CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Sham-Controlled Study to Evaluate the Safety and Tolerability of Glutamic Acid Decarboxylase Gene Transfer to the Subthalamic Nuclei in Participants with Parkinson's Disease

Investigational product:	Two recombinant adeno-associated virus (AAV) serotype 2-glutamic acid decarboxylase (GAD) vectors, GAD65 and GAD67, mixed in a 1:1 ratio (AAV-GAD)
Protocol number:	MGT-GAD-025
IND number	28482
Sponsor:	MeiraGTx, LLC 450 East 29th Street 14th Floor New York, NY 10016 USA
Version - date of protocol:	v6.0 - 22 Sep 2023
GCP statement:	This study is to be performed in full compliance with International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use and all applicable local Good Clinical Practice (GCP) guidelines and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality statement:	This document is confidential. It contains proprietary information of MeiraGTx (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the Investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Council for Harmonization (ICH) Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

DocuSigned by:
[redacted]
Signing Reason: I approve this document
Signing Time: 22-Sep-2023 | 12:08 BST
9367FED88C61498EA4E76BF2B70EA75F

22-Sep-2023 | 12:08 BST

Signature of Sponsor

Date
(DD-MMM-YYYY)

INVESTIGATOR'S AGREEMENT

I have read and approve this protocol. My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the ICH Guideline for GCP, the CFR, and the ethical principles that have their origins in the Declaration of Helsinki.

Signature of Investigator

Date
(DD-MMM-YYYY)

Printed Name of Investigator

CHANGES COMPARED TO PREVIOUS VERSION(S)

Protocol v6.0 (22 September 2023)

The changes between protocol Version 6.0 (dated 22 September 2023) and protocol Version 5.0 (dated 18 July 2023) are highlighted below.

Version n° and date were adapted throughout the document (including headers and footers). The List of Abbreviations was updated and the Section "Changes Compared to Previous Version(s)" was completed.	
Section	**Change/Rationale**
Section 4.2	Removed exclusion criterion 22, which excluded individuals with poorly controlled diabetes (as evidenced by HbA1c >7%). Medically and surgically, these individuals do not need to be excluded from this study.

Protocol v5.0 (18 July 2023)

The changes between protocol Version 5.0 (dated 18 July 2023) and protocol Version 4.0 (dated 18 January 2023) are highlighted below.

Version n° and date were adapted throughout the document (including headers and footers). The Table of Contents was updated and the Section "Changes Compared to Previous Version(s)" was completed.	
Section	**Change/Rationale**
Synopsis and Section 3.1	Clarified that the study will be carried out at approximately 5 sites in the United States.
Schedule of Activities, Section 5.5.3, Section 5.5.4, Section 5.5.6.2, and Section 8.8	The cranial anchor kit will not be removed after completing the infusion. Consequently, specific MRI conditions are to be taken into account for post-surgical MRI scans and participants are to be provided with a patient implant card.
Section 4.2	Exclusion criterion 11 updated to clarify that evidence of lesions or other significant abnormalities on cranial neuroimaging suggesting findings compatible with a probable diagnosis other than Parkinson's disease is exclusionary.
Section 8.2.8	Updated the safety contact information (contact details for reporting of SAEs and pregnancies).

Protocol v4.0 (18 January 2023)

The changes between protocol Version 4.0 (dated 18 January 2023) and protocol Version 3.0 (dated 21 September 2022) are highlighted below.

Version n° and date were adapted throughout the document (including headers and footers). The Table of Contents and the List of Abbreviations was updated and the Section "Changes Compared to Previous Version(s)" was completed.	
Section	**Change/Rationale**
Synopsis, Section 3.1, Section 5.1, Section 5.2, Section 5.3, Section 5.5.1.1, Section 5.5.3,	Updated to reflect that a total of 14 participants will be randomized to receive either AAV-GAD at a dose of 3.5×10^{10} vg/STN (5 participants), AAVGAD at a dose of 10.45×10^{10} vg/STN (5 participants) or sham surgery (4 participants). The rationale for adding a higher dose group is provided in Section 5.2.

Section 5.5.4, and Section 10.1.6	
Synopsis, Section 2, Section 10.1.4.1	Updated wording on the planned statistical analyses and the endpoints to account for the additional dose group.
Schedule of Activities, Section 6.2	Clarified that during visits that include the MDS-UPDRS assessment, the MDS-UPDRS Part 3 "off" state assessment should preferably be performed before any other assessments or questionnaires.
Schedule of Activities, Section 5.5.5, Section 8.5	To avoid accidental unblinding, the text has been updated to specify all timepoints for vital signs assessments in relation to the start of the infusion. Also, the actual volume infused will no longer be collected in the CRF.
Section 1.1, Section 1.2, and Section 1.3	Included additional information related to the doses used in the previous clinical studies and the doses that will be used in this study.
Section 4	Clarified that individuals who have not completed the screening assessments within the specified time period may be rescreened, after discussion with the Sponsor
Section 5.6.1	Text updated to align with the language in the exclusion criteria
Section 8.2.6.4	Clarified that the Sponsor will report all information related to serious and unexpected adverse reactions to all relevant Competent Authorities
Section 8.2.8	Updated the safety contact information.
Section 12.4	Clarified that protocol amendments must be submitted to the relevant Competent Authorities in accordance with regulatory requirements.

