGI-S	Clinical Global Impression-Severity
CMP	complete metabolic profile
CMV	cytomegalovirus
CNS	central nervous system
CRF	case report form
CRO	clinical research organization
CsA	cyclosporine A
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DA	dopamine
DBS	deep brain stimulation
DICOM®	Digital Imaging and Communications in Medicine
DNA	deoxyribonucleic acid
DSMC	data safety monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay

Abbreviation or Specialist Term	Explanation
FDA	Food and Drug Administration
FIMR	Feinstein Institute for Medical Research
^{18}F-DOPA	fluorodopa F 18
FOXA2	forkhead box protein A2
fVM	fetal ventral mesencephalic
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GRE	gradient recalled echo
H&E	hematoxylin and eosin
HAM-D	Hamilton Depression Scale
HCV	hepatitis C virus
hESCs	human embryonic stem cells
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
hNA	human nuclear antigen antibody
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	independent ethics committee
IHC	immunohistochemistry
IND	investigational new drug application
IRB	institutional review board
IS	immunosuppression monitoring visit
ISO	International Organization for Standardization
ISTA	International Safe Transit Association
IV	intravenous
LSO	Life Science Outsourcing
mDA	midbrain dopamine
MDS	International Parkinson and Movement Disorder Society
MMR	measles, mumps, rubella vaccine
MoCA	Montreal Cognitive Assessment

Abbreviation or Specialist Term	Explanation
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
NACU	Neurosurgical Advanced Care Unit
NCI	National Cancer Institute
NHP	non-human primate
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NMSS	Non-Motor Symptoms Scale
6-OHDA	6-hydroxydopamine
PACU	Post-Operative Care Unit
PCR	polymerase chain reaction
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire-39
PET	positron emission tomography
PI	Principal Investigator
PKG	Personal KinetiGraph
PO	per os (orally)
PoOV	post-operative evaluation
PrOV	pre-operative evaluation
PT	prothrombin time
PTT	partial thromboplastin time
qPCR	quantitative polymerase chain reaction
QUIP	Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease
RBC	red blood cells
SAEs	serious adverse events
SAP	statistical analysis plan
SC	screening
spMRI	surgical planning magnetic resonance imaging
TH	tyrosine hydroxylase
TMT-A	Trial-Making Test A
TMT-B	Trial-Making Test B
TOPF	Test of Premorbid Functioning

Abbreviation or Specialist Term	Explanation
UDysRS	Unified Dyskinesia Rating Scale
UK	United Kingdom
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
UTI	urinary tract infection
V	visit
VC	ventricular cannula
VDRL	Venereal Disease Research Laboratory
WA09 hESC	cell line 0062 in NIH registry
WBC	white blood cells

4. INTRODUCTION

4.1. Disease Overview

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is estimated to affect 7 to 10 million subjects worldwide (Valente, 2012). PD is a progressive and disabling disease with cardinal clinical signs of bradykinesia, rigidity and resting tremor (Parkinson, 2002). These are attributed for the most part to progressive degeneration of dopaminergic input from the substantia nigra to the striatum. Oral medications that restore dopaminergic tone become less effective in advanced PD, and in particular lead to disabling motor complications. These complications of levodopa therapy include (1) motor fluctuations, in which levodopa duration of action is shortened and results in development of "off" periods in which PD symptoms are poorly controlled, and (2) presence of dyskinesia, that is, abnormal involuntary movements most commonly occurring at peak levodopa dose, which may limit therapy and become disabling. For patients with moderate-to-advanced PD in whom medications do not provide adequate control of symptoms, some are eligible for surgical intervention using deep brain stimulation (DBS), which has been Food and Drug Administration (FDA)-approved since 2002 for advanced PD and since 2016 for PD with motor complications and at least 4 years disease duration. DBS involves surgical insertion of small electrodes that provide continuous high frequency electrical stimulation to a specific target, usually the subthalamic nucleus or the globus pallidus pars interna. These electrodes are connected to a battery/programming device, permanently located in the anterior chest wall of the patient. DBS surgery is a current standard of care in advanced PD, but limitations include the need for indwelling hardware in the brain, reliance on batteries implanted in the chest or abdomen, and the lack of any possibility to restore physiologic dopaminergic inputs. In clinical trials, surgical intervention providing bilateral DBS has resulted in reduced "off" periods (when medications are ineffective) of 70%, and reduction in dyskinesia by 60% to 70% at best. Other studies have found lower efficacy. Complications include hemorrhage, stroke, infection, seizures, and others. Moreover, DBS provides suboptimal relief of speech, gait, and balance difficulties in some individuals. Later stage symptoms, like dyskinesia (comprising random involuntary movements) are likely caused by the continuing degeneration of dopamine (DA) terminals in the striatum resulting in the increased pulsatility of DA receptor stimulation following levodopa therapy.

Cell-based therapies are therefore particularly attractive in that they have the potential to deliver DA in a more physiologic manner than is possible from medications and via synaptic integration, retain functionality of downstream striatal circuits required for long-term motor function. Several cell sources have now been tested in published clinical trials in PD, including fetal ventral mesencephalic (fVM) tissue (Barker, 2013). These studies are summarized briefly in Section 4.6, and provide valuable experience that has aided the trial design. The most extensive experience and most encouraging results derive from the numerous fVM transplant studies undertaken, and an ongoing study, named TRANSEURO, is currently underway (NCT01898390, University of Cambridge, United Kingdom [UK]) to further test fVM transplant in a more highly selected subject group. However, there are many advantages of a stem cell rather than fVM-based therapy, including improved homogeneity of cell type in the final product, scalability, and reproducibility, as well as routine, "off-the-shelf" access to a standardized cell source allowing for proper dosing studies. After extensive efforts in laboratories across the world, the Sponsor's team made a major discovery in 2011 (Kriks, 2011) that enables the derivation of nearly

unlimited numbers of authentic, engraftable DA neurons from human embryonic stem cells (hESCs). The Sponsor's team has extensive preclinical experience with this cell product and has further refined the production process since its last meetings with the FDA (pre-pre-Investigational New Drug Application [IND] 11 August 2014; pre-IND 23 May 2016). The scientific rationale for the therapy has been discussed in both the pre-pre-IND and the pre-IND documents and has been published by the Sponsor (Kriks, 2011). Moreover, plans for clinical translation have been developed as part of an international consortium, Gforce-PD, with key clinical translation considerations published in 2017 (Barker, 2017).

4.2. Study Interventions

4.2.1. Investigational Therapy: MSK-DA01

MSK-DA01 is an experimental cell product for the treatment of PD that is primarily composed of hESC-derived, midbrain dopamine (mDA) neurons. MSK-DA01 will be delivered using the ventricular cannula (VC) in conjunction with the neuro navigation system. The VC has been modified from the version with 510(k) approval; the modification has been cleared for investigational use in this study. Thawed and resuspended cryopreserved cells will be delivered by stereotactically guided surgical injection into 9 sites along 3 tracks in the postcommissural putamen of each hemisphere. Subjects will receive 0.9 million cells per putamen (Cohort A) or 2.7 million cells per putamen (Cohort B).

MSK-DA01 was manufactured at Memorial Sloan Kettering's Michael G. Harris Cell Therapy and Cell Engineering Facility. Representatives from the Sponsor will be on site in the Surgical Site laboratory to assist with thawing and formulating the cells and to deliver the product to the operating room. Necessary clearance and training for all representatives will be obtained prior to the first patient enrolled.

MSK-DA01 was found to match pre-established release criteria for viability, identity, purity, microbiology, virology, and endotoxin levels. Vials of 8×10^6 cells per mL are frozen in cryopreservation media and stored in liquid nitrogen at the Good Manufacturing Practice (GMP) facility.

4.3. Immunosuppressive Regimen

An immunosuppressive regimen will be administered over the period of 1 year comprising drugs that are routinely used in solid organ transplant. Administration of the immunosuppression drug regimen, in addition to monitoring and dose adjustment, will be undertaken by the Immunosuppression Clinician.

The regimen comprises basiliximab, methylprednisolone followed by prednisone, and tacrolimus (see Section 8.3.6 for details of dose, route, and schedule of administration).

Alternative medications: It is anticipated that the regimen will be well-tolerated and that side effects can be managed with dose reductions; however, in the unlikely event of a reaction, the patient will be managed according to standard of care in consultation with the Immunosuppression Clinician. For example, alternative or equivalent medications will be considered on an individual basis, such as cyclosporine (alternative to tacrolimus).

4.4. ^{18}F-DOPA Positron Emission Tomography (PET Imaging Site)

Fluorodopa (^{18}F-DOPA) is an FDA-approved imaging agent for PD and will be administered at the Positron Emission Tomography (PET) Imaging Site in the United States. The ^{18}F-DOPA PET protocol will be provided to the Clinical Site and filed in the Investigator Site File.

^{18}F-DOPA for injection will be manufactured at the PET Imaging Site. The proposed study involves administration of 5 mCi at baseline, 12, 18, and 24 months, which is within the range of dosimetric safety data available for this agent and for other radiopharmaceuticals for brain imaging.

Patients are scanned after an overnight withdrawal from their PD medications. They are pretreated with 150 mg of carbidopa given orally approximately 60 minutes (but no more than 120 minutes) prior to the injection of ^{18}F-DOPA. In the event of any unexpected delays with the production/delivery of ^{18}F-DOPA exceeding 120 minutes (post carbidopa administration), an additional 50 mg of carbidopa can be administered approximately 30 minutes prior to the injection.

4.5. Summary of Preclinical and Animal Data

MSK-DA01 is based on work published in Nature 2011 (Kriks, 2011), and validated in several follow-up studies including papers in Cell Stem Cell (2013) [Miller, 2013] and in Nature Biotechnology (2015) [Steinbeck, 2015].

In all the studies described here, and subsequently for the cell product to be used in subjects, the mDA neurons were derived from the WA09 hESC line (also referred to as cell line 0062 in the NIH registry), according to a protocol for the derivation of mDA neurons from hESCs. Using a step-wise differentiation of hESCs with small molecules and growth factors, large numbers of transplantable mDA cells could be generated by Day 16 of differentiation. **These steps do not include any genetic manipulation of the cells.** The mDA neurons were then tested in 3 animal models and the results are summarized herein.

In the original publication (Kriks, 2011), in **mouse**, 4.5-month survival assays were performed in adult, 6-hydroxydopamine (6-OHDA) lesioned (“Parkinsonian”) animals (NOD-SCID IL2yR null). These studies included 6 animals and were performed with Day 25 cells at 150,000 cells/animal. At the time of sacrifice, the mice were analyzed for the presence of human cells using human neural cell adhesion molecule and mDA neurons using tyrosine hydroxylase (TH) and forkhead box protein A2 (FOXA2) staining. Additionally, graft function after transplantation into the striatum of these mice was shown by measuring recovery of amphetamine-induced rotations at 4 months.

Additionally, independent transplantation studies into parkinsonian mice were performed in 2 follow-up publications that further validated the results and demonstrated mechanism of action of those grafts using optogenetic strategies (Miller, 2013, Steinbeck, 2015).

More than 500 mice have been transplanted since to further optimize and validate the differentiation protocol including the definitive tumorigenicity, biodistribution, and toxicology studies detailed below.

Robust graft function was further confirmed in the 6-OHDA lesioned rat model. The rat model, unlike the mice, allows for more complex behavioral assays. Lesioned rodent models of PD

remain the most robust and widely accepted in the field. The lesion is performed by stereotactically injecting 6-OHDA unilaterally in the striatum (in the mouse) or the median forebrain bundle (in the rat). The substance is retrogradely taken up by the axons of the DA neurons of the substantia nigra (SN), which project to the striatum. Once in the SN, 6-OHDA leads to selective DA neuron cell death and results in unilateral deficits referred to as hemiparkinsonism. The animals then start exhibiting stereotypical behavior, the most reliable being unilateral rotations, ipsilateral to the lesion, upon systemic injection with amphetamine. The rotations are quantitated: in general, a rat that exhibits >6 rotations per minute is considered parkinsonian (well lesioned) and is unlikely to experience any spontaneous recovery. Upon successful grafting, the rats start decreasing their rotations and eventually resume symmetric movements. This behavioral recovery, as well as a histological analysis of the grafted tissue, form the basis of the efficacy studies. Multiple sets of in vivo grafting have been performed using immunodeficient rats or Sprague-Dawley rats that received immunosuppression with cyclosporine A (CsA), thus allowing the evaluation of graft survival and function under immunosuppression. Published data with Sprague-Dawley rats (Kriks, 2011) show excellent graft survival, evidence of mDA fiber outgrowth and maintenance of midbrain-specific transcription factor expression confirming long-term survival of the hESC-derived neurons expressing authentic mDA neuron markers. Transplantation of mDA neurons derived from WA09 has been performed in >100 additional rats since the original report to optimize and validate the differentiation protocol and the cryopreservation method used.

The third pre-clinical model used to test the translational potential of the mDA neurons is the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned ("Parkinsonian") rhesus monkey. An initial set of studies was performed in 2 monkeys to test short-term (4-week) in vivo survival and maintenance of mDA neuron phenotype in the primate brain (Kriks, 2011). Day 25 mDA neurons derived from WA09 hESCs and from WA09-GFP hESCs (expression of GFP under control of EF1a promoter) were grafted into the striatum of adult MPTP lesioned rhesus monkeys (N=2, 1.25×10^6 cells/tract, 3 tracts/per putamen, 6 tracts in total, cell number of 3.75 million cells per putamen, in a volume of 30 µL). For both animals, 1 putamen each was grafted with unlabeled WA09-derived cells while the other putamen received cells derived from WA09-GFP cells. The animals received CsA for immunosuppression. Those studies showed robust survival of TH/FOXA2 positive mDA neurons and evidence of re-innervation of the host striatum. These findings were important and showed that grafting larger numbers of cells, similar to those ultimately required for future human grafting studies, is possible and results in robust mDA neuron survival.

Four batches of MSK-DA01 were manufactured in MSK's GMP facility and were used to qualify the differentiation process. All batches were tested for sterility, endotoxin, cell viability, markers for non-DA impurities, and markers for DA cells and passed release criteria. One lot was further tested for non-clinical safety and efficacy.

The following IND-enabling studies were conducted:

- Non-GLP study to assess the efficacy of MSK-DA01 in a rodent model of Parkinson's disease
- GLP study to assess biodistribution und toxicology of MSK-DA01
- GLP study to assess tumorigenicity of MSK-DA01

- Non-GLP study to assess MR-guided implantation of MSK-DA01 in the nonhuman primate (NHP) brain

4.5.1. Study at MSK: Study to Assess the Efficacy of MSK-DA01 in a Rodent Model of Parkinson's Disease

An efficacy study was conducted under near Good Laboratory Practice (GLP) conditions. Twenty-seven 6-OHDA lesioned rats (male:female ratio ~1:1) received MSK-DA01 intrastriatal injections (400,000 cells) and 14 rats received vehicle-only injections.

There were no treatment-related effects on morbidity or mortality.

Blinded assessment of behavioral testing demonstrated significant improvement in the rotational behavior down to normal values in the animals grafted with MSK-DA01 while the vehicle-injected control animals maintained their abnormal behavior throughout the study period. Recovery of animal behavior in MSK-DA01 treated animals was statistically significant as demonstrated by improvement in rotation scores at 5 and 8 months post grafting, compared to sham controls ($p<0.05$ and $p<0.0001$, respectively).

MSK-DA01 graft survival was observed histologically in 100% of the animals. The grafts demonstrated the presence of DA neurons with normal morphology and good innervation of the striatum. Assessment of the surviving cell numbers showed an average of 45,741 DA neurons out of an average of 592,698 cells, ie, 12%. Remaining cells represented closely related or still immature midbrain lineages similar to the cell types expected to be present in developing human fetal mDA neuron grafts. No serotonin+ neurons, a cell type previously associated with the risk of graft-induced dyskinesia in human fetal grafts, were detected.

There were no tumors or evidence of overgrowth of neural tissue and the proliferation rate of surviving graft cells at terminal sacrifice was low.

4.5.2. Study C17399 at WuXi Apptec in St. Paul, Minnesota: GLP Study to Assess Biodistribution and Toxicology of MSK-DA01

To assess the biodistribution, toxicity, and persistence of the test article, MSK-DA01-002-051016 cells, at low and high doses, were injected unilaterally into the right striatum of NOD scid gamma (NSG; immunodeficient) mice. This is considered the most sensitive mouse model to detect tumor formation in a xenografting paradigm (Quintana, 2008).

Animals were observed for general health, mortality, and moribundity, clinical observations, body weights, and clinical chemistry. At terminal sacrifice, necropsies were performed and tissues collected for biodistribution/quantitative polymerase chain reaction (qPCR) or toxicology/histology. Four cases of early death occurred during the period covered by this study. All 4 cases of early death are unlikely to be related to the test article.

There were no treatment related deaths. There were no treatment related or clinically relevant effects on body weight, hematology, or clinical chemistry parameters.

Histologically, from Day 30 to Day 180, the injected cells transitioned from densely cellular clusters of small neural-progenitor-type cells to looser clusters of larger, more differentiated neuron-cell-body-like cells with much more abundant supporting neuropil that appeared more continuous with surrounding host neuropil. Growth of human-origin cell clusters from Day 30 to

180 was apparently slow, with the largest clusters only about twice the size at 180 days than at 30 days after injection. These findings suggested maturation of injected human-origin dopaminergic cells into grey matter-like tissue, and incorporation into the host tissue over time. Immunohistochemistry analysis demonstrated that grafts were maturing neuronal cells with a low potential for proliferation.

The biodistribution as assessed by qPCR detection of MSK-DA01 genomes in major organs showed that at time point Day 30, the human cells remained primarily at the injection site in the brain and did not extensively traffic outside that site. All samples in the negative control group tested below the limit of quantitation and were negative. All brain samples in the test article groups, low and high dose groups, tested positive except for the animal number C17-257 in the female low dose group, which tested negative. The positive results in the brain verify that the test article was injected in the target area of the brain. One negative incident could have been due to a mistake of sampling a wrong area of the brain or technical failure during cell injection.

4.5.3. Study C17400 at WuXi Apptec in St. Paul, Minnesota: GLP Study to Assess Tumorigenicity of MSK-DA01

To assess the tumorigenicity of human mDA neurons in immunodeficient mouse model, negative control (vehicle, Group 1), positive control (WA09 undifferentiated human ES cells, Group 2), Group 3 (mDA neurons + 0.1% WA09 undifferentiated human ES cells), Group 4 (mDA neurons + 0.01% WA09 undifferentiated human ES cells), and Group 5 (100%) cells were injected unilaterally into the right striatum of NSG mice.

Microscopic evaluation of individual animals in all groups was performed per protocol.

The negative control article, Reference I test article, Reference II test article, and MSK-DA01 were considered non-tumorigenic, as no animals in these groups developed a neoplastic mass at the injection site. However, the positive control article was considered tumorigenic, as 18/24 animals (75.0%) developed teratomas (ie, neoplasms that recapitulate multiple embryonic structures) at the injection site positive by immunohistochemistry (IHC) for human nuclear antigen antibody (hNA), consistent with origin from the WA09 cell line injected.

The majority of animals treated with Reference I test article, Reference II test article, and MSK-DA01 exhibited clusters of well-differentiated large neurons supported by neuropil with glial cells within the injection site or tract, positive by IHC for hNA. These findings were consistent with maturation into mature nervous tissue.

In the MSK-DA01 group, 3 out of 22 dosed male mice (13.6%) and 5 out of 22 dosed female mice (22.7%) died early or were euthanized. One male was euthanized early due to clinical signs associated with an unrelated spontaneous systemic lesion. Two male and 5 female animals died early due to unknown reasons, which the pathologist suggested might have been due to the mass effect of the large cluster of injected-cell-origin nervous tissue at the injection site within the brain. However, the grafts did not cause a midline shift and there was no evidence of herniation that would support a mass effect. Rather, the histological evidence supports the large cluster of cells are consistent with maturation of the injected MSK-DA01 cells into mature nervous tissue. Additionally, further IHC analysis demonstrated the cells were mature neuronal cells with a low potential for proliferation.

4.5.4. MR-Guided Implantation of ES-Derived Dopaminergic Cells (MSK-DA01) in the Nonhuman (NHP) Brain (Study No. S17-10657) and Preclinical Histological Study Report UCSF (Study No. SC-003)

The objective of this study was to evaluate implantation conditions and survival of MSK-DA01 in the non-human primate (NHP). Eight Rhesus monkeys (*Macaca mulatta*) were assigned to 2 dose groups with different immunosuppressant regimens: Groups 1A-1B were treated with mycophenolate mofetil, tacrolimus, and prednisone; and Groups 2A-2B were treated with tacrolimus and prednisone. MSK-DA01 was administered bilaterally in small deposits into the putamen: 6×10^6 cells in 3 deposits of 20 µL/hemisphere within 8 hours of preparation. Acute intracerebral infusions were achieved using a modified 16-gauge VC (MRI Interventions Inc., Irvine CA [now ClearPoint Neuro, Inc.]) attached to a 100-µL Hamilton® syringe and a syringe pump. Infusion was performed by advancing the cannula 2 mm ventrally after every 6 to 7 µL of infusion at an infusion rate of 2 or 10 µL/minute. All animals were euthanized 2 months post-implantation and their brains processed for histopathological signs of toxicity, and immunohistological evaluation of survival and migration of MSK-DA01 cells. The in-life portion of the study was conducted at Valley Biosystems, Sacramento, California, and the post-mortem/histological analysis was conducted at Memorial Sloan Kettering Cancer Center.

Key findings with respect to the administration procedure were as follows:

- The intracerebral infusion procedure was well tolerated, and surgical recovery was uneventful.
- The derived volumes were effectively administered to target locations.
- Cells were observed settling in the syringe.
- Cellular occlusion of the cannula was observed in 1 instance.
- Cellular implants identified in some, but not all of the deposit sites were attributed to the gravitational settling of cells in the syringe, resulting in inconsistency in cell density between deposits. Because in this study, the entire volume of cell suspension required for a single hemisphere was loaded in a single syringe, the cells sat at room temperature for an extended period of time, which resulted in gravitational settling and unequal deposition of cells. As described in the Cell Preparation and Delivery Manual, cells loaded into the syringe will be held on ice until administration to the patient. This was shown to resolve gravitational settling.
- Gross necropsy findings were limited to adhesion of the dura to the cerebral surface and skull and the craniotomy site is a single monkey.
- No signs of hemorrhage or damage related to the implantation procedure were identified in any of the subjects. No major histopathological signs of toxicity were observed in the brain tissue.
- Mild neuro-inflammation was associated with both the administration procedure and implanted cells.

Key findings associated with the immunosuppression regimen were as follows:

- Mycophenolate mofetil may be negatively affecting cell survival.

Key findings associated with engraftment of MSK-DA01 cells were as follows:

- The survival of the engrafted cells at 2 months post-implantation provides in vivo evidence that the cells were biocompatible with the ventricular cannula and lumen and that the 16-gauge cannula and Hamilton® syringe did not negatively affect cellular survival, for example by exerting excessive shear stress during administration.

4.6. Previous Experience with Cell Transplantation

Multiple cell sources have now been tested in published clinical trials in PD, including fVM tissue (Barker, 2013), adrenal medullary cells (Goetz, 1989), and most recently retinal pigmented epithelial cells (Gross, 2011). Of these, the best-studied reparative therapy in PD remains allotransplant of dopaminergic neuroblasts from fVM tissue, first performed in 1987 at Lund University, Sweden (Brundin, 1987; Brundin, 1988). These studies, carried out up until 2003, demonstrated graft survival as measured by neuroimaging modalities over a period of years. Moreover, analysis of tissue obtained at autopsy has demonstrated survival of engrafted tissue with dopaminergic neuron characteristics.

Recently, long-term data have confirmed that transplanted fVM tissue is capable of long-term survival in the host brain, although there is ongoing discussion as to how cell survival relates precisely to clinical effects (Kordower, 2017). Long-term symptomatic relief has been documented in 2 surviving subjects at 15 years and 18 years post transplant in 1 study (Kefalopoulou, 2014), and a recent report following autopsy demonstrated maintenance of DA transporter protein reflecting surviving engrafted tissue in 5 subjects from 4 to 14 years post transplant of fVM tissue (Hallett, 2014). An autopsy evaluation was performed in 5 individuals who had undergone bilateral putamen fVM tissue transplant in a sham surgery controlled clinical trial (Freed, 2001) 17 to 18 years previously. Clinical and neuroimaging results support (1) graft maintenance in each of 3 subjects undergoing neuroimaging, (2) evidence of graft activity based upon clinical signs, and (3) atypical outcomes with superior function to that expected, comparable with published data on long-term DBS outcomes, at up to 36 years of PD duration (Henchcliffe, 2016a; Henchcliffe, 2016b).

Data from these studies have been examined in detail to assist in clinical development planning (see Section 4.7 and Section 4.8), including development of inclusion and exclusion criteria, choice of study endpoints, study duration, and the use of an immunosuppression regimen. Of the fVM transplant studies, some studies found that subjects responded well while others have shown no or minimal improvements, but at least some of this heterogeneity may be due to different characteristics of the subjects enrolled, as well as choice of outcome measures, and various study durations. Data from 2 NIH-funded sham surgery controlled clinical trials have, in particular, provided valuable information based upon retrospective subgroup analyses in which younger subjects with better levodopa response and shorter disease duration experienced more benefit (Freed, 2001; Olanow, 2003). The studies also highlighted potential pitfalls. Some subjects experienced off-state graft-induced dyskinesias (Freed, 2001; Olanow, 2003; Hagell, 2001) that may be attributable in part to growth of non-dopaminergic, such as serotonergic neurons from grafted fetal tissue, but also possibly to irregular and patchy distribution of the surviving engrafted tissue and/or deficient innervation from graft to host. Finally, although some

subjects reported benefit early after the transplantation procedure (Freed, 2001), some study participants have not demonstrated clinical improvement until later (Kefalopoulou, 2014).

To note, the potential risk of bilateral injections is due to hemorrhage following injections. There is a track record in the field for bilateral implantation of devices and for bilateral fetal grafts. The advantage of a single session is (1) the elimination of a second session of intubation and general anesthesia and (2) the elimination of a concern over repriming a patient with allograft material, which may be detrimental, despite immunosuppression, upon second administration of the same material. A repeat injection of graft material would also likely require reloading with immunosuppressants. In the current study, intraoperative magnetic resonance imaging (MRI) will be performed after the 3 tracks are placed in each putamen, to exclude the possibility of significant hemorrhage before proceeding to the other side. In Canada, intraoperative MRI will be performed only if clinically indicated.

At present, there are several studies ongoing internationally that aim to examine effects of intracerebral cell transplantation in PD. The open-label TRANSEURO study (NCT01898390, University of Cambridge UK) is underway. This study will re-examine the effects of bilateral putaminal engraftment of fVM cells in a target of 40 participants. The study design is optimized based upon prior experiences: Eligible individuals are aged 30 to 68 years old, with PD duration of 2 to 13 years. A study to examine safety and tolerability of human fVM transplant in 15 patients is ongoing in the CHA Bundang Medical Center, Republic of Korea (NCT01860794). A study of neural stem cell-derived neurons for 12 participants is reported as planned but not yet recruiting (NeuroGeneration, NCT03309514). Two studies using pluripotent stem cell-derived neural stem cells in 10 and 50 patients, respectively, are being conducted in China (NCT03815071 and NCT03119636). Another study in Melbourne, Australia is examining the safety of neural stem cell (not DA neurons) transplantation derived from parthenogenetic stem cells in individuals aged 30 to 70 years old with PD up to 13 years (NCT02452723). Finally, an open label study, using induced pluripotent stem cell derived dopaminergic neurons, has started in Japan (http://www.kuhp.kyoto-u.ac.jp/ips-pd.html).

4.7. Study Design Rationale

Cell–based therapies have the potential to deliver DA to the DA-depleted striatum in a more physiologic manner than is possible from medications. The Sponsor has derived authentic, engraftable mDA neurons from hESCs using a novel, small molecule-based floor-plate differentiation strategy. These cells demonstrate excellent in vivo survival and function in animal models of PD with no evidence of tumor or excessive growth (see Section 4.5). The Sponsor will therefore implement an open label, non-randomized study, with the primary objective of evaluating safety and tolerability of transplantation of 2 dose levels of MSK-DA01 cells in individuals with advanced PD at 1 year post transplant. The rationale for key design features is described in this section.

4.7.1. Rationale for the Study Population

Ascertainment of diagnosis will combine formal criteria and evaluation by a movement disorders neurologist. The minimum time of 3 years' PD duration in the inclusion criteria will further enhance high diagnostic accuracy (87.9% based upon published autopsy data at ≥3 years versus 66.7% at <3 years) [Adler, 2021]. An upper limit of 20 years' PD duration, together with the

Hoehn and Yahr score of 0 to 3 “on” for Canada and 0 to 2 “on” and 3 to 4 “off” for the US, have been made to exclude subjects with the most advanced stages of PD, in whom more widespread pathology may impair ability of downstream neurons to respond to dopaminergic stimulation. The age ranges (≥50 to ≤78 years for Canada, ≥60 to ≤78 years for US) at time of study entry have been chosen to balance (a) on the lower end, allowing enrollment of younger subjects who may stand to benefit more (Barker, 2013; Freed, 2001) and (b) on the upper end, maintaining ability to enroll subjects with typical age of onset of PD while avoiding the inclusion of older subjects who may be more likely to develop comorbidities and experience more risk during such a study.

Other inclusion-exclusion criteria are designed to ensure:

- response to dopaminergic medications, which will reflect integrity of the striatal receptors anticipated to be necessary to generate a graft response
- avoiding significant dyskinesia that might worsen based upon previous fVM studies
- avoiding significant load of non-motor symptoms that are predicted to be non-DA responsive and might possibly worsen with increased dopaminergic stimulation, such as hallucinations, cognitive decline, or impulse control disorders

Subjects also must be deemed able to tolerate immunosuppression, and not to be at undue risk of immunosuppression. Anatomic findings on MRI scans that could lead to a potentially higher risk of surgical adverse events (AEs), such as the presence of significant subdural collections, significant generalized or striatal atrophy, have also been included in the exclusion criteria.

4.7.2. Rationale for Use of ^{18}F-DOPA PET Scan

PET scans of the brain using ^{18}F-DOPA as a radiotracer will be performed at the PET Imaging Site. The ^{18}F-DOPA PET scan is widely used to evaluate presynaptic DA neuron integrity due to uptake as ^{18}F-DOPA is a DA precursor in these neurons. This tracer binds to aromatic acid decarboxylase in the DA nerve terminals in the brain, and therefore has been extensively used in clinical trials as a measure of loss of DA neurons. It is a biomarker that reflects density of neuronal terminals that release DA into the striatum. Sensitivity and specificity for the diagnosis of PD are estimated to be 95% and 100% respectively, and it may therefore be used as a screening investigational tool that may correlate with graft survival and/or clinical progression. It has been used in multiple previous clinical trials of fVM tissue and cell transplantation in PD in order to detect increased uptake of DA precursors (specifically ^{18}F-DOPA) that is attributable to survival and differentiation of transplanted cells into dopaminergic neurons.

4.8. Dose Rationale

4.8.1. Rationale for Cell Dose

This is a first-in-human study of MSK-DA01 and therefore the optimal dose is not known in humans. However, the cell dose for injection was selected based upon target surviving cell dose, while knowing the cell survival rate of the same batch of cells nominated for clinical use from extensive preclinical studies. The target surviving cell doses are based upon:

(1) Knowledge of the number of cells lost in PD. Stereological counts of the substantia nigra indicate that a healthy individual has about 400,000 dopaminergic neurons per side (Rudow,

2008). It is estimated that >50% of DA neurons and about 80% of DA innervation to the striatum are lost by the time of diagnosis. In subjects with ongoing disease (average of 12 years), it was found that about 80% of DA neurons are lost (Rudow, 2008). This therefore provides an estimate of the number of cells that need to be replaced to approximate the threshold needed for DA function (Cohort A: 100,000 surviving DA cells) or to more closely approximate physiological numbers of DA neurons (Cohort B: 300,000 surviving DA cells). Albeit these are minimum estimates since it is likely that not all surviving transplanted DA cells, when placed in the adult PD brain, will provide the same degree of innervation to as would the host's own native cells during development.

(2) Autopsy data from previous fVM studies. The doses (target 100,000 surviving cells per putamen, Cohort A; 300,000 surviving cells per putamen, Cohort B) are based upon the observation that clinical improvement in subjects requires the survival of at least 100,000 surviving DA cells per putamen (Hagell, 2001). While 1 study has demonstrated 33% improvement in a subject with only 37,000 cells per putamen at autopsy (Freed, 2001), this is an isolated finding and upon careful review of the literature represents an exception (Hagell, 2001).

One uncertainty when proposing a cell dose based in part upon previous fVM transplant for a human ES-based mDA neuron product is the functional equivalency of human ES versus fVM-based mDA neurons. Detailed studies under the TransEURO effort (Rath, 2013) have established that in the rat model, the threshold for functional recovery in amphetamine-induced rotations using fVM tissue is 657 +/-199 neurons that immunostain positive for TH (TH+), that is, DA neurons. Recently, studies defining a functional threshold using hESC-derived mDA neurons by Parmar and colleagues show comparable cell numbers in the range of about 1,000 surviving TH+ neurons (Grealish, 2014). The Sponsor's own preliminary studies support a similar or slightly higher threshold of about a minimum of 1,000 to 2,000 surviving hESC-derived mDA neurons to achieve functional recovery in the 6-hydroxydopamine (6-OHDA) lesioned rat model. Therefore, existing evidence points to an approximate functional equivalency of fVM derived and human ESC derived mDA neurons.

The number of cells and volumes to be injected to achieve the desired surviving cell count is based upon the survival data in rodent studies, and the maximum concentration of 100,000 ± 10,000 cells/microliter. Volumes to be infused per putamen (10.5 and 33 µL for the low dose and high dose, respectively, ie, 3.5 and 11 µL per track, respectively) are expected to be feasible.

- Dose A: 0.9 million MSK-DA01 cells per putamen is estimated to provide the lower target of 100,000 surviving cells.
- Dose B: 2.7 million cells per putamen is estimated to provide the higher target of 300,000 surviving cells.

This dosing regimen takes into account safety and ethical considerations in the context of a clinical study. While the primary endpoint of the study is safety and tolerability, for a subject to undergo a surgical procedure that includes a 12-month immunosuppressive regimen, it is important to use a dose that is conservative but within the range of what might be expected to be therapeutic. It is acknowledged that fVM grafts have resulted in graft-induced dyskinesia in a subset of subjects, raising the concern that a high dose of MSK-DA01 could produce a similar effect. However, current evidence indicates that graft-induced dyskinesia is correlated to the extent of pre-existing L-Dopa-induced dyskinesia in grafted subjects, that it may be triggered in

part by a non-mDA component (serotonergic neurons) [Politis, 2012] in the graft that are largely absent in the Sponsor's preparation as confirmed in the Sponsor's clinical batch, or that it could be due to uneven survival and reinnervation ("hotspot" hypothesis [Maries, 2006; Carlsson, 2006]). In contrast, there is no well-established correlation of graft-induced dyskinesia with the number of surviving mDA neurons.

4.8.2. Rationale and Justification for Immunosuppression

Whether to provide immunosuppression for mDA neuron transplantation to improve graft survival remains an important question that has yet to be fully resolved. Some investigators have questioned the importance of a defined immunosuppression protocol for allogeneic cell transplantation into the central nervous system (CNS) [Freed, 1992]. Clinical, radiographic, and autopsy data have demonstrated maintenance of engrafted tissue to some degree in at least a subset of individuals without immunosuppression (Freed, 2001). However, fVM transplant recipients in this study had fewer surviving donor-derived DA neurons than expected when compared with other studies that had used a temporary immunosuppression regimen, raising the possibility that temporary immunosuppression might have provided benefit, although other factors than immunosuppression may have been responsible. Recent studies in monkey allografts of pluripotent-derived midbrain DA neuron showed lower DA neuron survival in allogenic versus isogenic hosts and showed that tacrolimus-based immunosuppression could significantly improve DA neurons survival in an allograft setting (Morizane, 2015). Furthermore, it is known that allografts to the brain are recognized by the immune system such that a peripheral challenge by injecting the same tissue peripherally can readily trigger graft rejection in the brain (Backes, 1990).

Therefore, there are now a number of lines of evidence that support judicious administration of a carefully monitored temporary immunosuppressive regimen.

a. Although the brain is traditionally considered an immunologically privileged site, such privilege is by no means absolute. Immune reaction to non-human leukocyte antigen (HLA) matched grafts of fetal neural and other allogeneic cells has been demonstrated in animals, with improvement with immunosuppression (Sayles, 2004).
b. Surgical intervention at the time of transplant compromises the blood-brain barrier (Kim, 2013), thus exposing the brain to circulating immune cells, and this structure is also abnormal in neurodegenerative conditions including PD (Cabezas, 2014).
c. Activated microglia and inflammatory responses have been documented at autopsy in recipients of allogeneic cell transplants into the CNS (Gross, 2011; Freed, 2001; Olanow, 2003; Lindvall, 1989). The risks of immunosuppression are well documented, with increased risk to the recipient of infection and (rarely) tumor formation.

Rationale for Duration of Immunosuppression

The majority of cell and tissue allograft transplantation trials involving the brain and spinal cord have incorporated a temporary phase of immunosuppression, but the duration has varied substantially. Most clinical trials have incorporated courses of immunosuppression ranging from 3 to 12 months after transplantation, although a minority have up to 2 to 4 years, particularly in early open-label studies. It has been suggested, although not proven, that worsened motor performance may have been related to withdrawal of immunosuppression at 6 months after fVM

tissue transplants in PD (Barker, 2013; Olanow, 2003). This observation supports extending the length of immunosuppression to 12 months. The choice of 12 months is also consistent with the consensus of other investigations currently underway or planned in cell-based studies in PD (Barker, 2017; Kirkeby, 2017). Ultimately, the relatively immuno-privileged status of the CNS should optimize conditions for long-term cell engraftment after planned cessation of immunosuppression.

Rationale for Choice of Agents

Drugs administered in previous studies have typically comprised a calcineurin inhibitor, often combined with an anti-proliferative agent, and a steroid, based upon experience in solid organ transplants. For example the "Lund protocol" employed an immunosuppressive protocol comprising cyclosporine, azathioprine, and prednisolone for at least 12 to 24 months (Lindvall, 1989; Lindvall, 1990; Lindvall, 1992; Lindvall, 1994; Sawle, 1992), while in a sham surgery-controlled study, investigators elected to administer a single immunosuppressant, cyclosporine, over a 6-month period (Olanow, 2003). The question of immunosuppression and design of an appropriate regimen was discussed with a group of transplant experts. An immunosuppression clinician will be enrolled as an investigator to focus on the immunosuppressive component of the study.

All subjects who receive any amount of cell dose will undergo a 12-month course of immunosuppressive therapy with tacrolimus. Tacrolimus is a well-established drug for allogeneic solid organ transplantation, and is the leading immunosuppressive agent used in renal transplantation in North America (Smith, 2013). It has been shown to be successful in reducing the incidence of graft rejection in these cases by suppressing T-cell response and is generally well tolerated with known human safety profiles.

In addition, subjects will receive perioperative administration of intravenous (IV) basiliximab and IV methylprednisolone. The use of basiliximab and methylprednisolone will provide an additional level of immunosuppression (via distinct immunological pathways) in the immediate post-operative period. This corresponds to the time of maximal disruption of the blood brain barrier secondary to the surgical transplant procedure when the donor cells are potentially exposed to systemic immuno-surveillance.

Once subjects have undergone surgery, the steroid administered will be changed to oral prednisone, to be continued at a low dose together with tacrolimus. This and related oral glucocorticoids are used to prevent graft rejection in solid organ transplant protocols and, as noted above, have been incorporated with good tolerability into the postoperative regimens of many individuals with PD who have undergone fVM transplant.

The management of the immunosuppressive agents will be under the guidance of the Immunosuppression Clinician. In addition, the data safety monitoring committee (DSMC) will monitor the safety of the immunosuppression, and the regimen can be adjusted or discontinued if the subject is showing poor tolerance or AEs. The study will also monitor subjects following termination of the immunosuppression in order to assess any clinical change that might indicate cell rejection or complications thereof.

In summary, there is a strong rationale for using transient immunosuppression. On balance, it seems prudent to include temporary immunosuppression to enhance the possibility for cell survival and function, while carefully monitoring for the known risks of such a regimen.

Rationale for Doses of Immunosuppressive Agents

Dosing regimens and rationales for the chosen immunosuppressive agents in this study are shown in Table 2. The rationale for each of the doses of the immunosuppressive medications shown in Table 2 was selected based on information obtained from the following sources:

- experience in previous clinical trials of fVM tissue grafting in PD patients
- Gforce-PD: A Global Initiative Around Stem Cell Based Therapies for Parkinson's Disease
- a roundtable discussion of the clinical trial design held by Memorial Sloan Kettering Cancer Center of key opinion leaders, including neuroimmunologists and solid organ transplant specialists
- a review of the literature for allogenic tissue grafts and prescribing information for immunosuppressants

Table 2: Dosing Regimens and Rationales for Immunosuppressive Regimens

Immunosuppressive Agent	Dose	Rationale
Tacrolimus	Dose PO BID Day 1 (recommended starting dose of 0.05 mg/kg BID [3 to 3.5 mg BID for a 70-kg person] beginning on the day after surgery) and adjusted to a target trough blood level of 4 to 7 ng/mL whole blood for the period of 1 year. Use of extended-release once daily formulation is permitted in place of BID to achieve a target trough blood level as noted in the Immunosuppression Manual.	Dose matches the regimen recommended for renal, lung, and liver prevention of acute rejection. Dosing adjustments are allowed per clinician's judgment. Use of extended-release tacrolimus is considered to be equivalent or better than tacrolimus BID for achieving the immunosuppression effect aimed at reducing the incidence of graft rejection and improving the survival of DA neurons in an allogeneic setting.

Immunosuppressive Agent	Dose	Rationale
Cyclosporine	Dose to be determined.	Dose selected will take into account other immunosuppressive agents taken by the subject and the dose and combination therapy used in fVM graft trials, such as the following: • Cyclosporine 6 mg/kg/day for 2 weeks before the first unilateral fVM graft, decreasing to 2 mg/kg/day 2 weeks after the contralateral graft procedure (Olanow, 2003) • Cyclosporine, 2 mg/kg BID (resulting in serum levels between 100 to 200 ng/mL); azathioprine, 2 mg/kg/day; and prednisolone, 40 mg/day, reduced to 5 mg/day by 12 weeks post dose (Barker, 2013).
Basiliximab	20 mg IV during surgery 20 mg IV post-operative Day 4	Dose matches the regimen recommended for prevention of acute rejection of renal, lung, and liver transplants.
Methylprednisolone	500 mg IV Day 0 (0 to 6 hours prior to surgery) 250 mg IV Day 1 in hospital	Doses match initial high-dose pulse therapy for select indications (*Methylprednisolone: Drug information*; UpToDate.Com, accessed 23 March 2021) whilst shortening the IV route of administration to allow subjects to be discharged from hospital on prednisone.
Prednisone	120 mg QD PO Day 2 60 mg QD PO Day 3 40 mg QD PO Day 4 20 mg QD PO Day 5 10 mg QD PO Day 6 5 mg QD PO from Day 7 to 1 year	Adaptation of taper and maintenance therapy for select indications such as renal transplantation. (Prednisone: Drug information; UpToDate.Com, accessed March 23, 2021; and Miller et al., Kidney transplantation in adults: Withdrawal or avoidance of glucocorticoids after kidney transplantation; UpToDate.Com, accessed 23 March 2021).

BID=twice daily; DA=dopaminergic; fVM=fetal ventral mesencephalic; IV=intravenous; PO=orally; QD=once daily.

4.9. Benefit-Risk Assessment

The Sponsor cannot and does not guarantee that the subject will receive any benefits from this study. The primary goal of the study is to test the safety and tolerability of transplantation of MSK-DA01 cells into the bilateral putamen of each of the study subjects, and therefore such parameters will primarily be evaluated. However, both cell doses used are within a range that is anticipated to result in potential efficacy and therefore, data that might support potential improvement in subjects' conditions will also be collected. The possible benefits to the subject, if

the cells survive and function as predicted by preclinical studies that led to this clinical trial, is that motor symptoms may improve. This may include improvement in movement and motor skills overall, less time spent in the "off" condition in which medication is not adequately controlling the symptoms, and it may lead to reduced need for anti-PD medications. However, these benefits may not be immediate, and could take months to years to become evident. Finally, other subjects with PD may benefit in the future from data collected in this research study.

5. TRIAL OBJECTIVES AND ENDPOINTS

5.1. Objectives

This first-in-human Phase 1 study will have the primary focus of testing safety and tolerability of the intervention in an open label design. Additionally, data will also be collected on clinical and radiologic changes observed longitudinally that may be used as a basis for further studies in the development of this product. Exploratory aims will also be included that will support learning how other clinical, neurophysiological, biochemical and molecular measures may be helpful in future clinical trials of these and other cell products.

5.1.1. Primary Objective

The primary objective of the study is to assess the safety and tolerability of MSK-DA01 cell transplantation at 1 year post transplant.

5.1.2. Secondary Objectives

The secondary objectives of the study are as follows:

1. to assess the evidence of transplanted cell survival and motor effects through 2 years post transplant
2. to evaluate continued safety and tolerability at 2 years
3. to assess feasibility of transplantation

5.1.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

1. to determine the effects of MSK-DA01 transplantation upon motor and non-motor signs and symptoms of PD and upon accelerometry-based measures of motor function
2. to assess the subject's perception of their quality of life
3. to collect biosamples for anti-HLA testing; to obtain blood for storage for xenotransplantation-related future testing; and to store leftover samples for future studies of biomarkers of PD, DA function, inflammation, and immune response to engrafted cells

5.2. Endpoints

Descriptions of the measures to be used as listed below (primary, secondary, and exploratory endpoints) are contained in Appendix 2.

5.2.1. Primary Endpoint

The primary endpoint of the study will be the incidence of serious adverse events (SAEs) at 1 year post transplant. The analysis will be undertaken for each of the 2 cohorts separately. Safety will be defined as 2 or fewer of Cohort A or Cohort B developing 2 or more SAEs related to surgery, presence of transplanted cells, or immunosuppression; as 2 or fewer of Cohort A or Cohort B developing a tumor or abnormal tissue overgrowth related to presence of transplanted cells; as 2 or fewer of Cohort A or Cohort B developing an intracerebral hemorrhage that is deemed life-threatening; and as 1 or zero deaths for Cohort A or Cohort B. All data collected on any subject lost to follow-up will be included in the assessment of safety.

This safety definition is designed to allow for greater toxicity than many Phase 1 studies, due to combined known risks of (1) the surgical procedure that is similar to the standard of care for advanced PD (DBS) and (2) immunosuppression.

5.2.2. Secondary Endpoints

The secondary endpoints of the study will be

1. Change in striatal ^{18}F-DOPA uptake using PET from baseline through 2 years
2. Changes from baseline in the following measures at 2 years post transplant: International Parkinson and Movement Disorder Society (MDS)-Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore in the "off" medication state, number of hours in the "on" state without troublesome dyskinesia, incidence of SAEs at 2 years post transplant, and incidence and type of AEs at 1 and 2 years post transplant
3. Feasibility, as defined by intra-operative delivery of at least 50% of the intended total number of deposits per brain in >50% of subjects. The intended number of deposits is defined as the neurosurgeon's planned trajectories times the number of cellular deposits as determined during the procedure. For example, the surgeon may plan 3 trajectories through each putamen with 3 deposits in each trajectory; thus, a bilateral administration with a total of 18 cellular deposits would be made (ie, 3 trajectories × 3 cellular deposits × 2 putamina = 18). An individual subject's surgical procedure will be determined to be feasible if 9 of the 18 deposits are made in that subject. During the surgery, the surgeon may elect to alter the surgical plan (ie, number of cellular deposits) based on intra-operative imaging. For example, the number of trajectories may change from 3 trajectories to 2 trajectories with 3 deposits in each trajectory. In this case, the intended deposits would be 2 trajectories × 3 cellular deposits × 2 putamina = 12 total cellular deposits. The surgeon would then increase the volume delivered at each deposit so that the total dose will be delivered regardless of the number of deposits. The study procedure would be deemed feasible for this subject if the surgeon then successfully implants 6 or more of the intended total number of deposits.

5.2.3. Exploratory Endpoints

The exploratory endpoints of the study will be

1. Changes in the following measures from baseline to 2 years in: total MDS-UPDRS scores; MDS-UPDRS Part 1 scores; MDS-UPDRS Part 2 scores; MDS-UPDRS motor subscore in the "on" state; MDS-UPDRS Part 4 scores; 10 meter walking test; anti-PD medications (daily levodopa equivalent dose); Modified Schwab and England Activities of Daily Living; Unified Dyskinesia Rating Scale (UDysRS); neuropsychological testing; non-motor measures including Montreal Cognitive Assessment (MoCA), Beck Anxiety Inventory (BAI-II), Beck Depression Inventory (BDI-II), Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease (QUIP), PD Non-Motor Symptoms Scale (NMSS); Clinical Global Impression-Severity (CGI-S); daily time in the "off," "on without dyskinesia," "on with non-troublesome dyskinesia," and "on with troublesome dyskinesia" states as measured by the Hauser diary; daily time in the "on," "on with dyskinesia," "off" states measured by the Personal KinetiGraph (PKG)

2. Quality of life as measured by Parkinson's Disease Questionnaire-39 (PDQ-39)
3. Sample collection for biorepository does not have pre-specified endpoints

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

6.1.1. Design

The study design is a multi-center, multi-site (Clinical Site, Surgical Site, PET Imaging Site), open label, non-randomized study to evaluate the safety, and tolerability of bilateral surgical implantation of 2 dose levels of MSK-DA01 into the post-commissural putamen, the site at which dopaminergic input from the substantia nigra is preferentially lost in PD.

- MSK-DA01 cells are GMP manufactured allogeneic, hESC (H9/WA09)-derived, cryopreserved mDA neuronal cells. This protocol is based upon data generated in rodent studies as detailed in Section 4.5, showing that transplantation of these cells is effective in treating standard animal models of PD.
- The intervention will comprise a single session of stereotactically guided, multi-deposit, surgical transplantation of MSK-DA01 cells to the post-commissural putamen bilaterally in approximately 12 subjects with advanced PD. Subjects will then undergo a limited period of 12 months of immunosuppressive therapy.
- Two dose levels will be explored in 2 cohorts. The first 5 subjects (Cohort A) will receive Dose A (0.9 million cells per putamen) and subsequent subjects (Cohort B) will receive Dose B (2.7 million cells per putamen). Data from Cohort A will be shared with the DSMC, the Medical Monitor, and the Principal Investigator(s) prior to initiating dosing in Cohort B. The decision to initiate dosing in Cohort B will be made consistent with the recommendation from the DSMC.
- In order to determine safety and tolerability, incidence of transplant-related AEs and immunosuppressive drug-related AEs will be determined for up to 1 year, and clinically significant changes from baseline in physical examination, laboratory values, and MRI of the brain from baseline to 2 years in addition to incidence of transplant-related AEs and of immunosuppressive drug-related AEs will be determined up to 2 years.

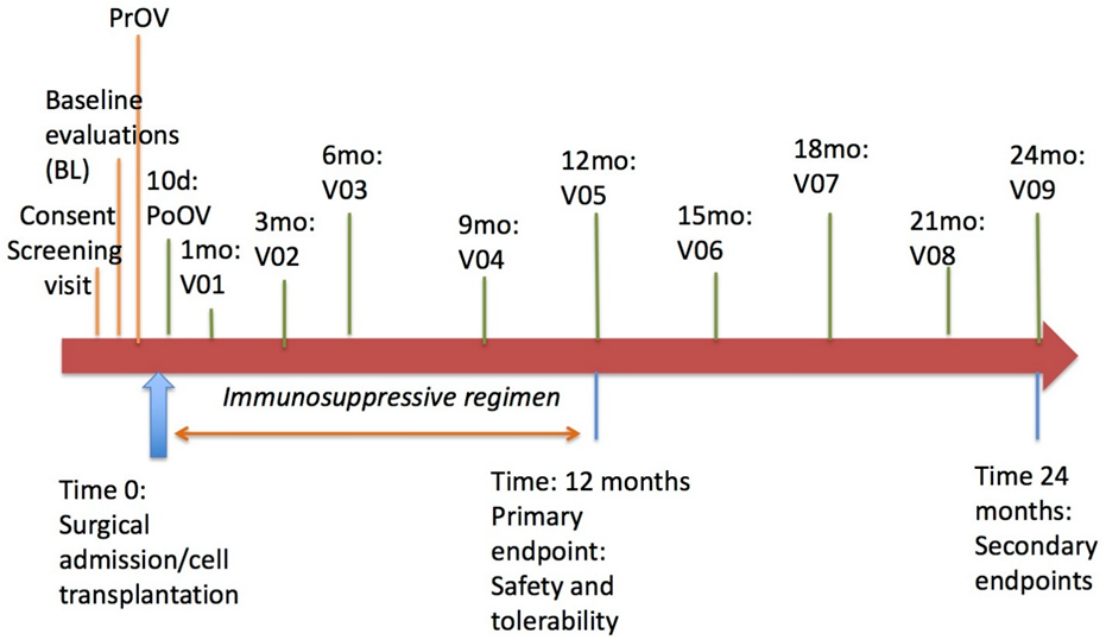
While the primary objective is to demonstrate safety and tolerability, imaging and clinical data will also be collected to determine transplanted cell survival that may provide a signal as to whether the intervention at 1 or both of the 2 cell doses can lead to improvement in motor symptoms of PD. To accomplish the secondary aims, neuroimaging using ^{18}F-DOPA PET will provide evidence of graft survival and clinical data that include efficacy measures which will inform future studies, should the safety and tolerability profile of this product be deemed sufficient to proceed with further development of this product.

The study design is shown in Figure 1.

There will be 3 institutions with activities as follows:

- Recruitment, informed consent, and Screening (SC) will comprise clinical evaluations and MRI of the brain (Clinical Site).
- Pre-operative evaluation (PrOV) visit with Neurosurgery will include surgical consent, pre-operative clearance, and MRI for surgical planning (Surgical Site).
- Baseline visit (Clinical Site) will comprise clinical evaluations (Clinical Site), laboratory testing (Clinical Site), ^{18}F-DOPA PET consent and neuroimaging (PET Imaging Site).
- Surgical admission: Subjects will be admitted by the Surgical Site on the day of surgery. Surgical transplantation of cells will occur under general anesthesia. Immunosuppressive regimen will begin on Day 0 intraoperatively. Subjects will be transferred to the Neurosurgical Advance Care Unit (Surgical Site). Subjects will then be discharged to home approximately 1 to 2 days post end of surgery.
- Post-operative evaluation (PoOV) and suture/staple removal will occur approximately 10 days after the surgery (any Clinical or Surgical Site).
- Post-operative clinical evaluations will take place at the Clinical Site for visits V01 to V09 and IS01 to IS12. (Visits for immunosuppression monitoring alone are designated “IS,” visits in which immunosuppression monitoring coincides with other study visits are designated “V.”)
- MRI of the brain will be performed at the Clinical Site at V01, V02, V03, V05, V07, V09 (ie, at 1 month, 3 months, 6 months, then every 6 months for a total 24-month duration).
- ^{18}F-DOPA PET neuroimaging will take place at the PET Imaging Site as part of the baseline, V05, V07, and V09 visits.

Figure 1: Study Design



Abbreviations: BL=baseline; d=day; mo=month; PoOV=post-operative evaluation – Neurology (Day 7)/Neurosurgery (Day 10); PrOV=pre-operative evaluation visit; V=visit.

All evaluable subjects will be asked to enroll in a separate follow-up study to continue to have comprehensive visits, including neurological examination and MRI, following their completion of this study.

6.1.2. Intervention

The study intervention comprises 2 parts: surgical intracerebral transplantation of MSK-DA01 cells and administration of immunosuppressive drugs over the period of 1 year.

6.1.2.1. Surgical Intervention

In this study, subjects with PD who fulfill the eligibility criteria will undergo a surgical intervention that involves a single session stereotactic injection of DA neurons (MSK-DA01) in both putamen. The intervention is a surgical procedure that will be performed stereotactically under general anesthesia. Cells will be injected in 3 separate tracks through a single burr hole in the frontal area of the first putamen, with 3 cell deposits per track. Once the injections are complete in the first putamen, the subject will undergo an MRI to exclude the possibility of hemorrhage due to the injections. In Canada, this MRI will be performed only if clinically indicated. The criteria for evaluation of the MRI are listed in Section 8.3.3.1. If the MRI passes the criteria, a second identical procedure will be performed on the contralateral side of the brain, followed by MRI. At minimum, 2 MRIs will be performed, but more may be performed at the discretion of the investigator, if felt needed to assess safety of the patient. At the end of the procedure, the subject will be transferred to the recovery room, and subsequently, to an acute care unit, preferably the Neurosurgical Advanced Care Unit (NACU) at the Surgical Site. The trial will examine 2 cell dose levels. The first 5 subjects (Cohort A) will receive Dose A (0.9

million cells per putamen) and subsequent subjects (Cohort B) will receive Dose B (2.7 million cells per putamen). The final decision to initiate Cohort B ultimately lies with the Sponsor.

Please see Section 4.8.1 for the rationale for choice of cell doses.

Please see Section 8.2 for a description of the Administration Device System.

6.1.2.2. Schedule of Surgical Interventions

The dates of surgery will be staggered within each surgical site by approximately 2 weeks (see Section 12.2.2). If necessary, the surgical date for an individual subject may be delayed by up to 8 weeks without the need for rescreening.

6.1.2.3. Immunosuppression

The protocol comprises induction with IV basiliximab, IV methylprednisolone and prednisone taper, and then tacrolimus and low-dose prednisone over 1 year. The latter 2 agents will be administered for 1 year following the transplant and will be under the supervision of the investigator with expertise in immunosuppression.

- Basiliximab 20 mg will be administered intravenously in the operating theater during surgery.
- Basiliximab 20 mg will be administered intravenously in any Clinical or Surgical Site on post-operative Day 4.
- Methylprednisolone 500 mg will be administered intravenously 0 to 6 hours prior to surgery (Day 0), followed by an oral taper and chronic therapy as follows:
  - Day 1: 250 mg methylprednisolone administered intravenously in hospital prior to discharge
  - Day 2: 120 mg prednisone administered once orally (PO)
  - Day 3: 60 mg prednisone administered once PO
  - Day 4: 40 mg prednisone administered once PO
  - Day 5: 20 mg prednisone administered once PO
  - Day 6: 10 mg prednisone administered once PO
  - Day 7 and continuing to 1 year: 5 mg prednisone daily PO
- Tacrolimus taken orally BID will be started on the day after surgery (Day 1) (recommended starting dose of 0.05 mg/kg BID [3 to 3.5 mg BID for a 70-kg person]) and adjusted to a target trough blood level of 4 to 7 ng/mL for the period of 1 year. Use of extended-release once daily formulation is permitted in place of BID to achieve a target trough blood level as noted in the Immunosuppression Manual.
- In the rare circumstance where oral tacrolimus cannot be tolerated by the subject, the treating investigator must consult the Principal Investigator (PI) and obtain approval to administer tacrolimus intravenously, prior to administration.

- Medications related to immunosuppression protocol:
  - Sulfamethoxazole/trimethoprim (Bactrim) 400 mg/80 mg once daily PO will be started on Day 1 and continued to 6 months (see Section 8.3.5)
  - Omeprazole 20 mg once daily PO will be started on Day 1 and continued to 1 year

6.2. Number of Subjects

It is planned to recruit and consent approximately 12 evaluable subjects at the Clinical Site. For the purposes of lessening patient burden, subjects will sign 1 consent document at the Clinical Site that includes the Surgical Site, Clinical Site, and PET Imaging Site consent components. Evaluable subjects are defined as those who provide informed consent, meet all inclusion criteria and no exclusion criteria, and successfully undergo surgical intervention to receive cell transplantation. Subjects may receive any amount of cells to be considered evaluable. For any subject who has provided informed consent and is eligible to proceed but either chooses not to proceed or proceeds to the implantation procedure, receives the first dose of immunosuppression but does not receive cells, may be replaced by recruiting another subject, such that approximately 12 evaluable subjects are reached in this study. In the event that a subject proceeds to the implantation procedure and does not receive cells for any technical reason, if the subject wishes to remain in the study, then screening and baseline visits will be repeated prior to rescheduling the surgical admission. All efforts will be made to include women and minorities in recruitment for this study.One study participant partner per subject will also be recruited and consented to this study.

Discussion Process

The consenting professionals at the Clinical Site will provide information on the study to any potential subject. That individual will be invited to an in-person meeting with the PI or an alternate consenting professional. The individual will be asked to bring a study participant partner of their choice (usually a relative or spouse), who will also be consented. During this visit at the Clinical Site, details of the study as contained in the informed consent form will be explained to the potential subject and study participant partner. Subjects along with their study participant partner will be given adequate time to consider participation in this trial. During this time, the PI, the consenting professional (if different than the PI), and the study research coordinator(s) will be available to answer questions by phone.

Informed Consent Procedure

Each subject will be required to sign 2 original informed consent forms. At this visit when consent is signed, they will be accompanied by the study participant partner. The study participant partner will also sign 2 original informed consent forms. The consenting process will occur at the Clinical Site only.

6.3. Duration of Study

Duration of participation, from time of first contact, to time of completion of the 2-year scheduled evaluation, will be up to 26 months for an individual subject. Projected study duration is 44 months.

6.4. Treatment Assignment

This is an open label, non-randomized study. Two dose levels will be explored in 2 cohorts. The first 5 subjects (Cohort A) will receive Dose A (0.9 million cells per putamen), and subsequent subjects (Cohort B) will receive Dose B (2.7 million cells per putamen).

6.5. Criteria for Study Termination

Throughout the duration of the study, if there are any unexpected or unanticipated events that raise concerns about the safety risk of the subjects, the PI and/or the institutional review board (IRB)/independent ethics committee (IEC) has the authority to stop or temporarily suspend the study until further investigation and evaluation is completed. These decisions will be made in collaboration with all involved parties.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Each patient must meet all the following inclusion criteria to be eligible for enrollment in the study:

- Age:
  - Canada: ≥50 to ≤78 years old
  - US: ≥60 to ≤78 years old
- Idiopathic PD defined by the modified UK Parkinson's Disease Society Brain Bank criteria
- A minimum time of 3 years from time of PD diagnosis and a maximum time from PD diagnosis of 20 years
- Prior sufficient treatment comprising levodopa and at least 1 adjunct therapy, and additional appropriate therapy such as physical therapy
- Defined levodopa response of ≥30% improvement on the basis of MDS-UPDRS Part 3
- Hoehn and Yahr score:
  - Canada: 0 to 3 "on"
  - US: 0 to 2 "on" and 3 to 4 "off"
- For US only: Not eligible for deep brain stimulation or have refused deep brain stimulation after evaluation by an independent neurologist or neurosurgeon
- PD medications allowed: any approved oral, transdermal, and/or injectable PD medication and medications must be stable for ≥1 month prior to enrollment
- Abnormal Involuntary Movement Scale (AIMS) rating scale score of ≤2 for dyskinesia on each of Sections 1 to 10 of the 12-item AIMS
- "Off" time of ≥2 hours daily
- MoCA score ≥26, or ≥22 if no significant cognitive impairment by neuropsychological testing per assessing clinical discretion
- Hamilton Depression Scale (HAM-D) score ≤17
- Dysthymia allowed with single or 2 antidepressant medications if at stable dose for >6 months
- Normal endocrine, renal, and liver function as measured by standard laboratory testing unless abnormality is not clinically significant; no blood dyscrasias; no bleeding disorder; and no cardiovascular contraindications for surgery, except for stable and controlled conditions including diabetes type 2 and hypothyroidism

- All other concomitant disorders must be stable and well controlled, must not constitute a contraindication to general anesthesia or surgery, or interfere with scheduled study assessments
- Women of childbearing potential must agree to use a highly effective method of contraception from screening until at least 4 weeks after cessation of the oral immunosuppression medication regimen
- Able to participate in all study visits and evaluations, including brain MRI
- Able to give informed consent for study participation and sign the informed consent form
- Existence of a study participant partner who may act as potential surrogate over the long term for ongoing consent

7.2. Subject Exclusion Criteria

- Clinical features suggestive of a neurodegenerative diagnosis other than PD
- PD with only tremor-based symptoms
- Diagnosis of primary mitochondrial disorder, epilepsy, stroke, multiple sclerosis or other neurodegenerative diseases such as Alzheimer's disease
- Any current or relevant previous history of serious, severe, or unstable physical, neurological, or psychiatric illness that may make the subject unlikely to fully complete the study (including significant depression, psychosis, anxiety, cognitive impairment, or impulse control disorder)
- Receiving DA receptor-blocking agents, including typical neuroleptics, prochlorperazine, and metoclopramide at the time of screening or within 3 months prior to screening
- ^{18}F-DOPA PET imaging inconsistent with DA deficiency
- Ongoing treatment with intrajejunal or subcutaneous infusion therapies for PD (Subjects who permanently discontinue these treatments are eligible to enroll after 2 months.)
- History of DBS, lesion therapy, or gene therapy for PD
- Prior surgical or radiation therapy to the brain or spinal cord
- Per assessing clinician discretion, any abnormality on brain MRI that would preclude cell transplantation
- Significant concomitant medical disease limiting life expectancy to less than 24 months from study inclusion, or significant and serious concomitant medical disease that is poorly controlled
- Signs of active malignant disease or other clinically relevant abnormality on chest X-ray

- Clinically relevant abnormalities on standard safety laboratory tests, including blood count, partial thromboplastin time (PTT), blood chemistry (glucose, blood urea nitrogen (BUN), creatinine, electrolytes), and liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase, total protein, bilirubin)
- Presence of a condition resulting in high risk of immunosuppressive drugs, including any active infectious disease of any nature, including clinically active viral infections (seropositive for human immunodeficiency virus (HIV), hepatitis C virus, hepatitis B virus, cytomegalovirus (CMV), and Venereal Disease Research Laboratory (VDRL) unless related to immunization or past CMV exposure, or positive QuantiFERON-TB gold Plus)
- Inability to temporarily stop anti-platelet agents or other anti-coagulants without significant risk
- Previous or currently active malignant disease within the past 5 years, except basal cell carcinoma or in situ uterine cervical carcinoma that have been definitively treated
- Use of immunosuppressive drugs including systemic steroids within the previous 3 months
- Severe obesity (>350 lb [159 kg]) or any condition that prevents use of PET/MRI
- Known substance abuse (recent history of abuse of alcohol or other drugs such as barbiturates, cannabinoids, and amphetamines) within last 5 years
- In the opinion of the investigator, presence of any cognitive, behavioral, or psychiatric symptoms that would be deemed contraindications to cell transplantation
- Pregnancy or breastfeeding
- Unable to cooperate or complete self-assessment scales and diaries
- Unable to provide and sign the informed consent form
- Receipt of another investigational agent or device within the 3 months prior to enrollment
- Contraindication to surgery or general anesthesia
- Contraindication to taking immunosuppressive drugs
- In the opinion of the investigator, any other condition regarded as making subject unsuitable for the trial

7.3. Study Participant Partner Inclusion Criteria

- Ability to act as potential surrogate over long term for the subject

7.4. Study Participant Partner Exclusion Criteria

- Inability to cooperate or complete questionnaires

7.5. Screen Failures

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

7.6. Subject Withdrawal Criteria

7.6.1. Suspension of Study

Any of the following occurrences will result in suspension of further enrollment and transplantation procedure while the events are under investigation:

- Any death during the study
- Any subject developing Grade III-IV toxicity as a result of immunosuppressive drug administration
- Any subject experiencing a medically important event warranting further evaluation
- Any subject developing severe, sustained, clinically significant, and unexplained dyskinesias that do not respond to standard interventions and persist off levodopa treatment
- Any radiographic evidence of tumor in the brain
- Any occurrence of a malignancy
- Any clinical evidence of graft rejection or other serious immune-related event

In each of these situations, subjects who have already undergone cell transplantation surgery will continue to maintain the protocol schedule until the situation has been assessed and full recommendations are in place, and subjects who have already enrolled into the study but who have not yet undergone cell transplantation surgery will await recommendation with their procedures either postponed or cancelled.

In the event of study suspension, the DSMC (see Section 12.2.2.1) will review data relevant to the occurrence that triggered suspension and will receive input from the Investigator before providing appropriate recommendations. Possible outcomes include cessation of the study, restarting with a modified subject cohort based upon modified inclusion/exclusion criteria, a cessation or change in immunosuppressive drug dosing, restarting with a change in product preparation or in cell administration, or a change in the study monitoring plan.

The sponsor may terminate this study at any time after informing the investigators. In such a case, the sponsor will notify the investigators and appropriate regulatory authorities.

7.6.2. Withdrawal From Study

Time of Consent to End of Study

- Non-compliance with the screening evaluation procedures
- The subject may also withdraw consent
- Lost to follow-up

Subject survival status will be followed until the end of the study unless the patient withdraws consent for follow-up. In the event that a subject is lost to follow-up, the family of the subject will be asked for the subject's survival status and/or public record search.

Investigational Treatment Stopping Prior to Completion

Investigational treatment may be aborted or stopped prior to completion under the following circumstances:

- Surgical complication: In the event that a severe complication from surgery occurs, such as significant hemorrhage, cell delivery will not be performed.
- Clinical deterioration during injection. This may be defined by the surgeon or anesthesiologist during surgery and includes, but is not limited to, the cardiovascular/hemodynamic or respiratory compromise during the operation.
- Recognition of significant intraparenchymal hemorrhage or occurrence of other events during surgery as discussed in Section 8.3.3.
- Deterioration in the subject's clinical condition immediately prior to the study.
- Elective termination: A subject or family may decline further treatment at any point in the study.
- Loss to follow-up: The subject does not comply with follow-up mandated over the 24-month period post transplant.

The reason for interruption/termination will be documented.

Time of Surgical Transplantation

Once the study subject has undergone surgical implantation of MSK-DA01 cells, it is anticipated the cells may persist for the remainder of the subject's lifetime, and therefore it will not be technically possible to withdraw the intervention. The goal is therefore to retain subjects for all of the scheduled visits for the entire study, and extensive efforts will be made to ensure that this is the case. However, it is anticipated that circumstances including, but not limited to, severe, unexpected toxicities/side effects; recurrent, progressive, or new disease; subject non-compliance with the defined treatment plan; and the subject's right to withdraw consent for continued participation may lead to a subject withdrawing from the study.

7.6.3. Lost to Follow-up

The goal is to retain subjects for all of the scheduled visits for the entire study, and extensive efforts will be made to ensure that this is the case. However, due to unforeseeable circumstances, subjects may discontinue in-person follow-up. In this case, the Discontinuation of In-person Follow-up (DF) Visit will be conducted at the time the decision to stop in-person follow-up is made or as soon thereafter as possible (see Section 9.2.5.2).

For any subject who is unable to attend an in-person follow-up visit prior to Month 24, study staff will try to complete the visit activities that do not require face-to-face interaction by contacting the participant via telephone, telemedicine, email, or mail (see Section 9.2.5.3). Contact from the study staff will occur during the pre-established study visit windows.

8. TREATMENT OF SUBJECTS

8.1. Description of Investigational Study Cells

MSK-DA01 is an experimental cell product for the treatment of PD that is primarily composed of hESC-derived, mDA neurons. It is formulated for transplantation as described in the Cell Preparation and Delivery Manual.

8.2. Description of Investigational Administration Device System

8.2.1. Description for Canada

BlueRock's fit-for-purpose Administration Device System is comprised of multiple components. A description of these components and their function in the Administration Device System is provided in Table 3. As the manufacturer of record for the Administration Device System, all component parts are inspected, cleaned, tested, labeled for investigational use only, and released by BlueRock to the Surgical Site. The Administration Device System is designed to be used with an approved stereotactic frame and navigation software, which will be provided by the Clinical Site. Details with respect to the use of the Administration Device System are provided in the Cell Preparation and Delivery Manual.

Table 3: Components of Administration Device System for Delivery of MSK-DA01

Component	Sourced From	Description	Function
Aspiration Needle	Hamilton Robotics Company	18 gauge, Kel-F Hub needle	To draw the MSK-DA01 into the syringe
Gastight 1700 Series Syringe		25-µL capacity with a borosilicate glass body and Luer connection, with a PTFE plunger seal and stainless steel plunger	To aspirate MSK-DA01 dose and priming volume, followed by priming of the VC and administration of the dose via manual depression of the plunger
VC	ClearPoint Neuro, Inc.	A rigid, ceramic shaft (approximately 25 cm long) connected with a female Luer connector at the proximal end, via a flexible tether, and a tapered tip at the distal end (approximately 18 mm long) with markings on the shaft to permit control of insertion depth during surgical administration	To deliver MSK-DA01 cells to the post-commissural putamen of patients via stereotactically guided drug delivery
Depth Stop	ClearPoint Neuro, Inc.	A collar that is fitted onto the VC shaft at the desired depth marking	Controls the insertion depth of the VC inside the brain

Table 3: Components of Administration Device System for Delivery of MSK-DA01

Component	Sourced From	Description	Function
Stop & Guide Inserts	ElektaAB	Physically modified reusable accessories of the Leksell stereotactic frame kit	Aligns and holds the VC securely in the stereotactic frame

PTFE = polytetrafluoroethylene; VC = ventricular cannula.

8.2.2. Description for US

MSK-DA01 will be delivered using the ClearPoint Neuro SmartFlow® Neuro Ventricular Cannula (510(k): K102101) in conjunction with the ClearPoint Neuro Navigation System (510(k): K100836 and K142505). The SmartFlow® cannula has been modified from the version with 510(k) approval; the modification has been cleared for investigational use in this study. Thawed and re-suspended cryopreserved cells will be delivered by stereotactically guided surgical injection into 9 sites along 3 tracks in the postcommissural putamen of each hemisphere. Subjects will receive 0.9 million cells per putamen (Cohort A) or 2.7 million cells per putamen (Cohort B).

SmartFlow® Cannula (ClearPoint Neuro, Irvine, CA): The SmartFlow® Neuro Ventricular Cannula is currently cleared for administration of cytarabine or removal of cerebrospinal fluid from the ventricles during intracranial procedures (then called "SurgiVision, Inc.", 510(k): K102101, January 2011). The device will be used in accordance with the most recent version of the ClearPoint Neuro Instructions For Use document. The 510(k)-cleared cannula is modified by shortening the overall tubing length in order to reduce dead space. The SmartFlow® cannula packaging will be appropriately labeled to avoid confusion with the cleared device. As per 12 CFR 812.5, the investigational device package will bear a label with the following statement: "CAUTION- Investigational device. Limited by Federal (or United States) law to investigational use."

ClearPoint System (ClearPoint Neuro, Irvine, CA): This system is intended to provide stereotactic guidance and operation of instruments or devices during the planning and operation of neurosurgical procedures within the MRI environment and in conjunction with imaging. The ClearPoint System has been developed to accurately and precisely position the cannula to targeted anatomies in the brain utilizing MRI and surgical planning software in conjunction with a stereotactic apparatus. The ClearPoint System is intended as an integral part of procedures that have traditionally used stereotactic methodology. These procedures include biopsies, as well as catheter and electrode insertion. ClearPoint Neuro Navigation and all of its components are FDA cleared; 510(k) June 16, 2010 (k100836) and (K142505) in 2015. This 510(k)-cleared system is expected to be used consistent with its intended use (510(k): Number K171257).

Gastight 1700 Series Syringe (Hamilton Robotics Company, Reno, NV): The syringe has a 25 µL capacity (model 1702 LT, catalog #80201) with a borosilicate glass body and Luer connection, with a polytetrafluoroethylene (PTFE) plunger seal and stainless steel plunger.

Aspiration needle (Hamilton Robotics Company): The needle used to draw the Drug Product into the syringe is an 18-gauge, Kel-F Hub NDL needle supplied by the Hamilton Company (catalog #7750-15 Kf718/0.385/pt2).

8.3. Dose and Administration

The study intervention comprises 2 parts: surgical intracerebral transplantation of MSK-DA01 cells; and administration of immunosuppressive drugs over the period of 1 year. Assessments will take place over 2 years post transplant. All of the interventions and evaluations will be performed as related to this research study and will not be administered as standard of care.

For the purpose of this protocol, the day of surgery defines “Day 0.”

8.3.1. Cell Preparation

MSK-DA01 is formulated for transplantation as described in the Cell Preparation and Delivery Manual. Briefly, on the day of surgery, the product will be thawed and aseptically prepared for injection. The product will be delivered cooled (on wet ice or in a prechilled closed rack) to the operating suite, where it will be aspirated into the syringe and loaded into the VC.

In the operating room, cell vials will be kept cooled. Cells will be loaded into a Hamilton syringe, which will be then connected to the hub of the VC, which will be primed with the intended cell dose and the syringe kept on sterile ice until administration, as described below.

8.3.2. Surgical Intervention

8.3.2.1. Overall Treatment Plan

The subject will be admitted on the day of surgery. Each subject is planned to undergo stereotactic placement of cell grafts via the VC. The target area is the post-commissural putamen. The goal is to distribute the cell deposits relatively uniformly in the target area. Each subject will undergo a pre-operative non-contrast MRI for surgical planning (spMRI) within a week of the surgery date (see Section 9.1.2). Trajectories will be planned on the spMRI using the surgical navigation software, so that 3 separate cannula passes are performed through a single burr hole per putamen. Each track or cannula pass will be used to inject 3 cell deposits, the first one near the inferior aspect of the putamen as determined in the spMRI. The cannula is then withdrawn over ~3 to 5 mm and a second deposit is injected, followed by a third deposit after withdrawing the cannula for another ~3 to 5 mm. These distances are estimates and are expected to vary slightly across subjects, depending on their specific brain anatomy. The goal is to distribute the cells evenly in the putamen, along the needle track. Following the end of all injections in the first putamen (a total of 9 injections in 3 tracks), the subject will undergo an MRI. In Canada, this MRI will be performed only if clinically indicated. This will consist of a T1 non-contrast and a gradient recalled echo (GRE) axial sequence to identify any hemorrhage. Stopping criteria will be applied, based on the MRI results (see Section 8.3.3.1). If the MRI passes the stop criteria, the exact same procedure will be performed again, ie, single burr hole, 3 tracks and 9 cell deposits, in the contralateral putamen. This is followed by the same MRI, in order to identify any hemorrhage. As before, in Canada, this MRI will be performed only if clinically indicated. The subject is then transferred to the recovery room, and subsequently, to the NACU under the care of the Neurosurgery department at the Surgical Site. In case of bed unavailability, the subject may remain in the recovery room or may be transferred to the intensive care unit (ICU) for overnight observation.

The procedure may be performed in the MRI-equipped operating room or in a diagnostic MRI equipped for sterile procedures. Both locations are referred to as “operating room” in this protocol.

8.3.2.2. Surgical Procedure

Surgical planning of the trajectories is performed in the pre-operative setting, using the spMRI obtained within a week of surgery. On the day of surgery, the subject is brought into the operating room and general anesthesia with endotracheal intubation is induced. Antibiotic prophylaxis is administered, using a standard neurosurgical regimen (cefazolin, or vancomycin if penicillin-allergic), and redosed according to standard of care. Anesthesiology will require and place an arterial line for hemodynamic monitoring during surgery. The subject is positioned supine and the head is fixed in the frame. Bilateral entry sites that are preselected on a remote working station are marked on the scalp surface. An incision encompassing the entry points is designed for each putamen. The incision area is prepped and draped in a sterile fashion. A standard technique is then used to perform a burr hole at the desired site. The cortical surface is prepared using a standard method. A guide frame is then adjusted to provide the appropriate trajectory of the first track into the pre-established target site within the putamen. The infusion cannula is then passed through the guide frame to the cortical surface. At this point, an optional MRI scan can be performed to confirm accurate trajectory and alignment of the infusion cannula. The cannula is connected to the Hamilton syringe containing the cells and injection is initiated, at 2 to 10 µL per minute. For the low dose, this will involve the injection of 3.5 µL per track over less than a minute (Table 4), and for the high dose this will amount to 11 µL per track, which will require an infusion time of about 2 minutes (Table 5). The cannula is retrieved after the first deposit by a distance determined by the pre-operative plan, and the second cell injection is performed at the same rate. The cannula is retrieved to the next deposit level and the third injection is completed. The cannula is left in place for an additional 5 minutes and then slowly withdrawn. The trajectory of the second track is then set in the software. The cannula is inserted along this trajectory into the predetermined second target site and 3 cell deposits are made in a similar manner as for the first track, followed by a 5-minute waiting time after the last deposit. An alignment scan may be required before each trajectory. The cannula is then retrieved and the system set to the third trajectory. A set of 3 cell deposits is then injected in a similar fashion to the first 2 tracks. At this point, the injections in the first putamen are considered complete.

Next, identical steps are performed in the contralateral putamen. In brief a contralateral burr hole is made, and the cannula is inserted along the trajectory of the first track towards the first putaminal target. A total of 3 cell deposits are made at pre-set intervals followed by a 5-minute waiting period. The cannula is withdrawn and the second set of deposits along the second trajectory is made and then followed by a third trajectory and 3 final sets of cell deposits. The cannula is withdrawn after 5 minutes. A bilateral procedure will likely require 5 to 6 hours, mostly due to the calculation of the multiple trajectories.

Table 4: Low Dose (Dose A, 0.9 Million Cells per Putamen)

Putamen	Track	Number of Deposits	Volume per Track (µL) Dispensed[1]	Target Number of Cells per Track Delivered	Cells per Putamen
First	1	3	3.5	300,000	0.9 million
	2	3	3.5	300,000	
	3	3	3.5	300,000	
Contralateral	1	3	3.5	300,000	0.9 million
	2	3	3.5	300,000	
	3	3	3.5	300,000	

[1] Volumes required to achieve the target cell numbers will have to include an allowance for volume / cell loss during delivery. The low dose was experimentally determined to be 3.5 µL and the high dose will be 11 µL to deliver optimal cell dose targets of 300,000 and 0.9 million cells respectively.

Table 5: High Dose (Dose B, 2.7 Million Cells per Putamen)

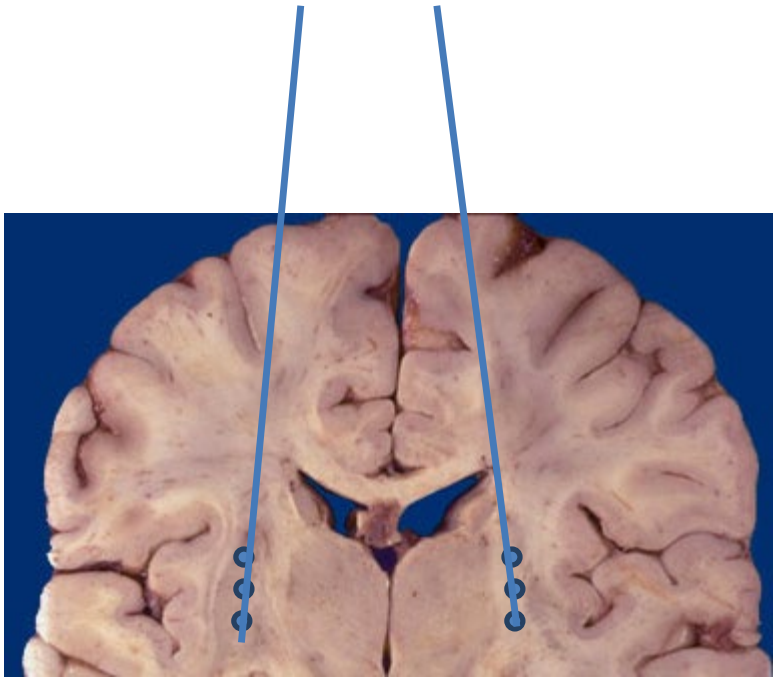
Putamen	Track	Number of Deposits	Volume per Track (µL) Dispensed[1]	Target Number of Cells per Track Delivered	Cells per Putamen
First	1	3	11	0.9 million	2.7 million
	2	3	11	0.9 million	
	3	3	11	0.9 million	
Contralateral	1	3	11	0.9 million	2.7 million
	2	3	11	0.9 million	
	3	3	11	0.9 million	

[1] Volumes required to achieve the target cell numbers will have to include an allowance for volume / cell loss during delivery. The low dose was experimentally determined to be 3.5 µL and the high dose will be 11 µL to deliver optimal cell dose targets of 300,000 and 0.9 million cells, respectively.

In each track, the volume will be divided between the deposits, as determined by the surgeon during surgery.

Figure 2 is a diagram depicting a needle track in each putamen, and 3 cell deposits, indicated by circles. Two additional tracks will be made on each side along the anteroposterior axis, targeting the remainder of the putamen.

Figure 2: Depiction of Tracks of Administration



8.3.3. Interruption of Surgical Treatment

8.3.3.1. Stopping Rules for Injection of the Contralateral (Second) Putamen

Cell injections will be performed sequentially, starting with the first putamen. Following the completion of injections in the first putamen, the subject will undergo MRI as a condition for resuming injections in the contralateral putamen. In Canada, this MRI will be performed only if clinically indicated. If the MRI shows hemorrhage exceeding a total of 1.5 cm in diameter in any area of the brain, or multiple hemorrhages along the 3 tracks, or other significant surgical concerns, the surgical procedure may be aborted at the discretion of the surgeon, and the subject awakened from anesthesia.

8.3.3.2. General Conditions for Interrupting the Procedure

The surgical procedure may be aborted or paused under the following circumstances:

a. Surgical complication: In the event that a severe complication from surgery occurs, cell delivery will not be performed. Such complications include, but are not limited to, unusual bleeding at any time.
b. Clinical deterioration during the procedure: This may be identified by the surgeon or anesthesiologist during surgery and includes, but is not limited to, cardiovascular/hemodynamic or respiratory compromise during the operation.

The reason for interruption of the procedure will be documented. If the subject receives any dose of cells, they will be considered evaluable, and continue on to receive the immunosuppressive regimen and all study activities.

If the subject does not receive any dose of cells, the subject will be considered not evaluable, and may be replaced with a future subject if they do not wish to be rescreened. Subjects who do not receive any cell dose will be followed through Visit 01, which is 1 month after surgery. The decision regarding continuation of immunosuppression, should the procedure be aborted, will be made on a case-by-case basis by the PI and co-investigators.

8.3.4. Post-operative Care Management Plan

The standard-of-care post-operative management plan for post-craniotomy surgery will be used per institutional standards, which may include the following:

- Patients are admitted to the Post-Operative Care Unit (PACU) and then to the NACU once cleared for transfer by a member of the anesthesia team.
- Neurological checks will be carried out per standard NACU protocol.
- Sequential compression devices will be used intra- and post-operatively.
- Regular home medications will be resumed as soon as safely possible post-operatively on the day of surgery.
- A computed tomography (CT) scan or MRI of the head will be performed on postoperative Day 1 to rule out delayed intracranial hemorrhage.
- Physical therapy/occupational therapy consults will be scheduled for subjects on post-operative Day 1, with plans for early mobilization and ambulation.
- Discharge will be planned to take place at approximately 24 hours post end of surgery if the patient is deemed medically ready.
- Detailed written and verbal discharge instructions, including contact numbers at the sites, will be provided prior to discharge.

8.3.5. Supportive Care During Hospitalization

Following surgery, subjects will be monitored per institutional standards such as follows:

- Subjects will be transported to the PACU at the Surgical Site immediately postoperatively.
- Antibiotics (cefazolin, or vancomycin if allergic), started at the onset of surgery, will continue to be administered according to routine post-surgical care protocol for a total of 24 hours.
- The subject's home medications will be continued unless not indicated in the immediate postoperative setting.
- Oral immunosuppressive drugs will be administered (see Section 6.1.2.3).
- Analgesics will be administered as clinically needed.
- When cleared by anesthesia, the subject will be transferred to the NACU at the Surgical Site or the ICU, if NACU beds are unavailable. Otherwise, they will remain in the recovery room.

- Diet will be advanced as tolerated.
- Activity will be advanced as tolerated in coordination with the Physical Therapy team who will evaluate the subject post-operatively and daily thereafter.
- The subject may be transferred to the Neurosurgery floor on the morning after surgery, if stable.
- Changes in neurological status or new abnormalities on neurological examination may be further evaluated by appropriate imaging (CT scan or MRI of the brain) and treated as clinically indicated.
- Laboratory studies, including complete blood count (CBC), full chemistry panel, and coagulation profile will be performed as deemed necessary by the clinical service, but at least once in the first 24 hours.
- Brain MRI (with contrast if deemed necessary in the opinion of the neurosurgeon and/or neurologist investigators) may be repeated prior to discharge, in the case of clinical concerns.

The subject will be discharged to home when deemed medically ready for discharge by the PI or co-investigators. A 24-hour stay is anticipated, but if extension of this time period is required in the opinion of the investigative or clinical team, the hospitalization may be longer.

8.3.6. Immunosuppressive Therapy

Immunosuppressive drugs will be administered intravenously and orally. The immunosuppressive protocol is planned to begin 0 to 6 hours prior to surgery, with basiliximab induction therapy, short-term methylprednisolone and prednisone taper, and then tacrolimus and low-dose prednisone over 1 year, with standard monitoring and dose adjustments as per protocol.

- Basiliximab 20 mg will be administered intravenously in the operating theater on Day 0.
- Basiliximab 20 mg will be administered intravenously in the outpatient suite at any Clinical or Surgical Site on post-operative Day 4 (Visit IS-0).
- Methylprednisolone 500 mg will be administered intravenously 0 to 6 hours prior to surgery (Day 0), followed by an oral taper and chronic therapy as follows:
  - Day 1: 250 mg methylprednisolone administered intravenously in hospital
  - Day 2: 120 mg prednisone administered once PO
  - Day 3: 60 mg prednisone administered once PO
  - Day 4: 40 mg prednisone administered once PO
  - Day 5: 20 mg prednisone administered once PO
  - Day 6: 10 mg prednisone administered once PO
  - Day 7 and continuing to 1 year: 5 mg prednisone daily PO

- Tacrolimus taken orally BID will be started on the day after surgery (Day 1) (recommended starting dose of 0.05 mg/kg BID [3 to 3.5 mg BID for a 70-kg person]) and adjusted to a target trough blood level of 4 to 7 ng/mL for the period of 1 year. Use of extended-release once daily formulation is permitted in place of BID to achieve a target trough blood level as noted in the Immunosuppression Manual.
  - In the rare circumstance where oral tacrolimus cannot be tolerated by the subject, the treating investigator must consult the PI and obtain approval to administer tacrolimus intravenously, prior to administration.
- Medications related to immunosuppression protocol:
  - Sulfamethoxazole/trimethoprim (Bactrim) 400 mg/80 mg once daily PO will be started on Day 1 and continued to 6 months (see Section 8.3.5)
  - Omeprazole 20 mg once daily PO will be started on Day 1 and continued to 1 year

Alternative medications to the specific antibiotics and proton-pump inhibitor listed here could be prescribed, at the discretion of the PI and the Transplant Immunosuppression team, in case of intolerance or other clinically relevant reason.

For any subject who receives only a partial cell dose or if adverse effects of the immunosuppression drugs occur, early termination of immunosuppression will be discussed with the subject by the PI and a clinical transplant specialist investigator. The threshold for advising termination of immunosuppression will depend upon a combination of the severity of the adverse effects of the immunosuppressive drugs experienced by that subject and the estimated percentage of the intended cell dose delivered.

For subjects who do not receive any cell dose, the decision regarding continuation of immunosuppression should the surgical procedure be aborted, will be made on a case-by-case basis by the PI and co-investigators.

Although the risks of stopping immunosuppressants is not known, there is a possibility that the transplant will not function as well without the immunosuppressant therapy. If the subject would like to withdraw, they will be advised that it is beneficial for them to continue with the protocol as long as it is safe to do so and continue to receive immunosuppressants per protocol. If they do not agree and would like to no longer be a part of the study, the patient will be asked to come to the clinic for the Early Withdrawal Visit procedures.

Subjects will be advised not to receive vaccinations with live viruses (eg, measles, mumps, rubella [MMR], Varicella) while on immunosuppression therapy. Influenza vaccination with killed virus will be allowed prior to immunosuppression as directed by the Transplant Immunosuppression team. Expectant treatment for possible infections will be incorporated while subjects are receiving immunotherapy. The Transplant Immunosuppression team will monitor the study subjects for infection, including clinical monitoring for fungal and all other infections, and with blood (CMV polymerase chain reaction [PCR]) and urine tests (urinalyses) as detailed in Appendix 1.

Decisions to delay, reduce, or discontinue immunosuppressive drugs prior to 1 year will be made by the Immunosuppression Clinician in collaboration with the Study Neurologist and

Neurosurgeon, who may seek the input of outside experts, including the Immunosuppression Clinicians from other sites and the DSMC. These decisions will be informed by the prescribing information for each immunosuppressive agent (see Table 6 for examples of adverse events related to the immunosuppression medications, and general guidance for actions to be taken in response). The decision to delay, reduce, or prematurely discontinue immunosuppression will be assessed in the context of a risk/benefit analysis on a case-by-case basis and in consideration of known toxicities for the immunosuppressive drugs versus ensuring graft survival.

The immunosuppression regimen is planned for 1 year. The recommendation is based on published literature on clinical studies (Barker, 2013; Olanow, 2003) to help ensure long-term graft survival, as discussed in Section 4.8.2. The Sponsor does not recommend continuing immunosuppressive therapy beyond 1 year.

Table 6: Guidelines for Delaying, Reducing, or Discontinuing Immunosuppressive Drugs

Immunosuppressive Agent	Issue	Guidance
Tacrolimus	Nephrotoxicity: eg, increases in creatinine by >15% from baseline	Consider decreasing dose or changing to cyclosporine, especially in context of high tacrolimus trough levels.
	Severe neurotoxicity, eg, posterior reversible encephalopathy syndrome	Consider withholding medication, decreasing dose, ceasing dose, or changing to cyclosporine.
	Neurotoxicity: disabling tremor	Consider decreasing dose or changing to cyclosporine.
	Opportunistic infection: eg, Pneumocystis jirovecci pneumonia	Consider reducing dose, treat infection.
	Hyperkalemia	Consider reducing dose.
	Severe aesthenia	Consider decreasing dose or changing to cyclosporine.
	Severe diarrhoea	Reduce dose.
Cyclosporine	Gingival hyperplasia	Consider decreasing dose, or cessation if severe.
	Nephrotoxicity: eg, increases in creatinine by >15% from baseline	Consider reducing dose.
Basiliximab	Acute reaction: severe hypersensitivity reaction	Omit second dose.

Immunosuppressive Agent	Issue	Guidance
Methylprednisolone/prednisone	Severe hyperglycaemia	Decrease dose, consider insulin coverage.
	Acute psychosis	Consider withholding dose, perform more rapid dose taper.
	Hypertension	Treat hypertension, consider decreasing dose.
	Acute reaction: severe hypersensitivity reaction.	Decrease/consider cessation.
	Adrenal insufficiency	Prevention: on cessation of steroid therapy, warn subjects to report symptoms and signs of adrenal insufficiency, eg, postural dizziness or unexplained hypotension, weakness, fatigue, aesthenia, etc. Establish diagnosis if symptomatic: cortisol levels 2 weeks after cessation of steroid therapy. Treatment: restart steroids therapy and perform a slow taper over 8 weeks.
	Gastric ulcer	Increase omeprazole, decrease dose.
	Oedema	Decrease dose, prescribe diuretics.

8.3.7. Study Drug Preparation, Handling, and Storage

Study drug preparation, handling, and storage are described in the Cell Preparation and Delivery Manual.

8.4. Concomitant Medications

There is no plan to adjust the medications according to a fixed paradigm. While the subjects are admitted to the Surgical Site for transplantation, the study neurologists may adjust their medications if needed. In addition, the study neurologists may make recommendations to the treating neurologists based upon information obtained from the study subjects. However, the study participants will be advised to follow up with their usual PD care with their own treating neurologist, who will be expected to make medication adjustments according to their own clinical judgment, and these changes will be captured at the scheduled (or any unscheduled) study visits. The study neurologists will be available for consultation to the subjects' own regular neurologists if required for questions or discussion.

8.5. Treatment Compliance

Compliance with immunosuppression drug regimen and prophylactic agents will be estimated via pill count at each visit.

8.6. Randomization and Blinding

This is an open-label study. There is no randomization procedure.

9. STUDY ASSESSMENTS

Please refer to Appendix 1.

Details of all evaluations are provided in Appendix 2.

9.1. Screening/Baseline Assessments

Prior to the planned intervention, subjects will undergo a screening visit to ensure that each subject meets inclusion/exclusion criteria for the study (SC: Clinical Site), a pre-operative evaluation and visit with the neurosurgeon (PrOV: Surgical Site), and then a Baseline Visit (BL: Clinical Site, with the exception of ^{18}F-DOPA PET to be undertaken at the PET Imaging Site) for collection of all baseline data for the study. All of these visits must be completed within a 28-day period prior to the admission to the Surgical Site for surgical intervention.

Patients are required to have been vaccinated against SARS-CoV-2 no less than 10 days prior to administration of MSK-DA01. If the vaccine is administered in 2 doses, the first dose must be administered ≥2 days prior to screening and the second dose must be administered ≥10 days prior to surgery. If the vaccine is a single-dose vaccine, it must be administered ≥2 days prior to screening.

The following assessments will be administered at each time point:

9.1.1. Screening Visit (may be conducted over 1 to 2 days within 28 days prior to dosing surgery)

- Obtain written informed consent
- Review all inclusion/exclusion criteria
  - Evaluation of levodopa response will be made as follows. The MDS-UPDRS Part 3 will be administered to subjects in the “off” and “on” medication states, and the difference (improvement) will be calculated between these 2 scores. For “off” measures, subjects will come to the study visit in a “practically defined off” state, having withdrawn from anti-PD medications since their last dose of the day prior. For “on” state measures, subjects will be evaluated on their usual medication. If the subject reports an unexpected “off” at the time scheduled for “on” evaluation, then the evaluation will be delayed until the “off” resolves (either spontaneously or after the next medication dose).
- Obtain demographic information
- Obtain medical history, including smoking, alcohol, and caffeine information
- Obtain neurological history
- Review and document anti-Parkinson’s medications
- Review and document concomitant medications
- Perform general medical examination with vital signs
- Perform general neurological examination

- Assess and document AEs
- Administer AIMS for the inclusion/exclusion (or other screening for dyskinesia)
- Provide Hauser diary with instruction for subject to self-complete immediately following the Screening Visit.
- Administer MDS-UPDRS
- Provide QUIP questionnaire to subject for self-administration
- Administer HAM-D for inclusion/exclusion criteria (or other screening for depression)
- Administer MoCA test
- Obtain blood for laboratory tests (See Appendix 1 and Appendix 2 for a list of tests to be performed and timing.)
- Urinalysis
- Neuroimaging
  - MRI, with optional contrast, if indicated

9.1.2. Pre-operative Evaluation (PrOV) [within 7 days prior to dosing surgery]

This visit will take place with the Surgical Site physicians who provide a routine presurgical testing service.

- Review of medical history
- Review of concomitant medications
- Perform general medical examination
- Electrocardiogram (ECG)
- Chest X-ray
- Obtain blood for laboratory tests (See Appendix 1 and Appendix 2 for a list of tests to be performed and timing.)
- Urinalysis
- Neuroimaging
  - Neuro Navigation (pre-operative) MRI (contrast scans may be performed if clinically indicated)
- Subjects older than 70 years are cleared by the Geriatrics service. At the discretion of the presurgical unit, cardiac or pulmonary clearance may be requested, depending on the subject's medical history.

9.1.3. Baseline Visit (may be conducted over 1-2 days within 28 days prior to dosing surgery)

- Re-review inclusion/exclusion criteria
- Review and update of medical and neurological history
- Review and update of concomitant medications
- Review and update of anti-PD medications
- General medical exam with vital signs
- Neurological exam
- Assess and document AEs
- ECG
- Hauser Patient Diary
  - Diary will be supplied for completion at home within 1 week prior to Baseline Visit
- Administer MDS-UPDRS
  - Part 3 will be administered in the "on medication" state only, and the exam will be video-recorded
- Assess Modified Schwab and England Activities of Daily Living
- Administer UDysRS
- Administer 10-Meter Walk Gait Speed Test
- Provide BDI-II, BAI-II, QUIP, and PDQ-39 questionnaires to subject for self-administration
- Administer Columbia Suicide Severity Rating Scale (C-SSRS)
- Administer CGI-S
- Administer MoCA test
- Administer PD NMSS
- Laboratory tests (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Neuropsychological evaluation and testing (Table 9; no need to repeat if performed at screening and screening assessment will be used as baseline)

  A formal neuropsychological evaluation will be conducted to assess the subject's cognition and mood. This is based upon standard of care for subjects undergoing DBS (Defer, 1999), due to concerns that cognitive performance might be impacted by bilateral DBS (Xie, 2016). The cognitive evaluation will consist of a robust battery of standardized tests to measure brain functioning across a variety of cognitive domains, including overall cognition, attention/executive functioning, learning and memory,

language, and visuospatial skills. Mood and neurobehavioral status will be examined with a combination of clinician rating scales and self-report measures. Neuropsychological findings can be useful in documenting baseline cognitive and emotional status as well as objectively quantifying the presence of post-operative changes and will be used to evaluate post-operative cognitive changes over time with annual evaluations over the course of the study. The following tests will supplement more frequent testing of non-motor functions as assessed by MoCA, BAI-II (Beck, 1993), BDI-II (Beck, 1996), and C-SSRS.

- Neuroimaging
  - ^{18}F-DOPA PET (at the PET Imaging Site)
  - Women of childbearing potential will be subject to a stat urine pregnancy test on the day of the PET scan, if a pregnancy test was not performed within 30 days prior to the scan.
- Obtain blood for exploratory biomarkers and DNA. Whole blood will be collected for DNA isolation at baseline. No specified genetic testing is planned as part of the present clinical trial, but the samples will be stored in a biorepository for future research.
- Obtain blood for storage for xenotransplantation-related future testing
- PKG
  - A research coordinator will program the PKG device, instruct the subject on how to use it, and provide the PKG device for the subject to take home. The device will be worn for 7 days and then returned to the Clinical Site investigators in a prepaid, pre-addressed envelope provided per standard clinical protocol.
  - In the event that surgery is scheduled within 7 days of the baseline visit, the PKG may be provided prior to that visit.

9.1.4. Review of Subject Suitability for Study Participation

Once an individual has been deemed to meet inclusion and no exclusion criteria by the PI, the PI will make the enrollment decision. Prior to deciding to proceed, on an as-needed basis, the PI or consenting professional may consult with a member of the Steering Committee (see Section 12.2.2.2).

9.1.5. Research Participant Registration

Confirm eligibility as defined in Sections 7.1 and 7.2. Obtain informed consent by following procedures defined in Section 12.1.1. During the registration process, registering individuals will be required to complete a protocol-specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed.

9.2. Evaluation During Treatment/Intervention

9.2.1. Evaluation During Hospitalization

Following surgery, subjects will be evaluated as follows:

- Vital signs and neurological examinations per standard post-operative protocol
- Laboratory studies, including CBC, full chemistry panel, and coagulation profile will be performed as deemed necessary by the clinical service, but at least once in the first 24 hours.

9.2.2. Outpatient Follow-Up

After hospital discharge, subject follow-up will be performed as follows:

- The subject will be followed 1 week post-operatively in the Neurology clinic for a neurological evaluation comprising vital signs, and collection of AEs (IS01).
- The subject will be seen approximately 10 days post-operatively in any Clinical or Surgical Site for a postoperative evaluation (PoOV) including wound check, suture/staple removal and neurological examination.

9.2.3. Study Evaluations Related to Transplantation: Outpatient

The following procedures and evaluations are to be performed at each visit (see Appendix 1 for descriptions). If subjects are unable to attend the clinic for blood draws, blood will be drawn at a local clinic and results sent to the Clinical Site.

Subjects will be given a pill diary to record at home medication administration. The patient should bring the diary as well as medication bottles to each clinic visit (even if empty). The diary will be reviewed by the study doctor or nurse at each clinic visit.

9.2.3.1. Visit 01/Month 1: (Month 1 ± 2 days from the time of surgery)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure and heart rate)
- Perform general neurological examination
- Review and document PD medications and concomitant medications
- Assess and document AEs
- Pill diary and medication bottle review
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Administer MDS-UPDRS
  - Part 3 will be administered in the “on medication” state only, and the exam will be video-recorded.
- Assess Modified Schwab and England Activities of Daily Living

- Administer UDysRS
- Administer C-SSRS
- Laboratory Blood Testing (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Tacrolimus level
- Urinalysis
- Brain MRI (no contrast)
- Obtain blood for exploratory biomarkers
- Obtain blood for storage for xenotransplantation-related future testing

9.2.3.2. Visit 02 (Month 3 ± 1 week)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure, heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications
- Assess and document AEs
- Pill diary and medication bottle review
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Administer MDS-UPDRS
  - Part 3 will be administered in the practically defined “off medication” state and in the “on medication” state, and the exam will be video-recorded in both states
- Assess Modified Schwab and England Activities of Daily Living
- Administer UDysRS
- Administer 10-meter Walk Gait Speed Test
- Provide BDI-II, BAI-II, QUIP, and PDQ-39 questionnaires to subject for self-administration.
- Administer C-SSRS
- Administer CGI-S
- Administer MoCA test
- Administer PD NMSS
- Laboratory Blood Testing (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Tacrolimus level

- Urinalysis
- Brain MRI (no contrast)
- PKG

  A research coordinator will program the PKG device, instruct the subject on how to use it, and provide the PKG device for the subject to take home. The device will be worn for 7 days and then returned to the Clinical Site investigators in a prepaid, pre-addressed envelope provided per standard clinical protocol.

9.2.3.3. Visit 03 (Month 6 ± 1 week)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure and heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications
- Assess and document AEs
- Pill diary and medication bottle review
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Administer MDS-UPDRS
  - Part 3 will be administered in the practically defined “off medication” state and in the “on medication” state, and the exam will be video-recorded in both states
- Assess Modified Schwab and England Activities of Daily Living
- Administer UDysRS
- Administer 10-meter Walk Gait Speed Test
- Provide BDI-II, BAI-II, QUIP and PDQ-39 questionnaires to subject for self-administration.
- Administer C-SSRS
- Administer CGI-S
- Administer MoCA test
- Administer PD NMSS
- Laboratory Blood Testing (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Tacrolimus level
- Urinalysis
- Brain MRI (no contrast)

- Obtain blood for exploratory biomarkers
- Obtain blood for storage for xenotransplantation-related future testing

9.2.3.4. Visit 04 (Month 9 ± 1 week)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure and heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications
- Assess and document AEs
- Pill diary and medication bottle review
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Administer MDS-UPDRS
  - Part 3 will be administered in the practically defined “off medication” state and in the “on medication” state, and the exam will be video-recorded in both states
- Administer UDysRS
- Administer 10-meter Walk Gait Speed Test
- Administer C-SSRS
- Laboratory Blood Testing (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Tacrolimus level
- Urinalysis

9.2.3.5. Visit 05 (Month 12)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure and heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications
- Assess and document AEs
- ECG
- Pill diary and medication bottle review
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior

- Administer MDS-UPDRS
  - Part 3 will be administered in the practically defined "off medication" state and in the "on medication" state, and the exam will be video-recorded in both states
- Assess Modified Schwab and England Activities of Daily Living
- Administer UDysRS
- Administer 10-meter Walk Gait Speed Test
- Provide BDI-II, BAI-II, QUIP and PDQ-39 questionnaires to subject for self-administration.
- Administer C-SSRS
- Administer CGI-S
- Administer MoCA test
- Administer PD NMSS
- Perform neuropsychological testing
- Laboratory Blood Testing (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Tacrolimus level
- Urinalysis
- Brain MRI (no contrast)
- ^{18}F-DOPA PET (PET Imaging Site)
  - Women of childbearing potential will be subject to a urine pregnancy test on the day of the PET scan.
- Obtain blood for exploratory biomarkers
- Obtain blood for storage for xenotransplantation-related future testing
- PKG
  - A research coordinator will program the PKG device, instruct the subject on how to use it, and provide the PKG device for the subject to take home. The device will be worn for 7 days and then returned to the Clinical Site investigators in a prepaid, pre-addressed envelope provided per standard clinical protocol.

9.2.3.6. Visit 06 (Month 15 ± 1 week)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure and heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications

- Assess and document AEs
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Administer MDS-UPDRS
  - Part 3 will be administered in the "on medication" state only, and the exam will be video-recorded
- Administer UDysRS
- Administer 10-meter Walk Gait Speed Test
- Administer C-SSRS
- Blood sample for exploratory biomarkers

9.2.3.7. Visit 07 (Month 18 ± 1 week)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure and heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications
- Assess and document AEs
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Administer MDS-UPDRS
  - Part 3 will be administered in the practically defined "off medication" state and in the "on medication" state, and the exam will be video-recorded in both states
- Assess Modified Schwab and England Activities of Daily Living
- Administer UDysRS
- Administer 10-meter Walk Gait Speed Test
- Provide BDI-II, BAI-II, QUIP and PDQ-39 questionnaires to subject for self-administration.
- Administer C-SSRS
- Administer CGI-S
- Administer MoCA test
- Administer PD NMSS
- Laboratory Blood Testing (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Brain MRI (no contrast)

- ^{18}F-DOPA PET (PET Imaging Site)
  - Women of childbearing potential will be subject to a urine pregnancy test on the day of the PET scan.
- Blood sample for exploratory biomarkers

9.2.3.8. Visit 08 (Month 21 ± 1 week)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure, heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications
- Assess and document AEs
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Administer MDS-UPDRS
  - Part 3 will be administered in the "on medication" state only, and the exam will be video-recorded
- Administer UDysRS
- Administer 10-Meter Walk Gait Speed Test
- Administer C-SSRS

9.2.3.9. Visit 09 (Month 24 ± 1 week)

- Perform general medical examination, including weight and orthostatic vital signs (blood pressure, heart rate)
- Perform general neurological examination
- Review and document concomitant medications, including PD medications
- Assess and document AEs
- ECG
- Hauser Patient Diary
  - Diary will be supplied for completion at home 1 week prior
- Administer MDS-UPDRS
  - Part 3 will be administered in the practically defined "off medication" state and in the "on medication" state, and the exam will be video-recorded in both states
- Assess Modified Schwab and England Activities of Daily Living
- Administer UDysRS

- Administer 10-meter Walk Gait Speed Test
- Provide BDI-II, BAI-II, QUIP and PDQ-39 questionnaires to subject for self-administration.
- Administer C-SSRS
- Administer CGI-S
- Administer MoCA test
- Administer PD NMSS
- Laboratory Blood Testing (See Appendix 2 and Appendix 1 for a list of tests to be performed and timing.)
- Perform neuropsychological testing
- Brain MRI (no contrast)
- ^{18}F-DOPA PET (PET Imaging Site)
  - Women of childbearing potential will be subject to a urine pregnancy test on the day of the PET scan
- Obtain blood for exploratory biomarkers
- Obtain blood for storage for xenotransplantation-related future testing
- PKG
  - A research coordinator will program the PKG device, instruct the subject on how to use it, and provide the PKG device for the subject to take home. The device will be worn for 7 days and then returned to the Clinical Site investigators in a prepaid, pre-addressed envelope provided per standard clinical protocol.

9.2.4. Study Procedures Related to Immunosuppression Regimen: Outpatient

Procedures in this section will be carried out at the Clinical Site under the supervision of the Immunosuppression Clinician. Administration of the immunosuppression drug regimen and prophylactic agents, in addition to monitoring and dose adjustment, will be undertaken by the Transplant Immunosuppression team. The schedule of laboratory testing described below is a minimum follow-up. Testing and visits may be more frequent at the discretion of the Transplant Immunosuppression team.

Compliance will be estimated via pill count at each visit. AE recording will be made at each visit and will be reported to the PI and/or an Investigator within 24 hours.

Blood samples will be drawn by routine venipuncture at visits scheduled as detailed in Appendix 1 and Appendix 2.

9.2.5. Unscheduled and Other Visits

9.2.5.1. Unscheduled Visit

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the Investigator. The date and reason for the unscheduled visit will be recorded in the source documentation.

In most cases, an unscheduled visit will be warranted due to an AE, significantly abnormal laboratory values, and/or permanent discontinuation of study drug(s).

The following procedures and evaluations at a minimum are to be performed at an Unscheduled Visit:

- Review and document concomitant medications
- Assess and document AEs
- Update the pill diary as needed
- If the reason for the unscheduled visit is that the subject is permanently discontinuing any study medication at the visit, whether by choice, or for reasons concerning the health or well-being of the subject, the following additional procedures and evaluations should be completed:
  - Retrieve all previously dispensed study drug and calculate compliance
  - Record last dosing on the pill diary
  - Obtain weight and orthostatic vital signs (blood pressure and heart rate)

Obtain blood and/or urine for additional study chemistry or hematology tests, or other laboratory testing if warranted based on the Investigator's judgment.

9.2.5.2. Discontinuation of In-Person Follow-Up

The goal is to retain subjects for all of the scheduled visits for the entire study, and extensive efforts will be made to ensure that this is the case. However, due to unforeseeable circumstances, subjects may discontinue in-person follow-up. In this case, the Discontinuation of In-person Follow-up (DF) Visit will be conducted at the time the decision to stop in-person follow-up is made or as soon thereafter as possible.

The following procedures and evaluations are to be performed at the Discontinuation of In-person Follow-up Visit:

- Review and document concomitant medications
- Assess and document AEs
- Obtain weight and orthostatic vital signs (blood pressure and heart rate)
- Obtain blood for safety laboratory tests: serum urate, CHEM-7 panel, liver function tests, thyroid-stimulating hormone, lipids, CBC with differential
- Retrieve previously dispensed study drug/bottles and calculate compliance

- Record last dosing on Dose Management Log
- Administer MDS-UPDRS
  - Part 3 will be administered in the practically defined “off medication” state and in the “on medication” state, and the exam will be video-recorded in both states. Provide MDS-UPDRS Parts IB and II, REM Sleep Behavior Disorder, and PDQ-39 questionnaires to subject for self-administration.
- Assess Modified Schwab and England Activities of Daily Living
- Administer MoCA

Any AE that remains active at the Discontinuation of In-person Follow-up Visit for such a subject will be followed up for 28 days or until resolved or stabilized, whichever occurs first.

9.2.5.3. Alternative Participant Contact After Missed In-Person Follow-Up

For any subject who is unable to attend an in-person follow-up visit prior to Month 24, study staff will try to complete the visit activities that do not require face-to-face interaction by contacting the participant via telephone, telemedicine, email, or mail. Contact from the study staff will occur during the pre-established study visit windows.

The purpose of these telephone / telemedicine / email / mail visits will be to collect information such as:

- Review and record concomitant medications
- Review and record AEs
- Review study drug dosing
- Study Medication Adherence
- Complete other study activities that do not require face-to-face interaction:
  - Collection of the Hauser Diary
  - Assess Modified Schwab and England Activities of Daily Living
  - Administer UDysRS
  - Provide BDI-II, BAI-II, QUIP and PDQ-39 questionnaires to subject for self-administration

10. ASSESSMENT OF SAFETY

Please refer to Appendix 1 for details regarding the schedule of assessments.

10.1. Safety Parameters

10.1.1. Demographic/Medical History

Demographic information will be taken at the Screening Visit. Neurological history and PD medications will be taken at Screening and Baseline Visits. Medical history and concomitant medications will be taken at Screening, Baseline, and PrOV.

10.1.2. Vital Signs, Orthostatic Changes, Weight, and Height

Blood pressure and heart rate (supine and standing), and body weight will be measured at every visit. Height will be measured at the Baseline Visit only.

10.1.3. General Medical Examination

A general medical examination comprised of a skin examination, head/neck/lymphatic, eyes, ears/nose/throat, cardiovascular, lungs, abdomen, musculoskeletal, neurological and psychiatric systems will be taken at Screening, Baseline, and PrOV.

10.1.4. Electrocardiogram

A standard 12-lead ECG will be performed. Results will be based upon the Investigator's interpretation of standard machine readings and upon the reading by the Clinical Site cardiology laboratory service or the Clinical Site physician responsible for pre-surgical screening.

10.1.5. Laboratory Assessments

Refer to Appendix 2 for details regarding laboratory assessments. Refer to Appendix 1 for the time points at which each laboratory assessment is performed.

10.1.5.1. Blood Sample for Long-term Storage

To permit exploratory investigations and the application of novel approaches to bioanalysis that may further elucidate the outcomes of this study, or potentially advance understanding of the safety, mechanism of action and/or efficacy of MSK-DA01, blood samples will be collected for long-term storage. These samples will be securely stored in a central biorepository for future testing.

Details regarding the collection, processing, storage, and shipping of samples will be provided in the Laboratory Manual.

Exploratory analysis of these biospecimens will be performed by BlueRock Therapeutics or its designees.

All study participants will be advised during the informed consent process of these biobanking details and the potential for exploratory investigation of their samples.

10.1.5.2. Pregnancy Testing

Pregnancy tests will be performed for women of childbearing potential only. Urine pregnancy testing (if applicable) will be performed on female subjects at Screening, PrOV, and Baseline Visits. Urine pregnancy tests will also be performed on the day of a PET scan if a pregnancy test was not performed within 30 days prior to the scan.

10.2. Adverse and Serious Adverse Events

10.2.1. Definition of Adverse Events

10.2.1.1. Adverse Event

An AE can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An AE can arise with any use of the drug (eg, off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Examples of AEs include the following:

- Any treatment-emergent signs and symptoms (events that are a change from the subject's baseline conditions, including an increase in frequency or severity)
- Clinically significant laboratory findings
- Disease-related (indication) signs and symptoms not present at baseline
- Any event or finding from the investigational treatment, including method of administration
- Injury or accidents
- Any other event or finding that the investigator feels is clinically significant

10.2.1.2. Serious Adverse Event

An AE is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening AE
- An AE that results in subject hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the subject or subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

10.2.2. Severity of Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE) term (AE description) and grade: The descriptions and grading scales found in the revised National Cancer Institute (NCI) CTCAE version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program web site (http://ctep.cancer.gov).

10.2.3. Relationship to Study Intervention

The relationship of each AE to the study intervention must be assessed and classified by the PI according to the temporal relationship and their clinical judgment considering the following:

- Temporal association between the study treatments (eg, immunosuppression or surgery) and the event
- Cessation or re-challenge (eg, of a suspected concomitant medication)
- Compatibility with known effects of the study treatments
- Known effects of concomitant medications
- Pre-existing risk factors
- A plausible mechanism
- Intercurrent illness (eg, the flu)
- Underlying diagnosis

All AEs will be attributed to the VC, MSK-DA01 cells, ^{18}F-DOPA PET scan, MRI, syringe, surgery, immunosuppression regimen, and/or disease.

Categories of attribution:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

10.2.4. Recording Adverse Events

The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study subject presenting for scheduled study visits, medical care, or by communication between visits, and they will be continuously collected. Treatment-emergent AEs will start after the first dose of any immunosuppressive medication.

All AEs will be recorded on a subject specific AE log with information as follows: event term, onset date, resolution date if any, whether serious or not, severity level, action taken with study drug, outcome, investigator's opinion of the possible relationship between the AE and the VC,

MSK-DA01 cells, ^{18}F-DOPA PET scan, MRI, syringe, surgery, immunosuppression regimen, and/or disease.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

All adverse events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation will be recorded, except for subjects who have withdrawn their consent for follow-up or subjects who are actively being followed in a BlueRock-sponsored follow-up study. At each study visit, the investigator will inquire about the occurrence of AE since the last visit. Events will be followed for outcome information until resolution or stabilization.

The AE log will be maintained by the research staff and kept in the subject's research chart.

10.2.5. Reporting Adverse Events

The investigators will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of AEs reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, X-rays, electrocardiographs, etc. When finalized test results will not be available prior to product release, the PI will electronically notify the IRB (and in the US, the review division's Regulatory Project Manager at FDA), within 30 days, in the event acceptance criteria are not met.

Reporting: All AEs occurring on this study will be reported to the IRB according to the IRB policy.

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study, except for subjects who have withdrawn their consent for follow-up.

10.2.5.1. Serious Adverse Events Require Immediate Reporting to Sponsor/Designee

SAE reporting is required from informed consent through the end of the study regardless of attribution.

SAE Reporting to the Clinical Research Organization

SAEs will be reported to the CRO. SAEs will be reported in writing within 24 hours of the investigator's knowledge of the event.

SAE Reporting to ClearPoint Neuro (US Only)

In the US, all SAEs related to the SmartFlow® cannula will be reported to ClearPoint Neuro, Inc. SAEs will be reported in writing within 24 hours of the investigator's knowledge of the event.

10.2.5.2. Sponsor Safety Reporting to Regulatory Authorities

The sponsor or its representative is required to report certain study events in an expedited manner to all country regulatory authorities where the study is being conducted, according to local applicable regulations.

The following describes the safety reporting timeline requirements for suspected unexpected serious adverse reactions (SUSARs) and other reportable events:

Immediately and within 7 calendar days

- Any suspected adverse event that is associated with the use of the study cells, is unexpected, and is fatal or life-threatening. Follow-up information must be reported in the following 8 days.

Immediately and within 10 calendar days

- Evaluations of unanticipated adverse device effects and the results of such evaluations will be reported to the regulatory authorities and to all reviewing IRBs and participating investigators within 10 calendar days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as the health authority requests.
  - Any unanticipated adverse device effect
  - Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application)
  - Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

Immediately and within 15 calendar days

- Any suspected adverse event that is associated with the use of the study cells, is unexpected and serious, but is not fatal or life-threatening, and there is evidence to suggest a causal relationship between the study cells and the reaction
- Any finding from tests in laboratory animals that suggest a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity
- Any event in connection with the conduct of the study or the development of the study cells that may affect the safety of the trial patients

In addition, periodic safety reporting to regulatory authorities will be completed by the sponsor or its representative according to national and local regulations.

10.2.5.3. Pregnancy Reporting

If a female patient or the female partner of a male patient becomes pregnant during the study or through 90 days after the last dose of study cells, the investigator must report the pregnancy to the sponsor or designee within 24 hours of being notified of the pregnancy. Details of the pregnancy will be recorded on the pregnancy reporting form. The patient should receive any

necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus.

The pregnancy should be followed by the investigator until completion. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy results in a postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, the investigator should follow the procedures for reporting an SAE as outlined in Section 10.2.5.1. Every infant will be followed for 2 months after delivery.

10.2.5.4. Overdose Reporting

An overdose is defined as any dose administered to or taken by a patient (accidentally or intentionally) that exceeds the highest daily dose, or is at a higher frequency, than specified in the protocol. It is the investigator's responsibility to decide whether a dose is to be considered an overdose, in consultation with the sponsor. Overdose must be recorded in the electronic case report form (eCRF).

All reports of overdose (with or without an AE) must be reported within 24 hours to the CRO.

11. STATISTICS

A detailed statistical analysis plan (SAP) will be written after finalizing the protocol and before database lock. The SAP will detail the implementation of all the statistical analyses in accordance with the principal features stated in the protocol.

Subjects will comprise approximately 12 evaluable subjects with advanced PD, who will undergo a single session surgical transplantation of MSK-DA01 cells to the bilateral post-commissural putamen, and with administration of a temporary (1 year) immunosuppression regimen. Two dose levels will be studied in 2 cohorts. The first 5 subjects (Cohort A) will receive cell Dose A (0.9 million cells per putamen) and subsequent subjects (Cohort B) will receive cell Dose B (2.7 million cells per putamen). There is no expectation that incidence of AEs will differ by dose level and immunosuppression regimen is the same for both cohorts. Assessments for the primary, secondary, and exploratory endpoints of this study will take place over 2 years post transplant.

11.1. Determination of Sample Size

11.1.1.1. Sample Size Justification

The sample size of approximately 12 evaluable subjects has been chosen to allow 2 doses to be explored in a small number of subjects. If an enrolled subject is not considered a part of the evaluable population as described in Section 6.2, additional subjects may be enrolled to reach approximately 12 evaluable subjects. This size cohort allows surgical procedures to be staggered in order to mitigate risk.

11.2. Statistical Methodology

- One year:
  - A formal analysis of the primary endpoint will be performed when all subjects dosed have reached Year 1 or discontinued from the study. At that time, a data cut will occur and the primary analyses to address safety and tolerability will be performed.
  - Analysis of secondary and exploratory aims is planned when all subjects dosed have reached Year 1 or discontinued from the study.
- Two years:
  - A formal analysis of secondary outcomes will be performed when all subjects dosed have reached Year 2 or discontinued from the study. At that time, a database lock will occur and the secondary and exploratory analyses will be performed.

Statistical analyses will be primarily descriptive in nature. Descriptive statistics will include baseline characteristics of the cohort enrolled. Surgical delivery of MSK-DA01 cells will be described, including numbers of tracks, numbers of deposits, position of deposits, estimated cell numbers delivered per deposit, and percentage of target deposits delivered per putamen.

11.2.1. Populations to be Analyzed

Evaluable subjects are defined as those who provide informed consent, meet all inclusion criteria and no exclusion criteria, and successfully undergo surgical intervention to receive cell transplantation. Subjects may receive any amount of cells to be considered evaluable. Any subject who has provided informed consent and is eligible to proceed but either chooses not to proceed or proceeds to the implantation procedure, receives the first dose of immunosuppression but does not receive cells, may be replaced by recruiting another subject, such that approximately 12 evaluable subjects are reached in this study. Although all of the subjects are expected to be able to be followed for the duration of the protocol, in the unlikely event that subjects are lost to follow-up, subjects lost prior to the 1-year primary endpoint may be replaced. In the event that subject proceeds to the implantation procedure and does not receive cells for any technical reason, if the subject wishes to remain in the study, then screening and baseline visits will be repeated prior to rescheduling the surgical admission.

11.2.2. Efficacy Analyses

No formal efficacy evaluations will be performed. However, the following information will be collected for preliminary descriptive analysis of any signals of efficacy using statistical measures such as median, mean, standard deviation, and range to describe:

- Change from baseline through 2 years post transplant in ^{18}F-DOPA PET uptake
- Change from baseline at 1 and 2 years post transplant in standardized measures of motor function: MDS-UPDRS Part 3 “off” state; hours of “on” time without troublesome dyskinesia as recorded by Hauser diary

11.2.3. Safety Analyses

11.2.3.1. Primary Endpoint Analysis

Incidence of SAEs (as defined in Section 10.2.1.2) will be tabulated at 1-year post transplant.

11.2.3.2. Secondary Endpoint Analysis

Continued safety and tolerability will be evaluated at 1 and 2 years post transplant. Severity of AEs (as defined in Section 10.2.1.1 and Section 10.2.2) will be tabulated. All AEs and related AEs will be summarized by body system, dose cohort, severity, and relationship to the administration of the study intervention. All SAEs and related SAEs will be categorized separately.

Number of evaluable subjects will be tabulated in whom at least 50% of the intended total number of deposits per brain are successfully intra-operatively delivered. If this occurs in >50% of subjects (eg, 7 subjects out of 12), MSK-DA01 cell transplantation will be deemed feasible.

11.2.3.3. Exploratory Endpoint Analysis

Exploratory outcomes (motor and non-motor signs, symptoms, and quality of life) will stem from various assessments given at baseline, 1 year, and 2 years post transplant.

In general, descriptive statistics including mean, standard deviation, median, minimum, and maximum will be presented for continuous parameters. Categorical parameters will be displayed

using counts and percentages. Various exploratory statistical tests may be applied to data generated from this study to generate hypotheses to be tested in subsequent trials. Longitudinal changes in designated outcome measures will be compared, and correlations between these measures will be examined.

12. Study Administration

12.1. Ethics and Regulatory Considerations

This study will be conducted in accordance with the protocol, all applicable government laws, regulations, and guidances where the study is being conducted including policies with foundations in the World Medical Association Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the Health Insurance Portability and Accountability Act of 1996 (HIPAA) in the US, the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada, and all other applicable medical privacy laws and regulations.

12.1.1. Written Informed Consent

Consent will be obtained for all patients at the Clinical Site, using a consent form with combined elements from the Clinical, Surgical, and PET Imaging Sites. Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign and date the consent form indicating their consent to participate. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, subjects will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of subject privacy concerning research specific information. In addition to signing the informed consent, all subjects must agree to the Research Authorization component of the informed consent form, if applicable.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

12.1.2. Ethics Review

This study will be conducted in accordance with the Good Clinical Practice (GCP) guidelines promulgated by the ICH and any applicable national and local regulations.

Information regarding risks of study participation, possible benefits, in addition to known toxicities and side effects will be provided to potential study participants and will be described in the informed consent document. Potential participants will be informed that an alternative is not to participate in this clinical trial, and that participation is voluntary.

Clinical information and study data will not be released without written permission of the subject, except as necessary for monitoring by the IRB/IEC, the health authorities, or the Sponsor. The PI will assure that the privacy of subjects, including their personal identity and personal medical information, will be maintained at all times, including following local privacy obligations to study subjects.

Subjects will be identified by code numbers on all case report forms (CRFs) and other documents.

12.1.3. Discontinuation of the Clinical Study

The study as represented by this protocol may be modified or discontinued at any time, with approval of the IRB or IEC as warranted, and/or government agencies as part of their duties to ensure that research subjects are protected. If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB or IEC will be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s). Through timely notification of investigators, the sponsor will encourage prompt notification of research subjects with instructions for study drug discontinuation and activities completion to ensure their health and well-being.

12.2. Data Quality Control and Quality Assurance

12.2.1. Data Handling

Subject information and all data collected during pre-enrollment assessment and during the course of the study will be entered onto source document worksheets that correspond to the eCRF. The worksheets will serve as source documents for the eCRFs in a study-specific database. An eCRF will be completed for each subject screened or enrolled according to the subject's source data on a per-visit basis. Authorized study personnel will each be granted access to the electronic data capture tool via provision of a unique password-protected user-ID that will limit access to enter and view data specifically for subjects enrolled. The database has been created by the CRO for this study.

12.2.2. Study Monitoring

12.2.2.1. Data Safety Monitoring Committee

This study will be monitored by a DSMC. Membership of the DSMC will include clinicians with expertise in Neurosurgical Medicine and PD.

The DSMC will initially meet at least quarterly. It will examine risks to which subjects are exposed, progress of the study, adequacy of data storage, and whether sufficient data is being entered into the eCRF. After all subject surgeries have been completed, the DSMC may decrease the frequency of meetings.

12.2.2.2. Steering Committee

The Steering Committee, comprised of the PI, selected investigators and individuals with clinical expertise in neurology, neurosurgery, and ethics, will serve in an advisory capacity to the PI. Meetings will convene on an as-needed basis.

12.2.2.3. Monthly Investigator Teleconferences

Monthly teleconferences will be held with the PI, investigators, and the sponsor to review study activities, including subject accrual, subject retention, study activities, AEs, and timeliness of activities.

12.3. Quality Assurance

The PI will be responsible for ensuring that data entries on the CRFs and in the database are proper and complete. Once the data are entered to the eCRF, they are accessible for review, and the cycle of electronic data entry, review, query identification/resolution, and correction will occur over the course of the study period until all subjects have completed the study.

The Sponsor will conduct standard required processes for quality control and assurance. Monitoring will be performed by the Sponsor or designee. Monitoring will include confirmation of subject eligibility, review of records to confirm that informed consent is properly obtained and procedures are performed according to study protocol, and monitoring of subject accrual. The patient's Electronic Medical Record will be used to compare to the eCRFs to ensure accuracy. Written and verbal feedback will be provided to investigators following all monitoring visits.

Clinical study documentation binders for the clinical protocol will be maintained for each study subject in a privacy-compliant manner. Documentation binders will be made available to the IRB or IEC and other regulatory bodies at any point during the study. Records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medical inventory records, will be retained by the PI in accordance with local health authority regulations. Data will be reported to the IRB or IEC at each continuing review, as required by IRB or IEC Approval.

The PI will review the study data from all visits at the Monthly Investigator Teleconferences. The PI is responsible for monitoring the clinical data and its accuracy, assuring protocol compliance, and conducting the safety reviews for reporting to health authorities.

12.4. Audits and Inspections

The study may be inspected by regulatory agencies, such as the FDA or Health Canada. These inspections may take place at any time during or after the study.

Periodically, the sponsor or its authorized representatives will audit clinical investigative sites as an independent review of core trial processes and documents to determine whether these activities were conducted and whether data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. Details concerning sponsor or its authorized representative's audit and inspections are included in the clinical trial agreement for this study.

A regulatory authority, an IEC, or an IRB may visit the site to perform audits or inspections, including source data verification. The investigator should contact the sponsor or designee immediately if contacted by a regulatory agency about an inspection.

12.5. Study Records Retention

Records and documents pertaining to the conduct of this study and the distribution of investigational drug will be retained by the PI for a duration of time in accordance with applicable local regulations.

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14. APPENDICES

APPENDIX 1. SCHEDULES OF ASSESSMENTS

Table 7: SOA Part 1: Pre-treatment Assessments, and Surgical Intervention and Follow-up

Assessments	**Visit**	**SC**	**BL[a]**	**PrOV[b]**	**Surgical admission[c]**	**Post Op**	**PoOV[d]**
	Week						**1.5**
	Day				**Day 0 is surgery**		**Day 10 (post surgery)**
Window		**-28 days of surgery**	**-28 days of surgery**	**-7 days of surgery**		**Day 1 post surgery**	**±2 days**
Written informed consent		X					
Review inclusion/exclusion criteria		X	X				
Demographic information		X					
Medical history		X	X	X			
Neurological history		X	X				
Concomitant medications		X	X	X			
Parkinson's medications		X	X				
General medical exam		X	X	X			
Neurological exam		X	X		X	X	X
Vital Signs		X	X				
ECG			X	X			
Adverse events[e]		X	X				
Surgical admission (PACU and NACU)					X		
Surgery and MSK-DA01 administration					X		
Use of SCDs					X		
Antibiotics					X		

Assessments	Visit	SC	BL[a]	PrOV[b]	Surgical admission[c]	Post Op	PoOV[d]
	Week						**1.5**
	Day				**Day 0 is surgery**		**Day 10 (post surgery)**
Immunosuppression regimen					X	X	
Physical therapy/occupational therapy consult						X	
Surgical discharge						X	
Suture/staple removal and wound check							X
PD Motor evaluations							
AIMS		X					
Hauser Patient Diary		X	X				
MDS-UPDRS Part III ("OFF" medication state) with video recording		X					
MDS-UPDRS ("ON" medication state) with video recording[f]		X	X				
Modified Schwab and England			X				
UDysRS			X				
10-Meter Walk Gait Speed Test			X				
PD Non-motor evaluations							
BAI-II			X				
BDI-II			X				
C-SSRS			X				
CGI-S			X				

Assessments	Visit	SC	BL[a]	PrOV[b]	Surgical admission[c]	Post Op	PoOV[d]
	Week						1.5
	Day				Day 0 is surgery		Day 10 (post surgery)
HAM-D		X					
MoCA		X	X				
PD Non-motor scale			X				
PDQ-39			X				
QUIP		X	X				
Laboratory testing[g]							
HbA1c		X					
CBC with differential		X		X	X	X	
CMP		X	X	X	X	X	
CMV		X	X				
HIV		X					
HCV		X					
Hepatitis B profile (HbcAb, HbsAb, HbsAg)		X					
QuantiFERON-TB gold Plus		X					
Lipid Profile		X					
Mg/Phos		X	X	X			
Pregnancy test (if applicable)[h]		X					
PT/PTT		X		X	X	X	
RPR (VDRL)		X					
Tacrolimus level							

Assessments	Visit	SC	BL[a]	PrOV[b]	Surgical admission[c]	Post Op	PoOV[d]
	Week						**1.5**
	Day				**Day 0 is surgery**		**Day 10 (post surgery)**
Type and Screen				X			
Uric acid		X	X				
Urinalysis		X		X			
Imaging							
CXR				X			
MRI (or CT if applicable)		X[i]			X	X	
Neuro Navigation MRI				X			
Intraoperative MRI[j]					X		
^{18}F-DOPA PET			X				
Exploratory motor and laboratory testing							
Blood sample for exploratory biomarkers			X				
Blood sample for xenotransplantation assays			X				
Blood sample (DNA)			X				
PKG			X				
Neuropsychological evaluation[k]							
Neuropsychological evaluation			X				

[a] Baseline is a separate visit from screening. Assessments listed in this column must be repeated at the baseline visit, even if they were previously performed at screening, with the exception of neuropsychological evaluation which does not need to be repeated at the baseline visit if performed at screening.
[b] This visit will be carried out either by Geriatrics or Internal Medicine services.
[c] See Section 8.3.2.1 and Section 6.1 for surgical evaluation and admission.
[d] IS01 will be done 7 days post-surgery. The PoOV is 8-12 days post-surgery. The neurological exam will occur at the PoOV, not IS01.

[e] Continuous monitoring of AEs will be performed. At visits marked with "X" subjects will be questioned on AEs during the scheduled study visits.
[f] MDS-UPDRS Part I, Part II, Part III, and Part IV are performed with the subject in the "on medication" state. After completion of the assessment for MDS-UPDRS Part III while "off medication," the subject will resume their current PD medication regimen. The complete MDS-UPDRS will then be assessed while "on medication" ≥60 minutes after the subject resumes their PD medication regimen.
[g] Blood for all laboratory testing for SC, BL, and V01-V09 will be collected by routine venipuncture at the Clinical Site and sent for designated tests. Blood for all laboratory testing for IS01-IS12 will be collected by routine venipuncture and sent for designated tests. Blood tests required for immunosuppression monitoring will be drawn at the Clinical Site during study visits V01-V05 and results will be available to the Immunosuppression Clinician for immunosuppression monitoring.
[h] Pregnancy testing will be performed per local standard of care procedures, at the location of where the pregnancy test will be performed.
[i] For the screening MRI, contrast will be optional.
[j] In Canada, intraoperative MRI will be performed only if clinically indicated.
[k] See Appendix 2 and Section 9.1 and Section 10 for full list of Neuropsychological evaluations
Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BAI-II=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory; BL=baseline; CBC=complete blood count; CXR=chest X-ray; CMP=complete metabolic profile; CMV=cytomegalovirus antibody (IgG, IgM); C-SSRS=Columbia Suicide Severity Rating Scale; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ^{18}F-DOPA PET=fluorodopa F 18 positron emission tomography; CGI-S=Clinical Global Impression-Severity; HAM-D=Hamilton Depression Scale; HbA1c=hemoglobin A1c; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HCV=hepatitis C antibody; HIV=human immunodeficiency virus -1 and -2 antibody enzyme linked immunosorbent assay; MDS-UPDRS=Unified Parkinson's Disease Rating Scale Parts I-V; Mg=magnesium; MRI=magnetic resonance imaging; MoCA=Montreal Cognitive Assessment; MRI=magnetic resonance imaging; NACU=Neurosurgical Advanced Care Unit; PACU= Post-Operative Care Unit; PD=Parkinson's disease; PDQ-39=Parkinson's Disease Questionnaire-39; Phos=phosphorus; PKG=Personal KinetiGraph; PoOV=post-operative evaluation – Neurology (Day 7)/Neurosurgery (Day 10); Post Op=post operation; PrOV=pre-operative evaluation visit; PT=prothrombin time; PTT=partial thromboplastin time; QUIP=Questionnaire for Impulsive Compulsive Disorders in PD; RPR=rapid plasma reagin; SC=screening visit (Clinical Site); SCD=sequential compression device; UDysRS=Unified Dyskinesia Rating Scale; VDRL=Venereal Disease Reference Laboratory.

Table 8: SOA Part 2: Immunosuppression Monitoring and Other Study Visits

Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
Concomitant medications						X				X			X			X			X	X	X	X	X	X	X
Parkinson's medications						X				X			X			X			X	X	X	X	X		
General medical exam			X			X				X			X			X			X	X	X	X	X	X	
Neurological exam						X				X			X			X			X	X	X	X	X		
Vital Signs			X			X				X			X			X			X	X	X	X	X	X	X
Weight						X				X			X			X			X	X	X	X	X		X
ECG																			X				X		
Adverse events[c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immuno-suppression regimen		X																							

Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal	Unscheduled[b]
	Week	**0.5 (D4)**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**16**	**22**	**26**	**30**	**34**	**39**	**43**	**47**	**52**	**65**	**78**	**91**	**104**		
	Month					**1**		**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**15**	**18**	**21**	**24**		
Window				**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**		
Pill diary and medication review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						X
PD Motor evaluations																									
Hauser Patient Diary						X				X			X			X			X	X	X	X	X		
MDS-UPDRS Part III ("OFF" medication state) with video recording										X			X			X			X		X		X	X	
MDS-UPDRS ("ON" medication state) with video recording[d]						X				X			X			X			X	X	X	X	X	X	

Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
Modified Schwab and England						X				X			X						X		X		X	X	
UDysRS						X				X			X			X			X	X	X	X	X		
10-Meter Walk Gait Speed Test										X			X			X			X	X	X	X	X		
PD Non-motor evaluations																									
BAI-II										X			X						X		X		X		
BDI-II										X			X						X		X		X		
C-SSRS						X				X			X			X			X	X	X	X	X		
CGI-S										X			X						X		X		X		
HAM-D																									
MoCA										X			X						X		X		X	X	
PD Non-motor scale										X			X						X		X		X		
PDQ-39										X			X						X		X		X		

Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
QUIP										X			X						X		X		X		
Laboratory testing[e]																									
HbA1c													X						X						
CBC with differential			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	
CMP			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	
CMV						X				X			X			X			X						
Lipid Profile																								X	
Mg/Phos										X			X			X			X						
Tacrolimus level			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Uric acid										X			X			X			X						
Urinalysis						X		X		X	X	X	X	X	X	X	X	X	X						
Imaging																									
MRI						X				X			X						X		X		X		
^{18}F-DOPA PET																			X		X		X		

Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
Exploratory motor and laboratory testing																									
Blood sample for exploratory biomarkers						X							X						X	X	X		X		
Blood sample for xenotransplantation assays						X							X						X				X		
Blood sample (DNA)																									
PKG										X									X				X		
Neuropsychological evaluation[f]																									
Neuropsychological evaluation																			X				X		

[a] See Section 6.1 for IS-0 visit for administration of IV basiliximab for induction phase of immunosuppression.
[b] Additional testing may be warranted based on the Investigator's judgment.
[c] Continuous monitoring of AEs will be performed. At visits marked with "X" subjects will be questioned on AEs during the scheduled study visits.

[d] MDS-UPDRS Part I, Part II, Part III, and Part IV is performed with the subject in the "on medication" state. After completion of the assessment for MDS-UPDRS Part III while "off medication," the subject will resume their current PD medication regimen. The complete MDS-UPDRS will then be assessed while "on medication" ≥60 minutes after the subject resumes their PD medication regimen.
[e] Blood for all laboratory testing for SC, BL, and V01-V09 will be collected by routine venipuncture at the Clinical Site and sent for designated tests. Blood for all laboratory testing for IS01-IS12 will be collected by routine venipuncture and sent for designated tests. Blood tests required for immunosuppression monitoring will be drawn at the Clinical Site during study visits V01-V05 and results will be available to the Immunosuppression Clinician for immunosuppression monitoring.
[f] See Appendix 1 and Section 9.1 and Section 10 for a full list of neuropsychological evaluations.
Abbreviations: BAI-II=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory; BL=baseline; CBC=complete blood count; CMP=complete metabolic profile; CMV=cytomegalovirus antibody (IgG, IgM); C-SSRS=Columbia Suicide Severity Rating Scale; D/d=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ^{18}F-DOPA PET=fluorodopa F 18 positron emission tomography; CGI-S=Clinical Global Impression-Severity; HAM-D=Hamilton Depression Scale; HbA1c=Hemoglobin A1c; IS=immunosuppression monitoring visit; MDS-UPDRS=MDS-Unified Parkinson's Disease Rating Scale Parts I-V; Mg=magnesium; MRI=magnetic resonance imaging; MoCA=Montreal Cognitive Assessment; PD=Parkinson's disease; PDQ-39=Parkinson's Disease Questionnaire-39; Phos=phosphorus; PKG=Personal KinetiGraph; QUIP=Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease; SC=screening visit (Clinical Site); V=visit; wk=week.

APPENDIX 2. DESCRIPTION OF CLINICAL EVALUATIONS AND RATING SCALES, LABORATORY TESTS, AND NEUROIMAGING PROCEDURES

Clinical Evaluations and Rating Scales

10-Meter Walk Gait Speed Test (National Institute of Neurological Disorders and Stroke [NINDS] Common Data Element)

The 10-meter Walk Gait Speed Test assesses walking speed in meters per second over a short duration. The subject will be instructed to walk a set distance of 10 meters 3 times. The time will be measured while the individual walks the set distance. The average time of the 3 attempts will be calculated.

Abnormal Involuntary Movement Scale (AIMS) [ECDEU, 1976]

The AIMS is a 12-item clinician-rated scale to assess severity of dyskinesias (specifically, orofacial movements and extremity and truncal movements) in patients taking neuroleptic medications. Additional items assess the overall severity, incapacitation, and the patient's level of awareness of the movements and distress associated with them.

Beck Anxiety Inventory (BAI-II) [Beck, 1993]

This is a 21-question multiple-choice self-report inventory that is used for measuring the severity of anxiety in children and adults. The questions used in this measure ask about common symptoms of anxiety that the subject has had during the past week.

Beck Depression Inventory (BDI-II) [Beck, 1996]

This is a 21-question multiple-choice self-report inventory. This test is used for measuring the severity of depression.

Chest X-ray

A standard chest X-ray will be performed at PrOV prior to surgery.

Columbia Suicide Severity Rating Scale (C-SSRS) [Posner, 2011]

The C-SSRS is a questionnaire used for suicide assessment developed by multiple institutions. The scale is evidence-supported and is part of a national and international public health initiative involving the assessment of suicidality. A trained professional administers the scale.

Electrocardiogram (ECG)

A standard 12-lead ECG will be performed. Results will be based upon the Investigator's interpretation of standard machine readings and upon the reading by the Clinical Site cardiology laboratory service, or the Clinical Site physician responsible for pre-surgical screening.

Clinical Global Impression-Severity(CGI-S) [Busner, 2007]

The CGI-S is a scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's experience with patients who have the same diagnosis.

Hamilton Depression Rating Scale (HAM-D) [Hamilton, 1960]

The HAM-D scale contains 17 items (HDRS17) pertaining to symptoms of depression experienced over the past week. The scale was designed for completion by the examiner after an unstructured clinical interview with the subject.

Hauser Patient Diary (Hauser, 2000)

The Hauser patient diary will be given out to subjects to be completed at home. Subjects will be given instructions on how to fill out the diary prior to each time they will be asked to fill it out. The home diary includes the categories ASLEEP, OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, and ON with troublesome dyskinesia. The diary data are adjusted for a 16-hour waking day. Patients are instructed to indicate their state based on those categories over the course of 3 days.

Montreal Cognitive Assessment (MoCA) [Nasreddine, 2005]

The MoCA is a rapid screening instrument like the MMSE but was developed to be more sensitive to patients presenting with mild cognitive complaints. It is designated as a NINDS CDE for PD. The MoCA assesses short term and working memory, visual-spatial abilities, executive function, attention, concentration, language and orientation. The total score ranges from 0 to 30 (highest function).

Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS) [Goetz, 2008a]

The same investigator will make every attempt to assess a given subject at all study visits.

The MDS-UPDRS has 4 parts:

- Part I (non-motor experiences of daily living) comprising:
  - Part IA concerning behaviors that are assessed by the investigator with all pertinent information from patients
  - Part IB that is completed by the patient, independently of the investigator.
- Part II (motor experiences of daily living) designed to be a self-administered questionnaire like Part IB but will be reviewed by the investigator to ensure completeness and clarity.
- Part III (motor examination) has instructions for the rater to give or demonstrate to the patient; it is completed by the investigator. The patient will be video-recorded
- Part IV (motor complications) with instructions for the rater and also instructions to be read to the patient. This integrates patient-derived information with the rater's clinical observations and judgments and is completed by the rater.

Subjects will also be scored on the Hoehn and Yahr scale as part of the MDS-UPDRS.

Neurological Exam

A neurological examination, including examination of cranial nerves, motor strength, reflexes, coordination, sensation, and gait and balance, will be performed and recorded.

Neuropsychological Evaluation

A formal neuropsychological evaluation will be conducted to assess each participant's cognition and mood. The cognitive evaluation will consist of a robust battery of standardized tests to measure a variety of cognitive domains, including overall cognitive function, attention/executive functioning, learning/memory, language, visuospatial, and constructional skills. Mood and neurobehavioral status will be examined with a combination of clinician rating scales and self-report measures in order to document baseline cognitive and emotional status as well as objectively establish the presence of postoperative changes. Analysis of cognitive and emotional variables will be used to evaluate post-operative cognitive changes over time with annual evaluations over the course of the study. These tests will supplement more frequent testing of non-motor functions as assessed by MoCA, BAI-II (Beck, 1993), BDI-II (Beck, 1996), and C-SSRS.

Table 9: Neuropsychological Evaluation and Testing

Domain Assessed	Measures
Overall cognitive function (baseline only)	Test of Premorbid Functioning (TOPF) [Pearson, 2009]
Multiple domains (including learning and memory, visuospatial skills, attention, executive function, language)	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [Randolph, 1998]
Attention/executive function	Trail-Making Test A and B (TMT-A and TMT-B) [Reitan, 1985] Stroop Color Word Test (Golden version) [Golden, 1978] Frontal Systems Behavior Scale (FrSBe) [Stout, 2003]
Language	Verbal Fluency: Oral Word Association Test Spreen, 1969)
Mood and neurobehavioral features	Neuropsychiatric Inventory - Questionnaire (NPI-Q) [Cummings, 1997]

- Test of Premorbid Functioning (TOPF) [Pearson, 2009]
  - The TOPF was designed to estimate subjects' cognitive and memory functioning prior to the onset of illness or disease. The test asks participants to read a list comprised of 70 words, in order of increasing difficulty, which feature irregular relationships between words' pronunciations as compared to the words' spellings (ie, words with irregular grapheme-to-phoneme translation). The ability to read and pronounce previously learned words of this type seems less affected by the cognitive dysfunction introduced by illness or disease than other measures of

intellectual and memory functioning; because of this, the TOPF provides a robust estimate of individuals' premorbid cognitive functioning with vocabulary level serving as a correlate to IQ. Test of Premorbid Functioning estimates an individual's pre-morbid cognitive and memory functioning. It is a revised and updated version of the Wechsler Test of Adult Reading™ and helps predict pre-injury IQ and memory abilities.

- The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [Randolph, 1998]
  - The RBANS is a reliable and valid measure of multiple cognitive domains including attention, visuospatial abilities, language, as well as both immediate and delayed memory, and it has been used extensively in a variety of patient populations. A major advantage of the RBANS is that it has the benefit of providing subscales scores for each of the domains assessed, as well as 1 total standard score that summarizes the individual's overall neurocognitive status. This instrument yields a concise set of summary scores that can promote efficient data analysis and interpretation.
- Trail-Making Test A and B (TMT-A and TMT-B) [Reitan, 1985]
  - TMT-A requires an individual to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper. Task requirements are similar for TMT-B except the subject will be asked to alternate between numbers and letters (eg, 1, A, 2, B, 3, C, etc.). The score on each part represents the amount of time required to complete the task.
- Stroop Color Word Test (Golden, 1978)
  - The Stroop Task is a test measuring executive function. It involves participants reading a list of words for colors, such as blue, red, or green, but the words are printed in a color different to the word itself. The goal of the task is to name the color of the ink the words are printed in.
- Frontal Systems Behavior Scale (FrSBe) [Stout, 2003; Batistuzzo, 2009]
  - The FrSBe provides a brief, reliable, and valid measure of 3 frontal systems behavioral syndromes: apathy, disinhibition, and executive dysfunction. It also quantifies behavioral changes over time by including both baseline (retrospective) and current assessments of behavior.
- Verbal Fluency: Oral Word Association Test (Spreen, 1969)
  - The Verbal Fluency Test involves asking the participant to name words beginning with a letter, excluding proper nouns, for 1 minute and this procedure is repeated 3 times. The most commons letters used are F, A, S because of their frequency in the English language.
- Neuropsychiatric Inventory- Questionnaire (NPI-Q) [Cummings, 1997]
  - The NPI-Q was developed to assess psychopathology and evaluates 12 neuropsychiatric disturbances in terms of severity and frequency: delusions,

hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behavior disturbances, and appetite and eating abnormalities. It is administered to the study participant partner.

Parkinson's Disease Questionnaire (PDQ-39) [Peto, 1995]

The PDQ-39 is a PD specific health status questionnaire comprising 39 items. Respondents are requested to pick 1 of 5 ordered response categories according to how often, due to their PD, they have experienced the problem defined by each item. Items are grouped into 8 scales that are scored by expressing summed item scores as a percentage score ranging between 0 and 100.

Personal KinetiGraph (Griffiths, 2012) [PKG; Global Kinetics Corporation]

This FDA-approved wearable device objectively measures bradykinesia and dyskinesia in PD. It is worn as a wristband. Measurements are based upon accelerometry, with a novel algorithm allowing collection of a bradykinesia score and dyskinesia score every 2 minutes over a standard 6-day period. It is in clinical use in a number of institutions, including the Clinical Sites. Participants will be asked to wear this device continuously for 7 days. Research assistants will verbally instruct them at the baseline visit, with refresher instructions at each subsequent visit. After the 7 days, the study participant will mail in the device to the study center using a pre-paid pre-addressed envelope. The data is uploaded to a cloud-based platform with results then provided to the PI by Global Kinetics. No identifying information, no clinical data, and no data collected other than that on the PKG device is uploaded nor supplied by any means to the Global Kinetics platform, nor Global Kinetics personnel.

PD Non-Motor Symptoms Scale (NMSS) [Chaudhuri, 2004]

The PD NMSS is a questionnaire administered by the investigator, aimed to assess non-motor symptoms in individuals with PD.

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) [Weintraub, 2012]

The QUIP is a self-administered rating scale is designed to measure severity of symptoms and support a diagnosis of impulse control disorders and related disorders in PD.

General Medical Exam

A general medical examination will be comprised of a skin examination, head/neck/lymphatic, eyes, ears/nose/throat, cardiovascular, lungs, abdomen, musculoskeletal, neurological, and psychiatric systems.

Modified Schwab and England Activities of Daily Living Scale (McRae, 2002)

The Schwab and England scale is an Investigator and subject assessment of the subject's level of independence. The subject will be scored on a percentage scale reflective of his/her ability to perform acts of daily living. Printed scores with associated descriptors range from 100% to 0% in increments of 10%, where 100% is "subject has full ability and is completely independent; essentially normal" and 0% is "vegetative functions such as swallowing, bladder and bowel

functions are not functioning; bedridden." Scores should be coded in increments of 5 (ie, 90%, 80%).

Unified Dyskinesia Rating Scale (UDysRS) [Goetz, 2008b]

The UDysRS is developed to evaluate involuntary movements often associated with treated PD. The scale has 2 parts: Historical and Objective. The scale provides measurements for "on-dyskinesia" and "off-dyskinesia."

Vital Signs, Orthostatic Changes, Weight, and Height

Blood pressure and heart rate (supine and standing), and body weight will be measured at every visit. Height will be measured at the Baseline Visit only.

Clinical Laboratory Assessments

- Blood tests performed as indicated in Appendix 1 include the following:
  - Hepatitis C antibody
  - Hepatitis B profile
  - Human immunodeficiency virus (HIV; HIV-1 and -2 antibody ELISA)
  - Lipid profile
  - Rapid plasma reagin (VDRL)
  - QuantiFERON-TB gold Plus
  - Type and screen
  - Prothrombin time
  - Partial thromboplastin time
  - Complete metabolic profile (CMP): The CMP is a made up of 14 tests – glucose, calcium, sodium, potassium, CO_2, chloride, blood urea nitrogen, creatinine, albumin, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and bilirubin. Gamma glutamyl transpeptidase will also be collected at screening.
  - CBC with differential (hematocrit, hemoglobin, platelet count, RBC indices, total RBC, total WBC, and WBC and differential)
  - Magnesium/phosphorus
- Hemoglobin A1c
- Uric acid
- The following blood tests for immunosuppression monitoring will be obtained:
  - CMP
  - CBC with differential

  - CMV (IgG, IgM) serum antibody screening
  - Tacrolimus level
  - Exploratory biomarkers. Please see details outlined in "Additional blood samples for archiving and exploratory endpoints" section of this document.
- Blood samples for storage as recommended in the case of xenotransplantation will be collected in accordance with Appendix 1 and cryopreserved.
- Urine pregnancy testing will be performed on female subjects of childbearing potential in accordance with Appendix 1.
- Urinalysis will be performed in accordance with Appendix 1.

Samples obtained at the Clinical Site will be analyzed at a local laboratory, except for blood for exploratory biomarkers and xenotransplantation.

Samples obtained at the Surgical Site will be analyzed at a local laboratory.

The investigators may order additional testing, if needed, to further assess an adverse event (AE), or if there is any suspicion that a subject may be pregnant, throughout the course of the study.

Neuroimaging Procedures

Brain Magnetic Resonance Imaging (MRI)

Brain MRI will additionally be performed at intervals during the study (see Appendix 1) in order to evaluate structural changes associated with engrafted cells, edema or inflammation, and importantly to monitor for cellular overgrowth, and development of structural abnormalities such as cysts, or development of potential tumors.

Sequences will be performed as follows:

Gadolinium contrast will be administered at the baseline MRI scan, for imaging with and without contrast. If subsequent MRI scans reveals abnormal signal that could reflect potential AEs, such as cell overgrowth, tumor formation, or edema, then after discussion of the radiologist with the investigators, a repeat brain MRI may be implemented with and without gadolinium contrast.

Pre-operative planning MRI: Brain MRI for surgical planning will be performed within 1 week of surgical admission.

^{18}F-DOPA positron emission tomography (PET) study (Luxen, 1990; Dhawan, 2002)

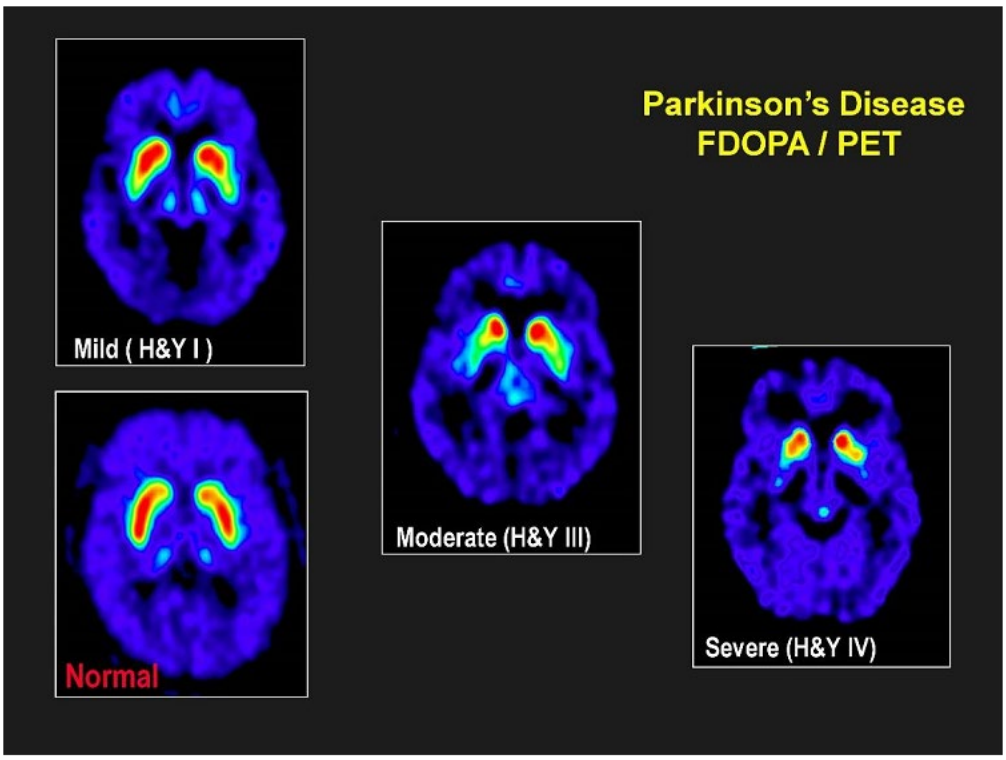
^{18}F-DOPA PET scanning will be performed at the PET Imaging Site.

^{18}F-DOPA PET scanning will be performed at Baseline, V05, V07, and V09 (see Appendix 1).

^{18}F-DOPA is produced on-site in the cyclotron/radiochemistry facility at the Feinstein Institute for Medical Research (FIMR) as reported elsewhere. All participants will receive nothing orally (except water) 4 hours prior to scanning and must stop antiparkinsonian medication 12 hours prior to scanning. Participants will be pretreated with 150 mg of carbidopa given orally within 120 minutes prior to the injection of ^{18}F-DOPA. (Carbidopa pre-administration is to prevent AAAD decarboxylation of ^{18}F-DOPA and thereby to increase the bioavailability of the drug substance in the brain. There are no known side effects for carbidopa when used alone.)

Participants are injected intravenously with 5.0 mCi of ^{18}F-DOPA with a lower limit of 3.0 mCi in the event that production yield is lower than expected. Subjects are encouraged to void approximately 70 minutes post injection in order to reduce radiation exposure to the bladder. A 9-second CT attenuation correction scan will be acquired followed by the acquisition of 3-dimensional PET images about 80 to 100 minutes (4 × 5 minute frames) post injection using a new high resolution/sensitivity PET tomograph (GE Discovery IQ-5 ring PET/CT scanner, General Electric Medical Systems, Milwaukee, WI: FWHM=5 mm, axial FOV=26 cm, slice thickness=3.3 mm, 79 slices) at FIMR. At the end of the scanning procedure, the patient is to void again to reduce bladder wall radiation. All women will be screened for pregnancy prior to scanning. Women of childbearing potential will be subject to a urine pregnancy test within 30 days prior to each PET scan.

Figure 3: Representative PET scan with ^{18}F-DOPA



Abbreviations: ^{18}F-DOPA=fluorodopa F 18; H&Y=Hoehn and Yahr; PET=positron emission tomography.

Figure 3 is an image of a representative PET scan with ^{18}F-DOPA at the PET Imaging Site demonstrating feasibility to perform PET scans at that site. Previous studies indicate that the signal of ^{18}F-DOPA uptake in the posterior putamen is reduced by approximately 40% compared to normal control values in PD patients. The Feinstein Institute has performed numerous previous studies using human ^{18}F-DOPA PET imaging.

Image Archival/Transfer

All PET scans will be stored as DICOM® (Digital Imaging and Communications in Medicine) files after removing any protected health information that may identify the subject. An electronic version of PET worksheet will also be created containing specifics such as subject weight, dose

administered and time of injection. These files will be saved on a password-protected computer server at the PET Imaging Site for further analysis or transfer to the sponsor. An online file transfer protocol site will be set up locally or at the sponsor site to facilitate secure electronic transfer of PET images and PET worksheet along with 1 high-resolution structural MRI scan acquired at the enrolling site (the latter is needed to define anatomical regions of interest in the striatum).

Image Analysis

^{18}F-DOPA PET images will be analyzed to calculate ^{18}F-DOPA uptake in the striatum. Definition of striatal subregions in each subject will be defined by using a high-resolution anatomical MRI scan acquired separately during neurosurgery. Additional analyses may be performed on the PET imaging data; further details regarding analysis methods and calculations will be outlined in the SAP.

Additional Blood Samples for Archiving and Exploratory Endpoints

(i) At Month 1, Month 6, Month 12, Month 15, Month 18, and Month 24 approximately 17 mL of whole blood will be collected in two 6 mL heparin tubes and one 5 mL standard serum tube, processed to separate out plasma or serum, and aliquoted for storage at -80°C. These samples will be used for inflammation assays, assessment of donor cell allo-recognition by anti-human leukocyte antigen screen and potential biomarkers for PD.

(ii) At Month 1, Month 6, Month 12, and Month 24, approximately 12 mL of whole blood (one 6 mL ethylene diamine tetra-acetic acid tube and one 6 mL heparin tube) will be collected and processed for storage at -80°C. These samples will be used for potential future study of latent viruses or pathogens.

(iii) At Baseline, 8.5 mL of whole blood will be collected for preparation of DNA by standard venipuncture into a PAXgene collection tube and processed for DNA biobanking and testing of the genetic signature of PD.

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SUMMARY OF CHANGES

The major changes incorporated into this protocol (Version 2.0) are summarized in the table below. Editorial and formatting changes are not included in this summary.

Section Number	Summary of Change	Rationale for Change
Synopsis (Endpoints) 5.2.2 Secondary Endpoints 11.2.2 Efficacy Analyses	Revised the secondary endpoint to "ON" time without troublesome dyskinesia, not "OFF" time.	More accurate description of measure of clinical state
Synopsis (Endpoints) 5.2.3 Exploratory Endpoints	Revised exploratory endpoints to enumerate other states measured by the Hauser diary that are not enumerated in secondary endpoints.	Clarification
4.3 Immunosuppressive Regimen	Revised language regarding choice of immunosuppressants to delete daclizumab.	Daclizumab is no longer approved for use worldwide.
Synopsis (Inclusion Criteria) 7.1 Subject Inclusion Criteria	Clarified that the Abnormal Involuntary Movement Scale (AIMS) score needed for subject inclusion refers to the rating per body part, not the total AIMS score.	Clarification
Synopsis (Inclusion Criteria) 7.1 Subject Inclusion Criteria	Revised language of inclusion criterion regarding clinical laboratory results to say "unless abnormality is not clinically significant."	Clarification
Synopsis (Exclusion Criteria) 7.2 Subject Exclusion Criteria	Clarified the use of QuantiFERON-TB gold Plus for the screening tuberculosis test.	Clarification
Synopsis (Exclusion Criteria) 7.2 Subject Exclusion Criteria	Added metric measurements along with imperial to maximum subject weight.	Clarification
6.1.2.1 Surgical Intervention 8.3.2.1 Overall Treatment Plan 8.3.2.2 Surgical Procedure 8.3.3.1. Stopping Rules for Injection of the Contralateral (Second) Putamen	Removed the stipulation to operate on the right putamen first; rephrased as "first putamen" and "contralateral putamen."	Clarification
6.1.2.2 Schedule of Surgical Interventions	Added language to allow for the surgical date to be delayed by up to 8 weeks without the need for rescreening.	Clarification/request of investigators
6.1.1 Design 6.1.2.3 Immunosuppression 8.3.6 Immunosuppressive Therapy 9.2.2 Outpatient Follow-up	Changed the location of the Day 4 basiliximab and the Day 10 suture/staple removal to any Clinical or Surgical site	Clarification/request of investigators to allow travel flexibility for subjects

Section Number	Summary of Change	Rationale for Change
8.3.6 Immunosuppressive Therapy	Revised language regarding post-surgery steroids to clarify that oral prednisone will be tapered.	Clarification
9.1 Screening/Baseline Assessments	Added language regarding the requirement for subjects to have been vaccinated against SARS-CoV-2.	Clarification
12.2.2.1 Data Safety Monitoring Committee	Added language allowing the data safety monitoring committee (DSMC) to decrease the frequency of meetings after all surgeries have been completed.	Clarification
Appendix 1 Schedules of Assessments (Table 4)	Added a footnote clarifying that baseline is a separate visit from screening and that assessments listed under the baseline visit should be performed even if they were done at screening.	Clarification requested by site coordinators
Appendix 1 Schedules of Assessments (Table 5)	Deleted X for neurological exam under Visit IS01, as it is already covered in Table 4.	Correction
Appendix 1 Schedules of Assessments (Tables 4 and 5)	Revised Schedule of Assessments to have separate lines for the MDS Unified Parkinson's Disease Rating Scale (UPDRS) in the "OFF" medication state and in the "ON" medication state.	Clarification
Appendix 2 Description of Clinical Evaluations and Rating Scales, Laboratory Tests and Neuroimaging Procedures	Added language to clarify that the data in the Hauser Diary are adjusted for a 16-hour waking day.	Clarification
Appendix 2 Description of Clinical Evaluations and Rating Scales, Laboratory Tests and Neuroimaging Procedures	Deleted text specifying the location at which MRIs will be performed.	Clarification

SUMMARY OF CHANGES

The major changes incorporated into this protocol (Global, Version 3.0) compared to the United States protocol, Version 2.0, are summarized in the table below. Editorial and formatting changes are not included in this summary.

Section Number	Summary of Change	Rationale for Change
4.2.1 Investigational Therapy: MSK-DA01	Revised description of the ventricular cannula to remove specific product name.	Harmonization of protocols for the United States and Canada into one global protocol.
4.3 Immunosuppressive Regimen	Added language regarding patients being managed according to standard of care in the event of a reaction.	Harmonization of protocols for the United States and Canada into one global protocol. Additional text requested by Health Canada added from the Canada protocol.
4.6. Previous Experience with Cell Transplantation 6.1.2.1 Surgical Intervention 8.3.2.1 Overall Treatment Plan 8.3.3.1 Stopping Rules for Injection of the Contralateral (Second) Putamen Appendix 1 Schedules of Assessments (Table 7)	Specified that in Canada, the intraoperative magnetic resonance imaging will be performed only if clinically indicated.	Harmonization of protocols for the United States and Canada into one global protocol.
Synopsis 4.7.1. Rationale for the Study Population	Specified the separate study age ranges for each country.	Harmonization of protocols for the United States and Canada into one global protocol.
Synopsis 4.8.2 Rationale and Justification for Immunosuppression 6.1.2.3 Immunosuppression 8.3.6 Immunosuppressive Therapy	Revised language regarding the recommended starting dose of tacrolimus to remove the specification to start at a dose of 1 mg and instead start at 0.05 mg/kg and adjust to a target trough level.	Allows for weight-based dosing and to obtain more rapid titration to therapeutic levels. Also allows for flexibility according to local clinical practice and for adjustments based on drug-drug interactions.
4.8.2 Rationale and Justification for Immunosuppression	Added rationale, including regimens, for doses of immunosuppressive agents.	Harmonization of protocols for the United States and Canada into one global protocol.
Synopsis 5.2.2 Secondary Endpoints 6.1.1 Design 6.1.2.1 Surgical Intervention 6.2 Number of Subjects 6.4 Treatment Assignment 11 Statistics	Changed number of total subjects from 10 to 12. Changed number of subjects in Cohort B from 5 to 7. Changed number of subjects in the definition of feasibility from 6/10 to 7/12.	To increase the size of the safety cohort prior to conducting Phase 2 studies.
6.1.1 Design	Added text about sharing data from Cohort A with the data safety monitoring committee, Medical Monitor, and Principal Investigator(s) to aid the decision to initiate dosing in Cohort B.	Harmonization of protocols for the United States and Canada into one global protocol.

Section Number	Summary of Change	Rationale for Change
6.1.2.1 Surgical Intervention	Add statement that the final decision to initiate Cohort B ultimately lies with the Sponsor.	Harmonization of protocols for the United States and Canada into one global protocol.
6.1.2.2 Schedule of Surgical Interventions	Revised language regarding the 3-week staggering of surgeries overall to require approximately 2-week staggering within a surgical site.	All post-surgical risks are evident within 2 weeks of the procedure, and the first 2 subjects receiving DA01 have not had surgical complications.
6.5 Criteria for Study Termination	Added the term "independent ethics committee" as authority to stop or temporarily suspend the study.	Harmonization of protocols for the United States and Canada into one global protocol.
Synopsis 7.1 Subject Inclusion Criteria	Revised language of inclusion criterion regarding age to provide separate ranges for the United States and Canada. Revised language of baseline Hoehn and Yahr score to provide separate criteria for the United States and Canada. Designated the inclusion criterion regarding deep brain stimulation as being for the United States only.	Harmonization of protocols for the United States and Canada into one global protocol.
8.2 Description of Investigational Administration Device System	Added separate subsections to apply to the United States and Canada (kept existing language for United States and added language for Canada).	Harmonization of protocols for the United States and Canada into one global protocol.
8.3.6 Immunosuppressive Therapy	Added text and table regarding decisions to delay, reduce, or discontinue immunosuppressive drugs prior to 1 year.	Harmonization of protocols for the United States and Canada into one global protocol. Additional text requested by Health Canada added from the Canada protocol.
9.1.1 Screening Visit Appendix 1 Schedules of Assessments (Table 7)	Specified that for the screening magnetic resonance imaging (MRI), contrast is optional.	Requested by sites to limit exposure to the contrast agent.
10.2.5 Reporting Adverse Events	Added language to clarify that the requirement for notifying the Regulatory Project Manager at the Food and Drug Administration (FDA) in case finalized test results are not available prior to product release applies only to the United States.	Harmonization of protocols for the United States and Canada into one global protocol.
10.2.5.1 Serious Adverse Events Require Immediate Reporting to Sponsor/Designee	Edited a subheading to clarify that serious adverse event reporting to ClearPoint Neuro is applicable only to the United States.	Harmonization of protocols for the United States and Canada into one global protocol.

Section Number	Summary of Change	Rationale for Change
10.2.5.2 Sponsor Safety Reporting to Regulatory Authorities	Added language clarifying that safety reporting will be done according to Canadian regulations as well as United States regulations.	Harmonization of protocols for the United States and Canada into one global protocol.
12.1 Ethics and Regulatory Considerations	Added language mentioning Canada's privacy act as well as the United States' Health Insurance Portability and Accountability Act (HIPAA).	Harmonization of protocols for the United States and Canada into one global protocol.
12.4 Audits and Inspections	Added mentions of Health Canada and independent ethics committee (IEC) in addition to United States-specific terms.	Harmonization of protocols for the United States and Canada into one global protocol.
Appendix 2 Description of Clinical Evaluations and Rating Scales, Laboratory Tests and Neuroimaging Procedures	Revised language regarding voiding post injection to change from "30 to 60 minutes" to "approximately 70 minutes" post injection. Added "Gamma glutamyl transpeptidase will also be collected at screening." To Complete Metabolic Profile.	Correction

SUMMARY OF CHANGES

The major changes incorporated into this protocol (Version 3.1, dated 12 August 2021) relative to the prior approved version (Version 3.0, dated 03 August 2021) are summarized in the table below. This change was included in the summary of changes and redline submitted for Version 3.0 but was inadvertently not included in the final version of the protocol. Editorial and formatting changes are not included in this summary.

Section Number	Summary of Change	Rationale for Change
Appendix 2 Description of Clinical Evaluations and Rating Scales, Laboratory Tests and Neuroimaging Procedures	Added "Gamma glutamyl transpeptidase will also be collected at screening" to Complete Metabolic Profile.	Correction

SUMMARY OF CHANGES

The major changes incorporated into this protocol (Version 4.0, dated 05 November 2021) relative to the prior approved version (Version 3.1, dated 12 August 2021) are summarized in the table below. Editorial and formatting changes are not included in this summary.

Section Number	Summary of Change	Rationale for Change
Synopsis Section 4.7.1 Rationale for the Study Population Section 7.1 Subject Inclusion Criteria	Increased the upper age limit from 76 to 78 years old	This change in the upper age limit is consistent with an advanced PD population, which is the target population for this study. The safety of including patients up to 78 years of age is not considered to be increased as these patients who also meet the other inclusion/exclusion criteria are not expected to be at any greater risk from treatment.
Synopsis Section 4.7.1 Rationale for the Study Population Section 7.1 Subject Inclusion Criteria	Lowered the minimum time from PD diagnosis from 5 to 3 years	This change allows for the inclusion of patients who may have had a delay in PD diagnosis. Assurance of enrolling a population with advanced PD is maintained through other inclusion/exclusion criteria, such as the daily "off" time, and 3 years is sufficient for confirmed diagnosis of PD. Delay in diagnosis is commonly observed in minorities and non-English speaking patients with PD; thus, this change will also help to facilitate enrollment of a more diverse population consistent with plans for latter development of MSK-DA01.
Synopsis Section 4.7.1 Rationale for the Study Population Section 7.1 Subject Inclusion Criteria	Increased the maximum time from PD diagnosis from 15 to 20 years	Time from PD diagnosis is not linearly correlated with disease severity, and patients with excessive disease severity will not be included in the study based on other inclusion/exclusion criteria. This change allows for the inclusion of patients who are consistent with an advanced PD population.
Synopsis Section 7.1 Subject Inclusion Criteria	Decreased defined levodopa response from ≥40% to ≥30% improvement	A defined levodopa response of ≥30% improvement is more consistent with the other inclusion/exclusion criteria to capture the target population for treatment with MSK-DA01.

Section Number	Summary of Change	Rationale for Change
Synopsis Section 4.7.1 Rationale for the Study Population Section 7.1 Subject Inclusion Criteria	For Canada, increased the Hoehn and Yahr score from "0 to 2" to "0 to 3"	A Hoehn and Yahr score of 3 is more consistent with the other inclusion/exclusion criteria (eg, "off" time of ≥2 hours daily) to capture the target population for treatment with MSK-DA01.
Synopsis Section 7.1 Subject Inclusion Criteria	Updated the text to indicate a MoCA score of ≥22 is allowed if no significant cognitive impairment as determined by the site neurologist by neuropsychological testing	MoCA is an efficient screening tool but a MoCA score of <26 does not always correlate with cognitive impairment; thus, MoCA ≥22 is allowed when paired with neuropsychological testing to provide a more robust assessment of cognitive impairment.
Synopsis Section 11.2 Statistical Methodology	Clarified that the analyses performed with 1 year's and 2 years' worth of data will take place when all available subjects have reached those timepoints	This clarification was made to account for subjects who may discontinue early from the study and will never have 1 year's or 2 years' worth of data.
Section 10.2.4 Recording Adverse Events Section 10.2.5 Reporting Adverse Events	Clarified that follow-up of AEs/SAEs after the last day of study participation will exclude subjects who have withdrawn their consent for follow-up and subjects who have signed informed consent for a BlueRock-sponsored long-term follow-up study	This clarification was made to abide by the rights of the patient to withdraw consent for follow-up and to avoid duplication of data collection between the treatment study and the long-term follow-up study.

SUMMARY OF CHANGES

The major changes incorporated into this protocol (Version 5.0, dated 08 November 2022) relative to the prior approved version (Version 4.0, dated 05 November 2021) are summarized in the table below. Nonsubstantial changes are bulleted below the table. Editorial and formatting changes are not included in this summary.

Section Number	Summary of Change	Rationale for Change
Synopsis Section 4.4 ^{18}F-DOPA Positron Emission Tomography Section 5.1.2 Secondary Objectives Section 5.2.2 Secondary Endpoints Section 6.1.1 Design Section 9.2.3.7 Visit 07 (Month 18±1 week) Section 11.2.2 Efficacy Analyses Appendix 1 Schedule of Assessments Appendix 2 Description of Clinical Evaluations and Rating Scales, Laboratory Tests, and Neuroimaging Procedures	Added an ^{18}F-DOPA PET scan to the PET Imaging Site Visit 07 (Month 18±1 week) and clarified that women of childbearing potential will be subject to a urine pregnancy test on the day of the PET scan. Also clarified that the change in ^{18}F-DOPA uptake using PET would be calculated from baseline through 2 years. Additional analyses may be performed on the PET imaging data; further details regarding analysis methods and calculations will be outlined in the SAP.	An additional scan is still within the dosimetric safety range for brain imaging and will provide another time point to assess engraftment and differentiation of MSK-DA01 cells over time.
Section 9 Study Assessments Appendix 1 Schedule of Assessments Appendix 2 Description of Clinical Evaluations and Rating Scales, Laboratory Tests, and Neuroimaging Procedures	Clarified that the modified Hoehn and Yahr scale will not be used.	The Movement Disorder Society Task Force for Rating Scales for PD concluded that the modified Hoehn and Yahr scale should not be used due to a lack of clinimetric testing. The electronic data capture system contains the standard scale as part of the MDS-UPDRS. Subjects will be scored on the standard Hoehn and Yahr scale at the Screening Visit, Baseline Visit, Months 1, 3, 6, 9, 12, 15, 18, 21, 24, and the Early Withdrawal Visit.

The nonsubstantial changes are as follows:

- Updated sponsor information and address.
- Removed the following sentence—Incidence of SAEs will be tabulated at 1 year post transplant—from the statistical methods section in the synopsis because it is redundant with the description of the primary endpoint analysis in the same section.
- In Section 4.2.1 and Section 8.2.2, clarified that the modification from the US 510(k)-approved SmartFlow® cannula was cleared for investigational use in this study.
- In Section 4.8.2, Section 6.1.2.3, and Section 8.3.6, clarified that use of tacrolimus extended-release once daily formulation is permitted, as noted in the Immunosuppression Manual.
- In Section 6.1.1, clarified that all evaluable subjects will be asked to enroll in a follow-up study upon their completion of this study. In Section 9.2.5 and Section 11, removed details of the follow-up study as it is a separate study and should not be included in the current study assessments or statistical analyses.
- In Section 9.2.3.3 and Appendix 1, clarified that MDS-UPDRS assessment in the "off medication" state is specific to Part III only; subjects will resume their current PD medication regimen before completing MDS-UPDRS Part I, Part II, Part III, and Part IV in the "on medication" state.
- In Section 10.2, clarified that AEs will be collected and attributed to the VC, MSK-DA01 cells, syringe, surgery, ^{18}F-DOPA PET scan, MRI, immunosuppression regimen, and/or disease for consistency throughout the protocol.
- In Section 10.2.5.1, clarified that SAE reporting is required from informed consent through the end of the study regardless of attribution.
- In Section 11.2, clarified that the database will be locked after all subjects dosed reach Year 2 or discontinue from the study.
- In Section 11.2.3.2, clarified that all AEs and related AEs will be summarized; all SAEs and related SAEs will be categorized separately.
- In Appendix 2, clarified blood samples for collection and storage to better align with the ICF; samples may be used for inflammation and biomarker assays as described in the ICF.

STATISTICAL ANALYSIS PLAN

BlueRock Therapeutics LP

MSK-DA01-101

Protocol Title:	Phase 1 Study To Assess the Safety and Tolerability of Human Embryonic Stem Cell-Derived Midbrain Dopamine Neuron Cell Therapy (MSK-DA01) For Advanced Parkinson's Disease (STEM-Parkinsons)
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Sponsor:	BlueRock Therapeutics LP 238 Main Street, 3rd Floor Cambridge, MA 02142 USA
Prepared By:	[redacted] Precision for Medicine 6005 Hidden Valley Road, Suite 170 Carlsbad, CA 92011
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1 STATISTICAL ANALYSIS PLAN APPROVAL

Sponsor:	BlueRock Therapeutics LP
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Protocol Title:	Phase 1 Study to Assess the Safety and Tolerability of Human Embryonic Stem Cell-Derived Midbrain Dopamine Neuron Cell Therapy (MSK-DA01) For Advanced Parkinson's Disease (STEM-Parkinsons)
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DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 24-May-2023 | 4:56:44 PM EDT
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[redacted] **Date**

[redacted], Biostatistics
BlueRock Therapeutics LP

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 24-May-2023 | 5:23:39 PM EDT
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[redacted] **Date**

[redacted] Clinical Development
BlueRock Therapeutics LP

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[redacted]
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[redacted]
[redacted]
Precision for Medicine

Date

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[redacted]
Signer Name: [redacted]
Signing Reason: I have reviewed this document
Signing Time: 24-May-2023 | 3:55:38 PM PDT
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[redacted]
[redacted] **Biostatistics**
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Date

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3 LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Definition
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BAI-II	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory
BMI	body mass index
BUN	blood urea nitrogen
CGI-S	Clinical Global Impression-Severity
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CMV	cytomegalovirus
CTCAE	Common Terminology Criteria for Adverse Events
DA	dopamine
DNA	deoxyribonucleic acid
DSMC	data safety monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
^{18}F-DOPA	6-[18F]fluoro-L-3,4-dihydroxyphenylalanine
FrSBe	Frontal Systems Behavior Scale
GGT	gamma glutamyl transpeptidase
HAM-D	Hamilton Depression Rating Scale
ICH	International Council for Harmonisation
INR	International Normalized Ratio
LDH	lactate dehydrogenase
LEDD	levodopa equivalent daily dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDS	Movement Disorder Society

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
NACU	Neurosurgical Advanced Care Unit
NCI	National Cancer Institute
NMSS	Non-Motor Symptoms Scale
NPI-Q	Neuropsychiatric Inventory – Questionnaire
PD	Parkinson's disease
PDQ-39	39-Item Parkinson's Disease Questionnaire summary index
PACU	Post-Operative Care Unit
PET	positron emission tomography
PI	principal investigator
PKG	Personal KinetiGraph
PoOV	post-operative evaluation
PT	prothrombin time; Preferred Term
QUIP	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease
RBC	red blood cell
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
SI	Système International
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TMT-A	Trail Making Test Part A
TMT-B	Trail Making Test Part B
TOPF	Test of Premorbid Functioning
UDysRS	Unified Dyskinesia Rating Scale
UPDRS	Unified Parkinson's Disease Rating Scale
WBC	white blood cell
WHO	World Health Organization

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for BlueRock Therapeutics Protocol MSK-DA01-101 (Phase 1 Study to Assess the Safety and Tolerability of Human Embryonic Stem Cell-Derived Midbrain Dopamine Neuron Cell Therapy [MSK-DA01] For Advanced Parkinson's Disease (STEM-Parkinsons)). The statistical methods applied in the design and planned analyses of this study are consistent with the International Council for Harmonisation (ICH) guideline *Statistical Principles for Clinical Trials* (E9) (1998).

This SAP will be finalized and approved prior to the data freeze for the primary analysis at Year 1. The Year 1 data freeze will correspond to the date of the last evaluable subject's 1 Year visit, to include all data from all evaluable subjects up to and including this date. The SAP may be amended after the Year 1 analysis is complete and prior to final database lock at Year 2 to include further details of the final analysis. Templates for tables, listings, and figures will be provided in a separate document. Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein.

5 STUDY OBJECTIVES

5.1 Primary Study Objective

The primary objective of this study is to assess the safety and tolerability of MSK-DA01 cell transplantation at 1-year post transplant.

5.2 Secondary Study Objectives

The secondary objectives of this study at Year 1 are to:

- Assess the evidence of transplanted cell survival and motor effects through 1-year post transplant
- Assess feasibility of transplantation

5.3 Exploratory Objectives

The exploratory objectives of this study are to:

- Determine the effects of MSK-DA01 transplantation upon motor and non-motor signs and symptoms of Parkinson's disease (PD) and upon accelerometry-based measures of motor function
- Assess the subject's perception of their quality of life

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design

This is a Phase 1 multi-site, multi-center, open-label study of MSK-DA01 in patients with advanced Parkinson's disease experiencing motor symptoms inadequately relieved by standard treatments. Approximately 12 subjects will undergo a single surgical transplantation of 1 of 2 different dose levels of MSK-DA01 cells to the post-commissural putamen bilaterally.

Initiation of an immunosuppressive regimen will occur during the surgical procedure and continue over the period of 1 year. In the event of a reaction to the immunosuppressive regimen, subjects will be managed according to standard of care in consultation with the Immunosuppression Clinician; dose reduction or alternative or equivalent medications may be considered.

Following surgery, subjects will receive supportive care. Subjects will be discharged to home once deemed medically ready by the Principal Investigator (PI) or co-investigators. Hospitalization may extend past 24-hours if required in the opinion of the investigative or clinical team.

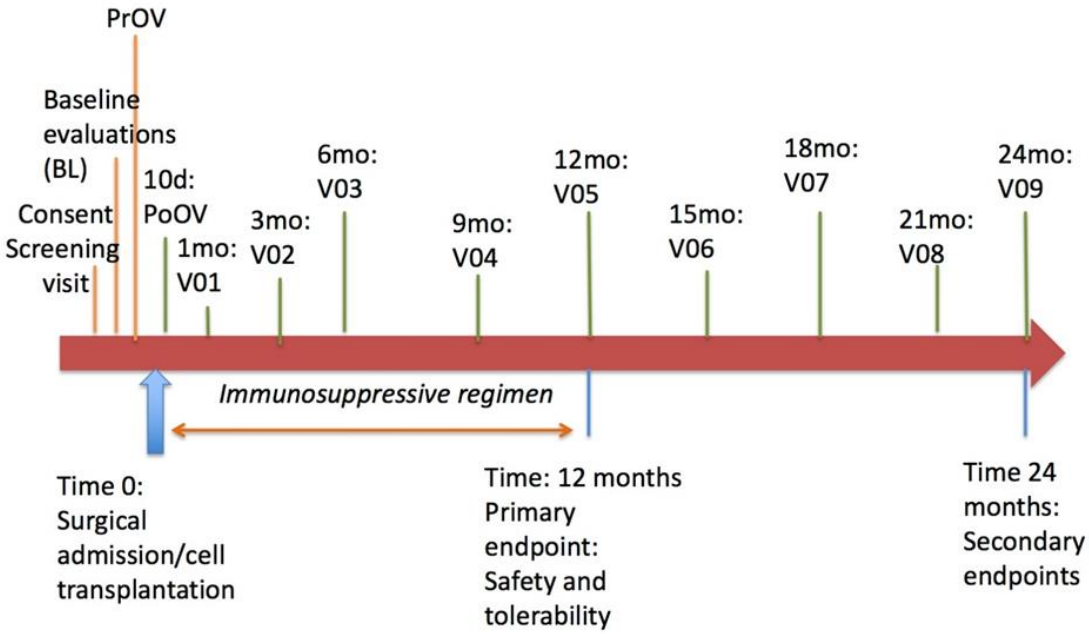
Following hospital discharge, subjects will have follow-up evaluations at approximately 7 days and 10 days post-operatively for post-operative evaluation (PoOV) including neurological evaluations. Figure 1 details the study design.

For any subject who is unable to attend an in-person follow-up visit, study staff will try to complete the visit activities that do not require face-to-face interaction by contacting the participant via telephone, telemedicine, email, or mail. Contact from the study staff will occur during the pre-established study visit windows.

All evaluable subjects will be asked to enroll in a separate follow-up study to continue comprehensive visits following their completion of this study.

This multi-site study includes a Surgical Site, Clinical Site, and positron emission tomography (PET) Imaging Site. Subjects will sign 1 consent document at the Clinical Site that includes consent components for the 3 sites. One study participant partner ("Caregiver") will be recruited and consented to the study with each subject. Three study centers are participating in this study.

Figure 1: Study Design



Abbreviations: BL=baseline; d=day; mo=month; PoOV=post-operative evaluation – Neurology (Day 7)/Neurosurgery (Day 10); PrOV=pre-operative evaluation visit; V=visit.

6.2 Schedule of Assessments

A detailed schedule of assessments for the study is provided in the Appendix, Table 3 and Table 4.

6.3 Treatments

6.3.1 Treatments Administered

6.3.1.1 Surgical Intracerebral Transplantation of MSK-DA01 Cells

MSK-DA01 is an experimental cell product for the treatment of PD that is primarily composed of heSC-derived mDA neurons. Subjects will undergo a surgical intervention that involves a single session stereotactic injection of dopamine (DA) neurons (MSK-DA01) in both putamina. Cells will be injected in 3 separate tracks through a single burr hole in the frontal area on each side, with 3 cell deposits per track. Two cell dose levels will be examined, Cohort A will receive

0.9 million cells per putamen (Dose A) of MSK-DA01 and Cohort B will receive 2.7 million cells per putamen (Dose B).

6.3.1.2 Immunosuppression

The immunosuppression regimen consists of the following:

- Basiliximab (administered intravenously)
- Methylprednisolone (administered intravenously)
- Tacrolimus (administered orally)
- Prednisone (administered orally)

The following medications are related to the immunosuppression protocol:

- Sulfamethoxazole/Trimethoprim (administered orally)
- Omeprazole (administered orally)

6.3.2 Method of Assigning Subjects to Treatment Groups

This is a first-in-human study of MSK-DA01 and therefore the optimal dose is not known in humans. The cell dose for injection was selected based upon a target of surviving cell dose, while knowing the cell survival rate of the same batch of cells nominated for clinical use from extensive preclinical studies.

The first 5 subjects (Cohort A) will receive Dose A (0.9 million cells per putamen) and subsequent subjects (Cohort B) will receive Dose B (2.7 million cells per putamen). Data from Cohort A will be shared with the data safety monitoring committee (DSMC), the Medical Monitor, and the Principal Investigator(s) prior to initiating dosing in Cohort B. The decision to initiate dosing in Cohort B will be made consistent with the recommendation from the DSMC.

6.4 Efficacy and Safety Variables

6.4.1 Efficacy Variables

6.4.1.1 Imaging

Change from baseline in striatal ^{18}F-DOPA uptake using PET. ^{18}F-DOPA is used to evaluate uptake of DA precursors attributable to survival and differentiation of transplanted cells into dopaminergic neurons. There will be two ^{18}F-DOPA methods performed: Method 1 (magnetic resonance imaging [MRI] based method) and Method 2 (PET based method). Method 1 will be used for analysis with Method 2 and any additional methods being considered for exploratory purposes only.

6.4.1.2 Levodopa Equivalent Daily Dose (LEDD)

Change from baseline in anti-PD medications use, as standardized to the levodopa equivalent daily dose (LEDD). The LEDD is the sum of daily anti-PD disease medications converted to the LEDD using appropriate conversion factors. All medications recorded on case report form (CRF) pages Prior and Concomitant Medications, Surgical Related Concomitant Medications, and Parkinson's Disease Medication Log will be considered in the LEDD (Appendix, Table 5 and Table 6.)

6.4.1.3 PD Motor Evaluations

- Baseline Abnormal Involuntary Movement Scale (AIMS) scores. AIMS is a 12-item clinician-rated scale to assess severity of dyskinesia patients taking neuroleptic medications (Appendix, Table 7).

- Change from baseline in the Hauser Patient Diary daily time in the following categories: asleep, off, good on (on without dyskinesia + on with non-troublesome dyskinesia), on without dyskinesia, on with non-troublesome dyskinesia, and on with troublesome dyskinesia. For each visit, subjects are instructed to indicate their state over the course of 3 days. The awake diary data are adjusted for a 16-hour waking day (Appendix, Table 8).

- Change from baseline in the Movement Disorder Society -Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores: Part I, Part II, Part III (ON State), Part III (OFF State), Part IV, Part 1 + Part II + Part III (ON State), and Part II + Part III (ON State), (Appendix, Table 9).

- Baseline Hoehn and Yahr score, as collected in the MDS-UPDRS Part III (ON State) and Part III (OFF State). Stage ranges from 0 (Asymptomatic) to 5 (Wheelchair bound or bedridden unless aided).

- Change from baseline in the Modified Schwab and England Activities of Daily Living Scale. The consensus rating is reflective of the subject's ability to perform acts of daily living ranging from 0% (Vegetative functions such as swallowing, bladder, and bowel functions are not functioning. Bedridden) to 100% (Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty). Scores are recorded in increments of 5%.

- Change from baseline in the 10-meter Walk Gait Speed Test time (meters/second). At each visit, the subject will be instructed to walk a set distance of 6, 8, or 10 meters 3 times and the average speed of the 3 attempts will be recorded.

6.4.1.4 PD Non-Motor Evaluations

- Change from baseline in the Beck Anxiety Inventory (BAI-II) total score. The BAI-II is used to measure the severity of anxiety on a 21-question self-reported inventory on a scale of 0 to

3 with a total possible score of 0 to 63 with a higher score indicating more severe anxiety (Appendix, 10).

- Change from baseline in the Beck Depression Inventory (BDI-II) total score. The BDI-II is used to measure the severity of depression on a 21-question self-reported inventory on a scale of 0 to 3 with a total possible score of 0 to 63 with a higher score indicating more severe depression (Appendix, Table 11).

- Change from baseline in the Clinical Global Impression-Severity (CGI-S) scale. The CGI-S requires the clinician to rate the severity of the illness at the time of the assessment, relative to the clinician's experience with patients who have the same diagnosis on a scale of 1 (Normal, not at all ill) to 7 (Among the most extremely ill patients).

- Change from baseline in the Montreal Cognitive Assessment (MoCA) total score. The MoCA is used for early detection of mild cognitive impairment and designated for use in PD (Appendix, Table 12).

- Change from baseline in the PD Non-Motor Symptoms Scale (NMSS) on the nine domains and total score. The NMSS is a 30-question item questionnaire administered by the investigator, aimed to assess non-motor symptoms in individuals with PD (Appendix, Table 13).

- Change from baseline in the Parkinson's Disease Questionnaire-39 (PDQ-39) sub scores and summary index score. Respondents are requested to pick 1 of 5 ordered response categories according to how often, due to their PD, they have experienced the problem defined by each of 39 items (Appendix, Table 14).

6.4.1.5 Neuropsychological Evaluations

- Change from baseline in the Test of Premorbid Functioning (TOPF) total raw and standard scores. The TOPF was designed to estimate subjects' cognitive and memory functioning prior to the onset of illness or disease and uses a revised and updated version of the Wechsler Test of Adult Reading. The TOPF is based on a reading paradigm, requiring reading and pronunciation of words in which the examinee stops after five incorrect responses. The total raw score ranges from 0 to 70.

- Change from baseline in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score. The RBANS is a reliable and valid measure of multiple cognitive domains resulting in subscale scores for each of the domains assessed, as well as 1 total standard score that summarizes a subject's overall neurocognitive status and a total scale score that ranges from 40 to 160 with a higher score being better (Appendix, Table 15).

- Change from baseline in the Trail-Making Test A and B (TMT-A and TMT-B) scored as time to complete each task in seconds. The tasks require the subject to draw lines or write

numbers/letters with TMT-A and TMT-B time being recorded separately. TMT-A has a maximum time of 150 seconds and TMT-B has a maximum time of 300 seconds.

- Change from baseline in the Stroop Color Word Test (Golden version) scores. The Stroop Color Word Test is a test measuring executive function involving reading a list of words for colors but the words are printed in a color different to the word itself. The goal of the task is to name the color of the ink the words are printed in.

- Change from baseline in the Frontal Systems Behavior Scale (FrSBe) scores. The 46-item FrSBe provides a measure of frontal systems behavioral syndromes and quantifies behavioral changes over time by including both baseline (retrospective) and current assessments of behavior. The 46-items are rated on a scale of 1 (almost never) to 5 (almost always). Four scores are obtained: Total, Apathy, Disinhibition and Executive. Scores greater than T = 65 are considered clinically significant, (Appendix, Table 166).

- Change from baseline in the Verbal Fluency: Oral Word Association Test score. This test involves asking the participant to name words beginning with a letter, excluding proper nouns, for 1 minute. The procedure is repeated 3 times with a total score to count the number of responses.

- Change from baseline in the Neuropsychiatric Inventory – Questionnaire (NPI-Q) scores. The NPI-Q assesses psychopathy and neuropsychiatric disturbances severity of symptoms present within the last month and the associated impact of the symptom manifestations (caregiver distress), (Appendix, Table 177).

6.4.2 Safety Variables

6.4.2.1 Adverse Events

An adverse event (AE) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An AE can arise with any use of the drug (eg, off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

All AEs with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for serious adverse events (SAEs)) after the last day of study participation will be recorded, except for subjects who have withdrawn their consent for follow-up or subjects who are actively being followed in a BlueRock-sponsored follow-up study.

Treatment-Emergent Adverse Events

Treatment-emergent AEs will start after the first dose of any immunosuppressive medication.

Serious Adverse Events

An AE is considered serious if it results in any of the following outcomes:

- Death
- A life-threatening AE
- An AE that results in subject hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the subject or subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

Relationship to Study Intervention

All AEs will be attributed to the cannula, cell product, ^{18}F-DOPA PET scan, MRI, syringe, surgery, immunosuppression regimen, and/or disease.

6.4.2.2 MRI

Brain MRIs will be performed (Appendix, Table 3 and Table 4). Post-operative MRIs will be performed to evaluate structural changes associated with engrafted cells, edema or inflammation, and importantly to monitor for cellular overgrowth, and development of structural abnormalities such as cysts, or development of potential tumors.

6.4.2.3 Laboratory Parameters

The following laboratory assessments will be collected:

- Hematology: hematocrit, hemoglobin, platelet count, red blood cell (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell (WBC), WBC differentials
- Chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, creatinine, gamma glutamyl transpeptidase (GGT), glucose, sodium, potassium, uric acid, magnesium, phosphorus, total bilirubin, total protein, lactate dehydrogenase (LDH)

- Coagulation: prothrombin time (PT), activated partial thromboplastin time (aPTT), International Normalized Ratio (INR)
- Urinalysis: specific gravity, pH, glucose, blood, protein, ketones, leukocytes, RBC, casts
- Serology: human immunodeficiency virus (HIV), hepatitis C antibody (HCV), hepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb), hepatitis B surface antigen (HBsAg), QuantiFERON-TB gold plus, rapid plasma reagin (RPR)
- Cytomegalovirus (CMV): IgG and IgM, CMV PCR test result
- Lipid Profile: cholesterol, HDL-C, LDL-C, triglycerides
- Tacrolimus
- HbA1c

6.4.2.4 General Medical Examination

A general medical examination will be performed including examination of skin, head/neck/lymphatic, eyes, ears/nose/throat, cardiovascular, lungs, abdomen, musculoskeletal, neurological and psychiatric systems.

6.4.2.5 Electrocardiogram (ECG)

A standard 12-lead electrocardiogram (ECG) will be performed (heart rate, PR interval, RR interval, QRS duration, QT interval, QTcB interval, QTcF interval, cardiologist interpretation). Results will be based upon the Investigator's interpretation of standard machine readings and upon the reading by the Clinical Site cardiology laboratory service or the Clinical Site physician responsible for pre-surgical screening.

6.4.2.6 Vital Signs

Systolic and diastolic blood pressure and heart rate (seated and standing), and body weight will be measured. Height will be measured at the Baseline visit only.

6.4.2.7 Feasibility of Transplantation

Feasibility of transplantation is defined by intra-operative delivery of at least 50% of the intended total number of deposits per brain in >50% of subjects. The intended number of deposits is defined as the neurosurgeon's planned trajectories times the number of cellular deposits per deposit as determined during the procedure.

6.4.2.8 Unified Dyskinesia Rating Scale (UDysRS)

Change from baseline in the Unified Dyskinesia Rating Scale (UDysRS) scores. The UDysRS evaluates involuntary movements often associated with treated PD. UDysRS is made up of two primary sections: Historical (On-Dyskinesia and Off-Dystonia) and Objective (Impairment and Disability), (Appendix, Table 188).

6.4.2.9 Columbia Suicide Severity Rating Scale (C-SSRS) and Hamilton Depression Rating Scale (HAM-D)

Change from baseline in the Columbia Suicide Severity Rating Scale (C-SSRS) scores. C-SSRS is part of a national and international public health initiative involving the assessment of suicidality (Appendix, Table 199).

Baseline Hamilton Depression Rating Scale (HAM-D) total score measuring symptoms of depression experienced over the last week. The HAM-D scoring is based on 17 items with a total score of 0 to 53. Categories for levels of depression can be derived from the total score (Appendix, Table 20).

6.4.2.10 Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease (QUIP)

Change from baseline in the Questionnaire for Impulsive Compulsive Disorders in PD (QUIP) scores. The QUIP is a self-administered rating scale designed to measure severity of symptoms and support a diagnosis of impulse control disorder and related disorders in PD (Appendix, Table 211).

6.4.2.11 Assessment of Dyskinesia

The following will be used for the assessment of dyskinesia:

- MDS-UPDRS Part III: Dyskinesia Impact on Part III Ratings (ON and OFF State)
- MDS-UPDRS Part IV: Time Spent with Dyskinesia
- MDS-UPDRS Part IV: Functional Impact of Dyskinesia
- MDS-UPDRS Part IV: Total Score
- UDysRS Historical Part 1A: Time Spent with On-Dyskinesia
- UDysRS Historical Part 1B: Patient Dyskinesia Questionnaire
- UDysRS Objective Part 3: Impairment

- UDysRS Objective Part 4: Disability
- Hauser Patient Diary daily on time with non-troublesome dyskinesia (adjusted for a 16-hour waking day)
- Hauser Patient Diary daily on time with troublesome dyskinesia (adjusted for a 16-hour waking day)
- Adverse Events of Dyskinesia
- LEDD

6.4.3 Description of Pharmacokinetic Variables

No pharmacokinetic endpoints are collected for this study.

6.4.4 Biomarker, Xenotransplantation Assays, and DNA

Blood samples will be collected and stored for future exploration of biomarker, DNA and xenotransplantation assays.

6.5 Data Quality Assurance

Report summaries will be generated using validated Base SAS® software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.

7 STATISTICAL METHODS

7.1 General Methodology

Statistical analyses will be reported with tables and listings, presented in rich text format, and using numbering recommended by International Council for Harmonisation (ICH). Output specifications for all tables and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the *Electronic Common Technical Document Specification* (Apr 2003).

7.1.1 Reporting Conventions

Tables will be summarized by cohort and overall. In general, all data collected, and any derived data, will be presented in subject data listings for all subject in the enrolled population. Listings of informed consent and eligibility criteria, re-consent, and screen failures will be presented for all subjects. Listings will be ordered by cohort, subject number, and assessment or event date.

In general, continuous variables will be summarized to indicate the study population sample size (N), number of subjects with available data (n), mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by the population size (N), number of subjects with available data (n), number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects in the dose cohort or total column being summarized. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of subjects in each category, as appropriate.

Non-zero, non-one hundred percentages will be rounded to one decimal place; zero and one hundred percentages will be displayed as a whole number. Tables that summarize categorical data will present data as "0," if the number of events is zero. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the electronic case report form [eCRF] or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization.
- Measures of variability (e.g., SD, SE) will be rounded to two more decimal places than the precision of the variable of summarization;
- Minimum and maximum values will be presented using the same precision as the variable of summarization; and
- Percent change from baseline calculations will maintain the precision of the change from baseline calculations.

Other statistics (e.g., CIs) will be presented using the same general rules outlined above or assessed for the most appropriate presentation based on the underlying data.

No formal statistical analysis will be performed to compare treatment groups. This study is exploratory in nature; descriptive statistics will be tabulated by cohort and reviewed to evaluate all study endpoints.

7.1.2 Summarization by Visit

Data summarized by study visit will be based on the nominal, scheduled visit label as reported on the eCRF.

Data collected at unscheduled visits will not be included in by-visit summaries but will be considered when endpoint derivations potentially include multiple visits (eg, determination of baseline value, determination of worst post-baseline value, etc.). All data will be included in subject listings.

7.1.3 Definition of Baseline

Unless otherwise specified, the baseline value is defined as the last recorded value prior to the first dose of immunosuppressive drugs or cell transplant surgery, whichever is earlier.

7.1.4 Standard Calculations

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on subject data listings, where study day will be determined as:

- The assessment/event date minus the date of surgery, if the assessment/event date is prior to the date of surgery; and
- The assessment/event date minus the date of surgery, plus one, if the assessment/event date is on or after the date of surgery.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated using the following conventions:
    - Later date – earlier date + 1, if the earlier date is on or after the date of surgery; or
    - Later date – earlier date, if the earlier date is prior to the date of surgery.
- **Months:** A duration expressed in months will be calculated by dividing the duration in days by (365.25 / 12);
- **Years:** A duration expressed in years will be calculated by dividing the duration in days by 365.25;
- **Change from Baseline:** Change from baseline will be calculated as the post-baseline value minus the baseline value;
- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100. When the

baseline value equals 0 and the change from baseline is not equal to 0, the percentage change is not calculated.

7.1.5 Partial Dates and Times

7.1.5.1 Start Dates (eg. event date, AE onset date, or start of medication)

- For missing start day only: Day will be imputed as the first day of the month (ie, 1) with the following exception: if the partial date falls in the same month and year as the date being used in the calculation (eg, first administration date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.

- For missing start day and month: Day and month will be imputed as the first day of the year (ie, 1 January) with the following exception: if the partial date falls in the same year as the date being used in the calculation (eg, first administration date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.

- Imputed start dates must be prior to the stop date.

7.1.5.2 Stop Dates (eg, AE resolution date, or stop date of medication)

- For missing stop day only: Day will be imputed as the last day of the month (ie, 28, 29, 30, or 31) with the following exception: if the partial date falls in the same month and year as the date being used in the calculation (eg, date of study discontinuation), then the partial date will be imputed to equal the date being used for the calculation.

- For missing stop day and month: Day and month will be imputed as the last day of the year (ie, 31 December) with the following exception: if the partial date falls in the same year as the date being used in the calculation (eg, date of study discontinuation), then the partial date will be imputed to equal the date being used for the calculation.

- For missing stop day, month, and year: The date will be imputed as the date that the patient discontinued the study.

- Imputed stop dates must be on or after the start date.

7.1.6 Data Handling Rules

Unless otherwise noted, values reported as less than some quantifiable limit (e.g., "< 1.0") will be set equal to that limit multiplied by ".999," and values reported as greater than or equal to some quantifiable limit (e.g., "≥1.0") will be set equal to that limit multiplied by "1.001," and summarized as such in tables and figures. Data will display on subject listings to include the sign.

7.2 Analysis Populations

The analysis populations are defined as follows:

- Safety Population: Includes all enrolled subjects who receive any immunosuppression drugs or undergo surgical intervention. The safety population will be used for all safety, baseline and demographic analyses.

- Evaluable Population: Includes all subjects who provide informed consent, meet all inclusion criteria and no exclusion criteria, and successfully undergo surgical intervention to receive any amount of cell transplantation. The evaluable population will be used for all efficacy analyses.

7.3 Study Subjects

7.3.1 Disposition of Subjects

Subject disposition will be summarized for all subjects by cohort and over all subjects combined. Summaries will include the number and percentage of subjects in each analysis population, ongoing in study, completed the study, and terminated the study early by the reason for termination.

A data listing of all the above disposition data will be presented by cohort and subject. Data listings by cohort and subject of informed consent (for subject and caregiver) and eligibility criteria details, re-consent (for subject and caregiver), and screen fail details will also be presented.

7.3.2 Protocol Deviations

Important protocol deviations will be summarized by cohort and over all subjects combined for the Safety Population. Important protocol deviations captured on-study are deemed by the Sponsor to potentially impact the efficacy or safety conclusions of the study.

Prior to the 1 Year data freeze, all important protocol deviations and eligibility violations will be determined and appropriately categorized. They may include, but are not limited to, the following groups:

- Inclusion/Exclusion – Subjects entered into the study even though they did not meet the inclusion criteria, diagnosis not confirmed as per protocol, major discrepancy between the medical history information in the source documents and the information used to determine eligibility, etc.

- Significant Lack of Adherence with Immunosuppression or Immunosuppression related medications

- Surgery

- Issue with Study Device (cannula/syringe)
- Cell Delivery (less than 50% of intended total deposits)
- Assessment conducted by unqualified personnel

- Missing baseline or safety measurements/assessments

The number and percentage of subjects with any important protocol violations as well as the number and percentage of subjects within each category will be presented. A data listing of all protocol deviations by cohort and subject will be presented.

7.4 Efficacy Evaluation

7.4.1 Datasets Analyzed

All efficacy summaries will be based on the Evaluable Population and will present all data up to and including the Week 52 (Year 1) visit.

7.4.2 Demographic and Other Baseline Characteristics

Demographic variables including age (as derived on the CRF), sex, childbearing potential of females, ethnicity and race will be summarized by cohort and over all subjects combined for the Safety Population.

Age will be summarized using descriptive statistics. Sex, childbearing potential of females, ethnicity, and race will be summarized with the number and percentage of subjects in each parameter category.

Baseline characteristics include height, weight, and body mass index (BMI). BMI will be calculated as: weight (kg) / [height (cm) / 100]^2.

Additional baseline measurements will be summarized including:

- Time since PD Diagnosis (years)
- Hoehn and Yahr (OFF state and ON state)
- MDS-UPDRS Part III (OFF state and ON state)
- MDS-UPDRS Total Score (Part I + Part II + Part III (ON state))
- Adjusted Hauser Patient Diary time (hours) in the following awake categories: OFF state, Good ON state, ON state without dyskinesia, ON state with non-troublesome dyskinesia, ON state with troublesome dyskinesia, and unadjusted asleep time.

- PDQ-39 Summary index
- AIMS

Baseline measures will be summarized for the Safety Population by cohort and over all subjects combined. Baseline measures will be summarized using descriptive statistics except for Hoehn and Yahr (OFF state and ON state) which will be summarized with the number and percentage of subjects in each category.

All demographic and baseline characteristic data will be listed by cohort and subject.

7.4.2.1 Medical and Neurological Histories

Medical and neurological histories will be coded to System Organ Class (SOC) and Preferred Term (PT) using MedDRA version 23.0 or later. Frequency counts and percentages will summarize medical and neurological histories by cohort and over all subjects combined and by SOC and PT for the Safety Population. At each level of summarization (SOC and PT), subjects reporting more than one medical or neurological history event are counted only once. All medical and neurological history data will be presented in data listings by cohort and subject.

7.4.3 Efficacy Endpoint Analysis Methods

7.4.3.1 ^{18}F-DOPA Uptake Using PET Scan

^{18}F-DOPA uptake will be summarized by cohort for the Evaluable population. Descriptive statistics will be presented for the observed uptake values and percent change in uptake from baseline at each visit where F-DOPA PET scans were performed. Subject data collected from the F-DOPA PET scans will be presented in listings by cohort and subject.

Additional exploratory F-DOPA analysis may also be performed.

7.4.3.2 Anti-PD Medication Use (LEDD)

LEDD will be summarized using descriptive statistics for observed values, change from baseline and percent change from baseline and cohort for the Evaluable population. Change from baseline mean figures will be presented by cohort in addition to individual subject figures of LEDD (mg) by study day. LEDD will also be summarized by study day in a listing by cohort and subject.

7.4.3.3 PD Motor, PD Non-motor, and Neuropsychological Evaluations

The following assessments will be summarized by cohort and overall using the Evaluable Population. Descriptive statistics will be presented for results, change from baseline and percent change from baseline at each visit where assessments were scheduled to be collected per the clinical study protocol:

PD Motor Evaluations: • Hauser Patient Diary Measures • MDS-UPDRS Scores • Modified Schwab and England Activities of Daily Living Scale • 10-Meter Walk Gait Speed Test Time
PD Non-Motor Evaluations: • BAI-II Score • BDI-II Score • CGI-S Scale • MoCA Score • NMSS Score • PDQ-39 Score
Neuropsychological Evaluations: • TOPF • RBANS Score • TMT-A and TMT-B Score • Stroop Color Word Test Score • FrSBe Score • Verbal Fluency: Oral Word Association Test Score • NPI-Q Score

HAM-D will be summarized with descriptive statistics for total score at the baseline visit in addition to summarizing the levels of depression with the number and percentage of subjects in each category.

In addition to descriptive statistics, CGI-S scores are categorized in the order of best to worst as, "Normal, Not at All Ill," "Borderline Ill," "Mildly Ill," "Moderately Ill," "Markedly Ill," "Severely Ill," or "Among the Most Extremely Ill," will be presented in a seven-by-seven contingency table to summarize the shift from the baseline category to the worst post-baseline measurement at each visit. Summary results will include the count and percentage of subjects within each shift category and cohort. Percentages are based on the number of subjects with available data at both baseline and post-baseline time points.

Hauser Patient Diary Measures, MDS-UPDRS Scores, and PQD-39 Score will be presented in figures. All PD motor, PD non-motor, and neuropsychological evaluation data will be presented in subject data listings by cohort and subject.

7.4.3.4 Measures of Correlation

Correlation between the following pairs of variables will be assessed separately:

- UPDRS Part III (OFF State) change from baseline score at Week 52 visit vs. age at screening

- UPDRS Part III (OFF State) change from baseline score at Week 52 visit vs. duration of PD at screening
- UPDRS Part III (OFF State) change from baseline score at Week 52 visit vs. MDS-UPDRS Part III (OFF State) score at screening
- FDOPA uptake % change from baseline at Week 52 visit vs. UPDRS Part III (OFF State) change from baseline score
- FDOPA uptake % change from baseline at Week 52 visit vs. age at screening
- FDOPA uptake % change from baseline at Week 52 visit vs. duration of PD at screening

Scatterplots of individual subject values will be provided, with Cohort A and Cohort B subjects denoted. The figures will also include the estimate resulting from a linear regression model. Additional measures of correlation may also be assessed for exploratory purposes.

7.4.4 Statistical/Analytical Issues

7.4.4.1 Adjustments for Covariates

There are no planned applications of covariate adjustments; all statistical results are descriptive in nature.

7.4.4.2 Handling of Dropouts or Missing Data

No imputations will be performed on missing data for the 1 Year analysis; all analyses will be based on observed data only. Imputations may be considered for the final analysis.

7.4.4.3 Interim Analyses and Data Monitoring

7.4.4.3.1 Primary Analyses

A formal analysis of the primary endpoint will be performed when the last evaluable subject has reached Week 52 (Year 1). At that time, a data freeze will occur and the primary analyses to address safety and tolerability will be performed. Analysis of secondary and exploratory aims is also planned.

The primary analysis will be performed on data collected as of the data freeze date (last evaluable subjects' Week 52 visit) to include all data from all evaluable subjects up to and including this date. Efficacy summaries will summarize through the Week 52 visit only.

Additional data cuts may be needed to support data analysis for internal business decision making, regulatory agency interactions, and updating the scientific community. In such cases, a

subset of the planned tables, figures and listings may be produced. The details of such a data cut will be provided in the footnotes of the associated tables, figures, and listings.

7.4.4.3.2 Data Monitoring

This study will be monitored by a DSMC. Membership of the DSMC will include clinicians with expertise in Neurosurgical Medicine and PD. It will examine risks to which subjects are exposed, progress of the study, adequacy of data storage, and whether sufficient data is being entered into the eCRF. This will be carried out as detailed in the DSMC charter and is outside the scope of this SAP.

7.4.4.4 Multicenter Studies

This is a multicenter and multisite study, with 3 sites expected to participate. Efficacy and safety data collected from all study centers and sites will be pooled for data analysis.

7.4.4.5 Multiple Comparisons/Multiplicity

There will be no adjustments for multiple comparisons in the efficacy analysis for this study. Results are descriptive in nature and there will be no formal comparisons made among cohorts.

7.4.4.6 Use of an "Efficacy Subset" of Subjects

The efficacy analyses will be performed on the Evaluable Population.

7.4.4.7 Examination of Subgroups

There are no planned analyses to assess efficacy results by subgroups.

7.5 Safety Evaluation

Safety analysis will be carried out for the Safety Population and will present all data included in the Week 52 (Year 1) data freeze. Subjects who do not complete the study, for whatever reason, will have all available data up until the time of termination included in the analysis.

7.5.1.1 Extent of Exposure and Compliance with Immunosuppression and Immunosuppressive Related Drug Regimens

The immunosuppression regimen and immunosuppression related medications will be summarized using the information recorded on the Immunosuppression Regimen and Immunosuppression Drugs Accountability Log CRFs. Summaries will present descriptive statistics for the Safety Population by cohort and overall for duration of exposure, total dose received, and compliance for each medication defined in Section 6.3.1.2. In addition to descriptive statistics, the number and percentage of subjects who are < 80% compliant and ≥ 80% compliant will be summarized. Descriptions for medication summaries are provided below:

Summary	Immunosuppression Regimen Medications and Immunosuppression Related Medications	Description of Summary
Duration of Exposure	Basiliximab Methylprednisolone Tacrolimus Prednisone Sulfamethoxazole/Trimethroprim Omeprazole	Duration of exposure in days will be determined as the date of the last dose of medication – the date of the first dose of the medication + 1.
Total Dose Received	Basiliximab Methylprednisolone Tacrolimus Prednisone Sulfamethoxazole/Trimethroprim Omeprazole	Total dose received will be determined by summing the total dose administered (Immunosuppression Regimen) and total dose dispensed (Immunosuppression Drugs Accountability Log) for the duration of exposure.
Compliance	Prednisone Sulfamethoxazole/Trimethoprim Omeprazole Tacrolimus	Compliance will be determined as the total dose taken divided by the expected total dose dispensed, multiplied by 100. Expected dose dispensed will be determined by Section 8.3.6 of the Protocol.
	Basiliximab Methylprednisolone	Compliance will be determined as the total dose administered divided by the total expected dose administered, multiplied by 100. Expected dose administered will be determined by Section 8.3.6 of the Protocol.
Therapeutic Range	Tacrolimus	Therapeutic range will be determined by number of Tacrolimus laboratory measurements in which Tacrolimus was in the therapeutic range of ≥ 4 ng/mL divided by the total number of Tacrolimus laboratory measurements, multiplied by 100.

In addition to summaries for each medication, combined summaries for immunosuppression compliance will be presented to include the following:

- Perioperative compliance defined as Basiliximab + Methylprednisolone compliance
- Postoperative compliance defined as Tacrolimus + Prednisone compliance

Subject data listings by cohort and subject will be presented for the individual and combined medication summaries. Individual subject figures of Tacrolimus (ng/mL) by visit will be presented with the therapeutic range included on the figure. Immunosuppression regimen, including the drug accountability log, will be presented in subject data listings by cohort and subject.

7.5.1.2 Surgical Delivery of MSK-DA01

Surgical information related to delivery of MSK-DA01 cells will be summarized using descriptive statistics for the Safety Population by cohort and overall and will include:

- Number of tracks – 0 to 6 (Right Hemisphere Anterior Trajectory, Right Hemisphere Mid Trajectory, Right Hemisphere Posterior Trajectory, Left Hemisphere Anterior Trajectory, Left Hemisphere Mid Trajectory, Left Hemisphere Posterior Trajectory)
- Number of deposits – 0 to 18 (3 per track)
- Position of deposits (Inferior, Middle, Superior)
- Estimated cell numbers delivered per deposit recorded during surgery (µL)
- Percentage of target deposits delivered per putamen (for target deposits refer to Table 4 and Table 5 of Protocol)

All surgical information will also be presented in a subject data listing by cohort and subject.

7.5.2 Adverse Events

Treatment-emergent adverse events (TEAEs) will be summarized by cohort and overall for number of subjects and number of events. Events reported with a partial onset date (e.g., month and year are reported but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of immunosuppressive drug based on the available date entries.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.0). Adverse events will be graded according to the U.S. Department of Health and Human Services National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

Summary	**Description**
Overall TEAE Summary	• Number of TEAEs • Number of treatment-emergent serious adverse events (TESAEs)

	• Number of TEAEs and TESAEs meeting various criteria
Overall TESAE Summary at 1 Year	• Number of TESAEs • Number of subjects and events with TESAEs related to surgery, cell product or immunosuppression • Number of subjects developing a tumor or abnormal tissue overgrowth related to presence of transplanted cells • Number of subjects developing an intracerebral hemorrhage that is deemed life threatening • Number of deaths including cause of death
TEAE Incidence	Number of TEAEs by MedDRA system organ class and preferred term
TESAE Incidence	Number of TESAEs by MedDRA system organ class and preferred term
TEAE Incidence by Grade	Number of TEAEs by MedDRA system organ class, preferred term, and CTCAE grade
TESAE Incidence by Grade	Number of TESAEs by MedDRA system organ class, preferred term, and CTCAE grade
TEAE Incidence Related	Number of TEAEs by MedDRA system organ class, and preferred term related to: • Cannula • Syringe • Cell Product • Surgery • F-DOPA scan • Immunosuppression • MRI • Disease • Device (Cannula + Syringe) • Procedure (Cannula + Syringe + Surgery)
TESAE Incidence Related	Number of TESAEs by MedDRA system organ class, and preferred term related to: • Cannula • Syringe • Cell Product • Surgery • F-DOPA scan • Immunosuppression • MRI • Disease • Device (Cannula + Syringe)

	• Procedure (Cannula + Syringe + Surgery)

At each level of summarization (e.g., any AE, system organ class, and preferred term), subjects experiencing more than one TEAE will be counted only once. In the summary of TEAEs by NCI-CTCAE grade, subjects will be counted once at the highest grade reported at each level of summarization; in the summary of TEAEs by relationship, subjects will be counted once at the closest relationship for each summary.

Events related to immunosuppressive drugs, MRI and disease include those reported as "Possibly Related" or "Related"; events considered not related are those reported as "Not Related". Events related to cannula, syringe, cell product, F-DOPA scan, or surgery include those reported as "Possible: The AE may be related to the intervention," "Probable: The AE is likely related to the intervention," or "Definite: The AE is clearly related to the intervention;" events considered not related include those reported as "Unrelated: The AE is clearly NOT related to the intervention" or "Unlikely: The AE is doubtfully related to the intervention."

Adverse event data will be presented in subject data listings by cohort and subject.

7.5.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All deaths during the study, will be listed by cohort and subject, to include the cause of death. Serious AEs, AEs related to cannula, syringe, cell product, ^{18}F-DOPA PET scan, surgery or immunosuppression regimen will be presented in subject data listings by cohort and subject.

7.5.4 Clinical Laboratory Evaluation

All descriptive summaries of laboratory results will be based on data analyzed by the local laboratory and presented in Système International (SI) units, as suggested by the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research *Position on Use of SI Units for Lab Tests* (Oct 2013). All data will be included in data listings by cohort and subject. Hematology and chemistry measurements identified as abnormal (i.e., outside the normal range) will also be listed separately by cohort, subject, laboratory test, and unit. In addition, normal ranges provided by the local laboratories will be presented in a separate listing.

Clinical laboratory measurements, including hematology, serum chemistry, cytomegalovirus, tacrolimus, and HbA1c will be summarized by cohort and overall. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected per the clinical study protocol. For Tacrolimus, only descriptive statistics for observed values at each visit will be presented.

HbA1c laboratory results will be classified as "low," "normal," or "high" with respect to the parameter-specific reference ranges (i.e., below the lower limit of the normal range, within the normal range, or above the upper limit of the normal range). Three-by-three contingency table will be presented to summarize the shift from the baseline category to the worst post-baseline measurement, defined as the value numerically farthest outside of the normal range across all

post-baseline visits through the end of the study. Summary results will include the count and percentage of subjects within each shift category and cohort. Percentages are based on the number of subjects with available data at both baseline and post-baseline time points.

The following hematology and chemistry results for select parameters will be assigned a toxicity grade based on the U.S. Department of Health and Human Services *Common Terminology Criteria for Adverse Events (CTCAE)*, version 5.0 (27 Nov 2017):

- Hematology
  - Hemoglobin (decrease)
  - Hemoglobin (increase)
  - Platelet Count (decrease)
  - WBC (decrease)
  - WBC (increase)
  - Absolute Neutrophils (decrease)
  - Absolute Lymphocytes (decrease)
  - Absolute Lymphocytes (increase)

- Chemistry
  - AST (SGOT) (increase)
  - ALT (SGPT) (increase)
  - Alkaline Phosphatase (increase)
  - Total Bilirubin (increase)
  - Albumin (decrease)
  - Creatinine (increase)
  - Urate (increase)
  - Sodium (decrease)
  - Sodium (increase)
  - Potassium (decrease)
  - Potassium (increase)
  - Magnesium (decrease)
  - Magnesium (increase)
  - Calcium (decrease)
  - Calcium (increase)
  - Glucose (decrease)
  - LDH (increase)

If the quantitative criteria for grading are equivalent for two grades and the differentiation is described by clinical interventions, the clinical intervention component will not be considered and the highest CTCAE grade will be assigned. Similarly, death related to AE (i.e., Grade 5) cannot be determined with available laboratory-based data collection and, thus, will not be summarized as a category. Laboratory parameters that include multiple sets of criteria for each direction (e.g., separate criteria for potassium measures to assess hyperkalemia and hypokalemia) will be summarized separately to reflect each set of criteria.

Contingency tables will be presented for lab tests where toxicity grading can be applied, to summarize the shift from the baseline grade to the worst post-baseline grade. Grades will be presented as none (Grade 0; ie, measurements did not meet any CTCAE criteria for Grades 1 through 4), mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Summary results will include the count and percentage of patients within each shift category. Percentages will be based on the number of subjects with available data for each laboratory test at baseline and post-baseline visits.

Hematology, chemistry, urinalysis, coagulation, serology, cytomegalovirus, lipid profile, tacrolimus, and HbA1C data will be presented in data listings by cohort and subject in terms of the SI units.

7.5.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

7.5.5.1 Vital Signs

Vital sign parameter measurements will be summarized by cohort and overall for the Safety population. Descriptive statistics will be presented for results in both the supine and standing positions. Change from baseline in the supine and standing positions will be presented at each visit where parameters are scheduled to be collected.

Vital signs data will be presented in subject data listings by cohort and subject.

7.5.5.2 12-Lead Electrocardiogram

Twelve-Lead ECG interval parameters will be summarized by cohort and overall. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected.

Twelve-lead ECG will be classified by the investigator as “normal,” “abnormal, not clinically significant,” or “abnormal, clinically significant.” Three-by-three contingency tables will be presented to summarize the shift from the baseline category to the worst post-baseline value. Summary results will include the count and percentage of subjects within each shift category and treatment group.

7.5.5.3 Neurological Examination

Neurological examination parameters will be summarized by the number and percentage of subjects in each result category by cohort and overall. Test results are categorized by the investigator as “Normal,” “Abnormal,” “Not Tested,” or “Unable to test.” Muscle Stretch Reflexes are categorized by the investigator as “Absent,” “Hypoactive,” “Normal,” “Hyperactive, no clonus,", "Hyperactive, clonus,” “Not tested,” or “Unable to test.” Planter Response Reflexes are categorized by the investigator as “Flexor,” “Extensor,” “Indeterminate," "Not tested,” or “Unable to test.” Four-by-four contingency table will be presented by parameter and cohort to summarize the shift from the baseline category to the worst post-baseline value, with the worst to best categorized as: “Abnormal,” “Indeterminate,” “Missing,” and “Normal.”

(Appendix, Table 222). The count and percentage of subjects within each shift category will be summarized.

Neurological examination data will be presented in subject data listings by cohort and subject.

7.5.5.4 Feasibility of Transplantation

The following feasibility summaries will be summarized by cohort and overall for the Safety Population:

- The count and percentage of subjects to experience intra-operative delivery of at least 50% of the intended total number of deposits
- Descriptive statistics for the percentage of the intended total number of deposits delivered

Surgical information will be presented in subject data listings by cohort and subject.

7.5.5.5 UDysRS, C-SSRS and QUIP

UDysRS, C-SSRS and QUIP will each be summarized by cohort and overall for the safety population. Descriptive statistics will be presented for observed values, change from baseline and percent change from baseline at each visit where parameters were scheduled to be collected.

7.5.5.6 Assessment of Dyskinesia

The data summarized in Section 6.4.2.11 will be summarized over time in an individual subject level figure in addition to a subject data listing by cohort and subject.

7.5.5.7 Prior and Concomitant Medications and Procedures

Medications and procedures will be coded using the World Health Organization (WHO)-Drug Global B3 version March 2020. Medications entered on the eCRF will be mapped to Anatomic Therapeutic Chemical (ATC) drug class (level 4) and drug name. Procedures entered on the eCRF will be mapped to ATC procedure class (level 4) and procedure name.

Prior and concomitant medications and procedures will be summarized separately, and the study phase of each medication will be determined programmatically based on immunosuppression start and end dates and surgical intervention date. A prior medication or procedure is defined as any medication or procedure administered prior to the date of the first dose of immunosuppression or surgical intervention. A concomitant medication or procedure is defined as any medication administered on or after the date of the first dose of immunosuppression or surgical intervention. A medication or procedure may be defined as both prior and concomitant. If it cannot be determined whether a medication or procedure was received prior to the start of immunosuppressant or surgical intervention due to partial or missing medication or procedure start and/or end dates, it will be considered a prior medication. Likewise, if it cannot be

determined whether a medication or procedure was received after the start of immunosuppressant or surgical intervention, it will be considered concomitant.

For both prior and concomitant summaries, the number and percentage of subjects receiving any medication or procedure will be summarized by cohort, as will the number and percentage receiving any medication or procedure by ATC drug/procedure class and generic drug/procedure name, and over all subjects combined. Prior and concomitant medications/procedures will also be summarized by assigned categories of indication using **Error! Reference source not found.**2 below.

Subjects reporting use of more than one medication or procedure at each level of summarization (any medication/procedure received, ATC class, and generic drug/procedure name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug/procedure names within each ATC class. Prior and concomitant records will be listed separately and the assigned categories of indication presented for each CRF page.

Table 2: Prior and Concomitant Medications: Assigned Category Indications

ASSIGNED CATEGORY INDICATION	**Directions for Assignment**
Immunosuppressant (Per Protocol)	EDC Recorded Medication Name = BASILIXIMAB METHYLPREDNISOLONE PREDNISONE TACROLIMUS
Immunosuppressant Related (Per Protocol)	EDC Recorded Medication Name = OMEPRAZOLE SULFAMETHOXAZOLE TRIMETHOPRIM
Surgical	EDC Recorded Medication Indication = Contains “SURGICAL” or “SURGICAL RELATED”
PD	EDC Recorded Medication Indication = “PARKINSON'S DISEASE” or WHO-Drug Global B3 ATC2 = “ANTI-PARKINSON DRUGS” Includes all entries recorded on the Parkinson’s Disease Medication CRF.
Non-PD	Assign if medication not assigned to Immunosuppressant, Immunosuppressant Related, Surgical, or PD Assigned Category Indication.
Procedure	Includes all entries recorded on the Concomitant Procedures CRF.

Note: Prior medications will only utilize Indications of PD or Non-PD.

7.6 Determination of Sample Size

The sample size of approximately 12 evaluable subjects has been chosen to allow 2 doses to be explored in a small number of subjects. This size cohort allows surgical procedures to be staggered to mitigate risk.

7.7 Changes in the Conduct of the Study or Planned Analyses

There were no changes to the study conduct or planned analyses identified within the development of this SAP, relative to the descriptions provided within the clinical study protocol.

8 APPENDIX

Table 3: Schedule of Assessments Part 1: Pre-Treatment Assessments, and Surgical Intervention and Follow-up

Assessments	**Visit**	**SC**	**BL[a]**	**PrOV[b]**	**Surgical admission[c]**	**Post Op**	**PoOV[d]**
	Week						**1.5**
	Day				**Day 0 is surgery**		**Day 10 (post surgery)**
Window		**-28 days of surgery**	**-28 days of surgery**	**-7 days of surgery**		**Day 1 post surgery**	**±2 days**
Written informed consent		X					
Review inclusion/exclusion criteria		X	X				
Demographic information		X					
Medical history		X	X	X			
Neurological history		X	X				
Concomitant medications		X	X	X			
Parkinson's medications		X	X				
General medical exam		X	X	X			
Neurological exam		X	X		X	X	X
Vital Signs		X	X				
ECG			X	X			
Adverse events[e]		X	X				
Surgical admission (PACU and NACU)					X		

Assessments	Visit	SC	BL[a]	PrOV[b]	Surgical admission[c]	Post Op	PoOV[d]
	Week						**1.5**
	Day				**Day 0 is surgery**		**Day 10 (post surgery)**
Surgery and MSK-DA01 administration					X		
Use of SCDs					X		
Antibiotics					X		
Immunosuppression regimen					X	X	
Physical therapy/occupational therapy consult						X	
Surgical discharge						X	
Suture/staple removal and wound check							X
PD Motor evaluations							
AIMS		X					
Hauser Patient Diary		X	X				
MDS-UPDRS Part III ("OFF" medication state) with video recording		X					
MDS-UPDRS ("ON" medication state) with video recording[f]		X	X				
Modified Schwab and England			X				
UDysRS			X				
10-Meter Walk Gait Speed Test			X				
PD Non-motor evaluations							

Assessments	Visit	SC	BL[a]	PrOV[b]	Surgical admission[c]	Post Op	PoOV[d]
	Week						**1.5**
	Day				**Day 0 is surgery**		**Day 10 (post surgery)**
BAI-II			X				
BDI-II			X				
C-SSRS			X				
CGI-S			X				
HAM-D		X					
MoCA		X	X				
PD Non-motor scale			X				
PDQ-39			X				
QUIP		X	X				
Laboratory testing[g]							
HbA1c		X					
CBC with differential		X		X	X	X	
CMP		X	X	X	X	X	
CMV		X	X				
HIV		X					
HCV		X					
Hepatitis B profile (HbcAb, HbsAb, HbsAg)		X					
QuantiFERON-TB gold Plus		X					
Lipid Profile		X					

Assessments	**Visit**	**SC**	**BL[a]**	**PrOV[b]**	**Surgical admission[c]**	**Post Op**	**PoOV[d]**
	Week						**1.5**
	Day				**Day 0 is surgery**		**Day 10 (post surgery)**
Mg/Phos		X	X	X			
Pregnancy test (if applicable)[h]		X					
PT/PTT		X		X	X	X	
RPR (VDRL)		X					
Tacrolimus level							
Type and Screen				X			
Uric acid		X	X				
Urinalysis		X		X			
Imaging							
CXR				X			
MRI (or CT if applicable)		X[i]			X	X	
Neuro Navigation MRI				X			
Intraoperative MRI[j]					X		
^{18}F-DOPA PET			X				
Exploratory motor and laboratory testing							
Blood sample for exploratory biomarkers			X				
Blood sample for xenotransplantation assays			X				
Blood sample (DNA)			X				

Assessments	Visit	SC	BL[a]	PrOV[b]	Surgical admission[c]	Post Op	PoOV[d]
	Week						**1.5**
	Day				**Day 0 is surgery**		**Day 10 (post surgery)**
PKG			X				
Neuropsychological evaluation[k]							
Neuropsychological evaluation			X				

[a] Baseline is a separate visit from screening. Assessments listed in this column must be repeated at the baseline visit, even if they were previously performed at screening, with the exception of neuropsychological evaluation which does not need to be repeated at the baseline visit if performed at screening.
[b] This visit will be carried out either by Geriatrics or Internal Medicine services.
[c] See Section 8.3.2.1 and Section 6.1 of the protocol for surgical evaluation and admission.
[d] IS01 will be done 7 days post-surgery. The PoOV is 8-12 days post-surgery. The neurological exam will occur at the PoOV, not IS01.
[e] Continuous monitoring of AEs will be performed. At visits marked with "X" subjects will be questioned on AEs during the scheduled study visits.
[f] MDS-UPDRS Part I, Part II, Part III, and Part IV are performed with the subject in the "on medication" state. After completion of the assessment for MDS-UPDRS Part III while "off medication," the subject will resume their current PD medication regimen. The complete MDS-UPDRS will then be assessed while "on medication" ≥60 minutes after the subject resumes their PD medication regimen.
[g] Blood for all laboratory testing for SC, BL, and V01-V09 will be collected by routine venipuncture at the Clinical Site and sent for designated tests. Blood for all laboratory testing for IS01-IS12 will be collected by routine venipuncture and sent for designated tests. Blood tests required for immunosuppression monitoring will be drawn at the Clinical Site during study visits V01-V05 and results will be available to the Immunosuppression Clinician for immunosuppression monitoring.
[h] Pregnancy testing will be performed per local standard of care procedures, at the location of where the pregnancy test will be performed.
[i] For the screening MRI, contrast will be optional.
[j] In Canada, intraoperative MRI will be performed only if clinically indicated.
[k] See Appendix 2 and Section 9.1 and Section 10 of the protocol for full list of Neuropsychological evaluations
Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BAI-II=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory; BL=baseline; CBC=complete blood count; CXR=chest X-ray; CMP=complete metabolic profile; CMV=cytomegalovirus antibody (IgG, IgM); C-SSRS=Columbia Suicide Severity Rating Scale; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ^{18}F-DOPA PET=fluorodopa F 18 positron emission tomography; CGI-S=Clinical Global Impression-Severity; HAM-D=Hamilton Depression Scale; HbA1c=hemoglobin A1c; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HCV=hepatitis C antibody; HIV=human immunodeficiency virus -1 and -2 antibody enzyme linked immunosorbent assay; MDS-UPDRS=Unified Parkinson's Disease Rating Scale Parts I-V; Mg=magnesium; MRI=magnetic resonance imaging; MoCA=Montreal Cognitive Assessment; MRI=magnetic resonance imaging; NACU=Neurosurgical Advanced Care Unit; PACU= Post-Operative Care Unit; PD=Parkinson's disease; PDQ-39=Parkinson's Disease Questionnaire-39; Phos=phosphorus; PKG=Personal KinetiGraph; PoOV=post-operative evaluation – Neurology (Day 7)/Neurosurgery (Day 10); Post Op=post operation; PrOV=pre-operative evaluation visit; PT=prothrombin time; PTT=partial thromboplastin time; QUIP=Questionnaire for Impulsive Compulsive Disorders in PD; RPR=rapid plasma reagin; SC=screening visit (Clinical Site); SCD=sequential compression device; UDysRS=Unified Dyskinesia Rating Scale; VDRL=Venereal Disease Reference Laboratory.

Table 4: Schedule of Assessments Part 2: Immunosuppression Monitoring and Other Study Visits

Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
Concomitant medications						X				X			X			X			X	X	X	X	X	X	X
Parkinson's medications						X				X			X			X			X	X	X	X	X		
General medical exam			X			X				X			X			X			X	X	X	X	X	X	
Neurological exam						X				X			X			X			X	X	X	X	X		
Vital Signs			X			X				X			X			X			X	X	X	X	X	X	X
Weight						X				X			X			X			X	X	X	X	X		X
ECG																			X				X		
Adverse events[c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immuno-suppression regimen		X																							

Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
Pill diary and medication review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						X
PD Motor evaluations																									
Hauser Patient Diary					X				X			X			X			X	X	X	X	X		
MDS-UPDRS Part III ("OFF" medication state) with video recording									X			X			X			X		X		X	X	
MDS-UPDRS ("ON" medication state) with video recording[d]					X				X			X			X			X	X	X	X	X	X	

Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
Modified Schwab and England						X				X			X						X		X		X	X	
UDysRS						X				X			X			X			X	X	X	X	X		
10-Meter Walk Gait Speed Test										X			X			X			X	X	X	X	X		
PD Non-motor evaluations																									
BAI-II										X			X						X		X		X		
BDI-II										X			X						X		X		X		
C-SSRS						X				X			X			X			X	X	X	X	X		
CGI-S										X			X						X		X		X		
HAM-D																									
MoCA										X			X						X		X		X	X	
PD Non-motor scale										X			X						X		X		X		

Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
PDQ-39										X			X						X		X		X		
QUIP										X			X						X		X		X		
Laboratory testing[e]																									
HbA1c													X						X						
CBC with differential			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	
CMP			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	
CMV						X				X			X			X			X						
Lipid Profile																								X	
Mg/Phos										X			X			X			X						
Tacrolimus level			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Uric acid										X			X			X			X						
Urinalysis						X		X		X	X	X	X	X	X	X	X	X	X						

Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
Imaging																									
MRI						X				X			X						X		X		X		
^{18}F-DOPA PET																			X		X		X		
Exploratory motor and laboratory testing																									
Blood sample for exploratory biomarkers						X							X						X	X	X		X		
Blood sample for xenotransplantation assays						X							X						X				X		
Blood sample (DNA)																									
PKG										X									X				X		

Assess-ments	Visit	IS0[a]	IS01	IS02	IS03	V01	IS04	IS05	IS06	V02	IS07	IS08	V03	IS09	IS10	V04	IS11	IS12	V05	V06	V07	V08	V09	Early Withdrawal	Unscheduled[b]
	Week	0.5 (D4)	1	2	3	4	6	8	10	12	16	22	26	30	34	39	43	47	52	65	78	91	104		
	Month					1		2		3	4	5	6	7	8	9	10	11	12	15	18	21	24		
Window				±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk		
Neuropsychological evaluation[f]																									
Neuropsychological evaluation																			X				X		

[a] See Section 6.1 of the protocol for IS-0 visit for administration of IV basiliximab for induction phase of immunosuppression.
[b] Additional testing may be warranted based on the Investigator's judgment.
[c] Continuous monitoring of AEs will be performed. At visits marked with "X" subjects will be questioned on AEs during the scheduled study visits.
[d] MDS-UPDRS Part I, Part II, Part III, and Part IV is performed with the subject in the "on medication" state. After completion of the assessment for MDS-UPDRS Part III while "off medication," the subject will resume their current PD medication regimen. The complete MDS-UPDRS will then be assessed while "on medication" ≥60 minutes after the subject resumes their PD medication regimen.
[e] Blood for all laboratory testing for SC, BL, and V01-V09 will be collected by routine venipuncture at the Clinical Site and sent for designated tests. Blood for all laboratory testing for IS01-IS12 will be collected by routine venipuncture and sent for designated tests. Blood tests required for immunosuppression monitoring will be drawn at the Clinical Site during study visits V01-V05 and results will be available to the Immunosuppression Clinician for immunosuppression monitoring.
[f] See Appendix 1 and Section 9.1 and Section 10 of the protocol for a full list of neuropsychological evaluations.
Abbreviations: BAI-II=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory; BL=baseline; CBC=complete blood count; CMP=complete metabolic profile; CMV=cytomegalovirus antibody (IgG, IgM); C-SSRS=Columbia Suicide Severity Rating Scale; D/d=day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ^{18}F-DOPA PET=fluorodopa F 18 positron emission tomography; CGI-S=Clinical Global Impression-Severity; HAM-D=Hamilton Depression Scale; HbA1c=Hemoglobin A1c; IS=immunosuppression monitoring visit; MDS-UPDRS=MDS-Unified Parkinson's Disease Rating Scale Parts I-V; Mg=magnesium; MRI=magnetic resonance imaging; MoCA=Montreal Cognitive Assessment; PD=Parkinson's disease; PDQ-39=Parkinson's Disease

Questionnaire-39; Phos=phosphorus; PKG=Personal KinetiGraph; QUIP=Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease; SC=screening visit (Clinical Site); V=visit; wk=week.

Table 5: LEDD - Drug Class, Drug, Trade/Brand Name, WHODrug and Conversion Factors

Drug Class	Drug (D)	Trade/Brand Name[a]	WHODrug Global B3				Conversion Factor
			ATC1	ATC2	ATC3	ATC4	
Decarboxylase Inhibitors	IR Levodopa + Carbidopa	Sinemet; Dhivy; *(taken by mouth)*	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	DOPA AND DOPA DERIVATIVES	DD x 1
	CR Levodopa + Carbidopa	Sinemet CR; Stalevo; Apo-Levocarb CR	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	DOPA AND DOPA DERIVATIVES	DD x 0.75
	ER Levodopa + Carbidopa	Rytary ER; Duopa-ER Enteral Suspension; Parcopa	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	DOPA AND DOPA DERIVATIVES	DD x 0.5
	Levodopa/ Carbidopa Intestinal Gel	Duodopa; *(not taken by mouth, intestinal suspension)*	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	DOPA AND DOPA DERIVATIVES	DD x 0.9
Levodopa	Levodopa, inhaled	Inbrija – dosage: 84 mg/dose, 420 mg/day	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	DOPA AND DOPA DERIVATIVES	DD x 1
COMT Inhibitors	Entacapone	Comtan	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	OTHER DOPAMINERGIC AGENTS	LD x 0.33[b]
	Tolcapone	Tasmar	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	OTHER DOPAMINERGIC AGENTS	LD x 0.5[b]
	Opicapone	Ongentys	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	OTHER DOPAMINERGIC AGENTS	LD x 0.5[b]
MAO-B Inhibitors	Selegiline oral	Eldepryl - oral	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	MONOAMINE OXIDASE B INHIBITORS	DD x 10

	Selegiline sublingual	Eldepryl – sublingual; Zelapar	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	MONOAMINE OXIDASE B INHIBITORS	DD x 80
	Rasagiline	Azilect	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	MONOAMINE OXIDASE B INHIBITORS	DD x 100
	Safinamide	Xadago	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	MONOAMINE OXIDASE B INHIBITORS	LD = 100 mg
Nonergot-Derived Dopamine Receptor Agonists	Apomorphine	Apokyn	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	DOPAMINE AGONISTS	DD x 10
	Piribedil	Pronoran	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	DOPAMINE AGONISTS	DD x 1
	Pramipexole, ER/IR	Mirapex	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	DOPAMINE AGONISTS	DD x 100
	Ropinirole, ER/IR	Requip	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	DOPAMINE AGONISTS	DD x 20
	Rotigotine, patch	Neupro	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	DOPAMINE AGONISTS	DD x 30
Anti-NMDA	Amantadine	Symmetrel; Gocovri	NERVOUS SYSTEM	ANTI-PARKINSON DRUGS	DOPAMINERGIC AGENTS	ADAMANTANE DERIVATIVES	DD x 1

DD = daily dose; LD = levodopa dose (Drug Class = Decarboxylase Inhibitors)
[a] List may not be comprehensive, providing examples of most common trade/brand names
[b] Result is then added the total L-Dopa daily dose.

Table 6: LEDD Calculation Details

1. Consider medications recorded in the EDC on the Prior and Concomitant Medications, Surgical Related Concomitant Medications, or Parkinson's Disease Medication Log which are ongoing at the time of surgery or start after surgery using Table 5: LEDD - Drug Class, Drug, Trade/Brand Name, WHODrug and Conversion Factors

2.	. • Only medications with WHODRUG ATC2 = ANTI-PARKINSON DRUGS need to be considered
3.	For each subject and medication record contributing to the LEDD, calculate the converted daily dose (DD) for the associated range of study days for each medication. • Utilize EDC recorded dose, unit, and frequency to calculate a daily dose (DD) received per medication • Assign conversion factors using Table 5: LEDD - Drug Class, Drug, Trade/Brand Name, WHODrug and Conversion Factors •
4.	For each subject and medication record contributing the LEDD, calculate the converted daily dose for the associated range of study days for each medication. • The converted daily dose for each medication is calculated using the daily dose (DD) and conversion factor • Each medication will have a converted daily dose (mg) for a range of study days (eg. Study days 1-98, etc).
5.	For each subject find the LEDD (mg) for each individual study day • Sum the converted daily dose for all LEDD medications taken on a given study day • Medications which are recorded as ongoing should be included for the remainder of the study days from the medication start date forward.
6.	Using the individual study day LEDD values, for each subject assign a LEDD value (mg) for each study visit associated with the MDS-UPDRS ("ON" medication state) assessment dates in Table 3 and Table 4. The assigned LEDD values for each study visit will be used for the change from baseline analysis of LEDD.

Note: Day of surgery is considered as Day 1 in LEDD calculations.

Table 7: AIMS Scoring

Items[1]	**Score**
Observed Movement Total Score: Items 1-7	0-28
Orofacial Movements: Items 1-4	0-16
Extremity and Truncal Dyskinesia: Items 5-7	0-12
Global Judgement: Items 8-10	0-12
Overall Severity Index: Item 8	0-4
Item 9	0-4
Item 10	0-4
Dental Status: Items 11-12	Yes/No

[1] Individual items 1-10 are scored on a scale of 0 (none) to 4 (severe).

Table 8: Hauser Diary Derivations

Diary Data Derivation Details	• Diary data from each visit is the average over 3 consecutive days, only valid diary days will be included.
	• A valid diary day is defined as at least 44/48 entries have been completed per instructions (22/24 hours)
	• The mean daily time per visit will be calculated using 3 valid days in the diary
	  ○ In cases where > 3 valid days are present per visit the most recent valid 3 days should be used for mean daily time per visit
	  ○ If there are only 2 valid days present within a visit, the mean daily time using these two days will be used.
	  ○ In the case of 1 valid day within a visit, the mean daily time will be assigned as the values from the 1 valid day.
	  ○ If there is not at least 1 valid day the visit will be excluded from analysis
	  ○ No missing data imputation will be performed.

16-Hour Waking Day Adjustment	Utilizing the mean daily time per visit: $Hauser\ Diary\ Daily\ Mean\ Time\ Adjustment\ for\ 16\ hour\ waking\ day =$ $\left(\frac{Hauser\ Diary\ daily\ mean\ time\ in\ awake\ category\ (hours)}{Hauser\ Diary\ daily\ mean\ time\ awake\ (hours)}\right) x\ 16$ Where awake category = off, on without dyskinesia, on with non-troublesome dyskinesia, on with troublesome dyskinesia.

Table 9: MDS-UPDRS Derivations

MDS-UPDRS Score	Derivation	Data Collection Details[1]
Part I Score (non-motor experiences of daily living)	13 individual items collected on a scale of 0 (normal) to 4 (severe) with a Part I score ranging from 0 to 52	Collected as part of full MDS-UPDRS in ON medication state
Part II Score (motor experiences of daily living)	13 individual items collected on a scale of 0 (normal) to 4 (severe) with a Part II score ranging from 0 to 52	Collected as part of full MDS-UPDRS in ON medication state
Part III Score ON State (motor examination)	33 individual items collected on a scale of 0 (normal) to 4 (severe) with a Part III ON state score ranging from 0 to 132	Collected as part of full MDS-UPDRS in ON medication state

Part III Score OFF State (motor examination)	33 individual items collected on a scale of 0 (normal) to 4 (severe) with a Part III OFF state score ranging from 0 to 132	Collected as part of MDS-UPDRS Part III in OFF medication state
Part IV Score (motor complications)	6 individual items collected on a scale of 0 (normal) to 4 (severe) with a Part IV score ranging from 0 to 24	Collected as part of full MDS-UPDRS in ON medication state
Total Score (Part I + Part II + Part III ON State Score)	Sum of Part I Score, Part II Score, and Part III ON State Scores with a Total score ranging from 0 to 236 (Part IV is not included in the Total Score)	Collected as part of full MDS-UPDRS in ON medication state
Total Part II and III Score (Part II + Part III ON State Score)	Sum of Part II Score and Part III ON State Score with a Total Part II and III Score ranging from 0 to 184	Collected as part of full MDS-UPDRS in ON medication state

[1] The full MDS-UPDRS (Part I, II, III, and IV) is collected in the ON medication state where the subject is evaluated on their usual medication. The MDS-Part III is also collected at select visits in the OFF medication state where the subject has withdrawn from anti-PD medications since their last dose of the day prior. See Table 3 and Table 4 for timing of the MDS-UPDRS assessments.

Table 10: BAI-II Scoring Levels of Anxiety

BAI-II Total Score	Levels of Anxiety
0-7	Minimal level of anxiety
8-15	Mild anxiety
16-25	Moderate anxiety
26-63	Severe depression

Table 11: BDI-II Scoring Levels of Depression

BDI-II Total Score	Levels of Depression
0-10	These ups and downs are considered normal
11-16	Mild mood disturbance
17-20	Borderline clinical depression
21-30	Moderate depression
31-40	Severe depression
Over 40	Extreme depression

Table 12: MoCA Scoring

Category	Score

Visuospatial/Executive	0-5
Naming	0-3
Attention	0-6
Language	0-3
Abstraction	0-2
Delayed Recall	0-5
Orientation	0-6
Total Score[1]	0-30

[1] One point is added to test-taker's total score if they have 12 years or less of formal education.
A total score of 26 or higher is considered normal.

Table 13: NMSS Scoring

Domain	Severity[1]	Frequency[2]	Severity* Frequency	Number of Individual Items	Score
Domain 1: Cardiovascular including falls	0-3	1-4	0-12	2	0-24
Domain 2: Sleep/fatigue	0-3	1-4	0-12	4	0-48
Domain 3: Mood/Cognition	0-3	1-4	0-12	6	0-72
Domain 4: Perceptual problems/hallucinations	0-3	1-4	0-12	3	0-36
Domain 5: Attention/Memory	0-3	1-4	0-12	3	0-36
Domain 6: Gastrointestinal tract	0-3	1-4	0-12	3	0-36
Domain 7: Urinary	0-3	1-4	0-12	3	0-36
Domain 8: Sexual function	0-3	1-4	0-12	2	0-24
Domain 9: Miscellaneous	0-3	1-4	0-12	4	0-48
Total Score	0-3	1-4	0-12	30	0-360

[1] Severity is rated on a scale of 0 (None) to 3 (Severe)
[2] Frequency is rated on a scale of 1 (Rarely) to 4 (Very Frequent)

Table 14: PDQ-39 Scoring

Subscore	Individual Questions Included	Number of Individual Questions	Individual Question Sum[1]	Score[2]
Mobility subscore	1-10	10	0-40	0-100
Activities of Daily Living subscore	11-16	6	0-24	0-100
Emotional Well-Being subscore	17-22	6	0-24	0-100

Stigma subscore	23-26	4	0-16	0-100
Social Support subscore	27-29	3	0-12	0-100
Cognition subscore	30-33	4	0-16	0-100
Communication subscore	34-36	3	0-12	0-100
Bodily Discomfort subscore	37-39	3	0-12	0-100

[1] Individual questions are collected on a scale of 0 (never) to 4 (always).
[2] The sum of the individual items is divided by the maximum possible subscale sum and multiplied by 100 for the final subscore score. The Summary Index score is the mean of all PDQ-39 subscores (0-100).

Table 15: RBANS Scoring

Domain	Score
List Learning Total Score	0-40
Story Memory Total Score	0-24
Figure Copy Total Score	0-20
Line Orientation Total Score	0-20
Picture Naming Total Score	0-10
Semantic Fluency Total Score	0-40
Digital Span Total Score	0-16
Coding Total Score	0-89
List Recall Total Score	0-10
List Recognition Total Score	0-20
Story Recall Total Score	0-12
Figure Recall Total Score	0-20
Total Score[1]	0-321
Total Scale Score	40-160

[1] Total Score is the sum of the individual scores (List Learning Total Score – Figure Recall Total Score)

Table 16: FrSBe Scoring

Score	Individual Question #[1]
Apathy	1, 8, 11, 14, 16, 21, 23, 24, 29, 38, 39, 41, 42, 46
Disinhibition	2, 4, 6, 9, 10, 12, 18, 27, 28, 30, 31, 32, 43, 44, 45
Executive Dysfunction	3, 5, 7, 13, 15, 17, 19, 20, 22, 25, 26, 33, 34, 35, 36, 37, 40
Total	1-46

[1] Individual Questions are collected on a scale of 0 (Almost never) to 5 (Almost always). The sum of the individual questions make up the Apathy, Disinhibition, Executive Dysfunction, and Total Scores.

Table 17: NPI-Q Scoring

Domain	Number of Individual Items	Rating Scale	Score
Severity (how it affects the patient)	12	1 (Mild) to 3 (Severe)	0-36
Distress (how it affects the caregiver)	12	0 (Not distressing at all) to 5 (Extreme or Very Severe)	0-60

Total Severity and Distress Score will be the sum of the two domain scores (0-96).

Table 18: UDysRS Scoring

UDysRS Part	Individual Questions Included[1]	Score
Historical: Sub-score	1-15	0-60
Historical: Part 1 (On-Dyskinesia)	1-11	0-44
Historical: Part 1A (Time Spent with On-Dyskinesia)	1	0-4
Historical: Part 1B (Patient Dyskinesia Questionnaire)	2-11	0-40
Historical: Part 2 (Off-Dystonia)	12-15	0-16
Historical: Part 2A (Time Spent with Off-Dystonia)	12	0-4
Historical: Part 2B (Patient Questionnaire)	13-15	0-12
Objective: Sub-score	16-26	0-44
Objective: Part 3 (Impairment)	16-22	0-28
Objective: Part 4 (Disability)	23-26	0-16

[1] Individual questions are rated on a scale of 0 (normal) to 4 (severe). The Total UDysRS score is the sum of Historical and Objective sub-scores (0 to 104).

Table 19: C-SSRS Scoring

Scale	Description	Score
Suicidal Ideation	A “yes” answer at any time to any one of the individual questions 1-5	Yes/No
Suicidal Ideation Intensity Rating	Sum of individual questions “Frequency”, “Duration”, “Controllability”, “Deterrents” and “Reasons for Ideation”, rated on a 1-5 scale	0-25
Suicidal Behavior	A “yes” answer at any time to any one of the individual questions (6-10)	Yes/No
Suicidal Ideation or Behavior	A “yes” answer at any time to any one of the individual questions (1-10)	Yes/No

Table 20: HAM-D Scoring Levels of Depression

HAM-D Total Score	Levels of Depression
0-7	Normal
8-13	Mild Depression
14-18	Moderate Depression
19-22	Severe Depression
≥ 23	Very Severe Depression

Table 21: QUIP Scoring

Subscore	Description[1]	Score
Gambling Subscore	Sum of 4 individual items	0-16
Sex Subscore	Sum of 4 individual items	0-16
Buying Subscore	Sum of 4 individual items	0-16
Eating Subscore	Sum of 4 individual items	0-16
Hobbyism-Punding Subscore	Sum of 8 individual items	0-32
PD Medication Use Subscore	Sum of 4 individual items	0-16
Total ICD Score	Sum of Gambling, Sex, Buying and Eating Subscores	0-64
Total Score	Sum of Gambling, Sex, Buying, Eating, Hobbyism-Punding, and PD Medication Use Subscores	0-112

[1] Individual items are scored on a scale of 0 (never) to 4 (very often).

Table 22: Neurological Exam Scoring

Investigator Reported Categories	Derived Categories for Shift Table
0=Normal 1=Abnormal 2=Not tested 3=Unable to test	Abnormal=1 Indeterminate=NA Missing=2,3 Normal=0
0=Absent 1=Hypoactive 2=Normal 3=Hyperactive, no clonus 4=Hyperactive, clonus 5=Not tested 6=Unable to test	Abnormal=1,3,4 Indeterminate=0 Missing=5,6 Normal=2

0=Flexor 1=Extensor 2=Indeterminate 3=Not tested 4=Unable to test	Abnormal=1 Indeterminate=2 Missing=3,4 Normal=0

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