Protocol v3.0 (21 September 2022)

The changes between protocol Version 3.0 (dated 21 September 2022) and protocol Version 2.0 (dated 23 August 2022) are highlighted below.

Version n° and date were adapted throughout the document (including headers and footers). The Table of Contents was updated and the Section "Changes Compared to Previous Version(s)" was completed.	
Section	**Change/Rationale**
Schedule of Activities and Section 7.3	Updated to specify that the Hauser Patient Diary should be completed twice per week (on 2 non-sequential days) for 3 consecutive weeks prior to the second screening visit (Day -7 to Day -3 visit) instead of prior to randomization.
Section 1.4.2	Text added to elaborate on the potential risks associated with the Acute Delivery System and how they have been mitigated.
Section 5.5.6.2	Updated to reflect that following implant and administration of AAV-GAD, all components of the Acute Delivery System are to be packaged in a sealed biohazard bag and stored until the end of the study when they will either be returned to MeiraGTx or designee or allowed to be destroyed.
Section 8.2.3	The descriptions of the adverse event causality definitions in Table 3 have been corrected.
Section 8.2.7	Updated for clarity.

Protocol v2.0 (23 August 2022)

The changes between protocol Version 2.0 (dated 23 August 2022) and protocol Version 1.0 (dated 9 May 2022) are highlighted below.

Version n° and date were adapted throughout the document (including headers and footers). The Table of Contents was updated and the Section "Changes Compared to Previous Version(s)" was added and completed.	
Section	**Change/Rationale**
Synopsis, Schedule of Activities	To allow sufficient time for study materials to be delivered between randomization and the day of the surgery, the screening visit window has been adjusted from Day-40 to Day-14 to Day-40 to Day-8 and the window for randomization has been shifted from Day-7 to Day-3 to Day-40 to Day-8. Footnote q remains applicable: 'Randomization will occur after all inclusion and exclusion criteria have been met and surgery is scheduled'.
Schedule of Activities, Section 5.5.3, Section 5.5.4, Section 5.5.6.2, and Section 8.8	The cranial anchor kit will be removed after completing the infusion. A commercially available burr hole cover may be used at the neurosurgeon's discretion to cover the burr hole created for the procedure. Consequently, specific MRI conditions are no longer to be taken into account for post-surgical MRI scans and participants are no longer to be provided with a patient implant card.
Section 5.5.3	Wording is added to specify that the pump is to be at approximately the same level as the infusion site and is to be maintained at the same height for the duration of the infusion.

SYNOPSIS

Title of study: A Randomized, Double-Blind, Sham-Controlled Study to Evaluate the Safety and Tolerability of Glutamic Acid Decarboxylase Gene Transfer to the Subthalamic Nuclei in Participants with Parkinson's Disease
Study short title: A double-blind study to evaluate the safety of Glutamic Acid Decarboxylase gene transfer in participants with Parkinson's Disease
Protocol number: MGT-GAD-025
Study center(s): To be conducted at approximately 5 sites in the United States (US)
Phase of development: 1/2
Objectives: The primary objective of this study is to evaluate the safety and tolerability of AAV-GAD delivered bilaterally to the subthalamic nuclei (STN) in participants with Parkinson's disease.
Study design: Phase 1/2, randomized, double-blind, sham-controlled, safety and tolerability
Methodology: This study is designed to evaluate the safety and tolerability of AAV-GAD administered bilaterally into the STN in participants with Parkinson's disease not adequately controlled with appropriate anti-Parkinsonian medications. The study will be carried out in the US at approximately 5 sites with established and highly experienced surgical programs for deep brain stimulation (DBS) treatment of Parkinson's disease. The principal investigators will be neurosurgeons or neurologists with expertise in the assessment and treatment of participants with Parkinson's disease and with strong backgrounds in clinical research. Each site will also have support personnel knowledgeable in the care of participants with this disorder. After discussion of the study risks and possible benefits with the Investigator, participants will provide written informed consent and be considered eligible for the study if they satisfy all inclusion and exclusion criteria. Approximately 14 participants will be randomized to receive 1 of 2 doses of AAV-GAD infused bilaterally into the STN (5 participants per dose group) or sham surgery (bilateral, partial-thickness, burr hole procedure with saline administration; 4 participants) and followed for 6 months. Day 1 will be defined as the day of AAV-GAD or sham treatment. Safety and tolerability of AAV-GAD gene transfer will be assessed by adverse events (AEs), vital sign measurements, neurological examinations, physical examinations, radiographic imaging of the head (computed tomography [CT] and magnetic resonance imaging [MRI]), clinical laboratory evaluations, electrocardiograms (ECGs), immune response, and the Columbia-Suicide Severity Rating Scale. A Data and Safety Monitoring Board (DSMB) will be established for this study to provide expert input on safety of the investigational product, surgical procedure, and related issues. Participants also will be assessed for potential clinical responses to AAV-GAD on Parkinson's disease signs, symptoms, and disabilities using assessments widely used in Parkinson's disease research for evaluating new medications and surgical procedures. Upon completion of this study, participants randomized to receive AAV-GAD treatment will be asked to enter a long-term (4.5 year) safety follow-up study (MGT-GAD-026) in accordance with applicable regulatory agency guidance for surveillance of participants who receive gene therapy. Participants randomized to the sham group in this study will be offered bilateral, open-label treatment with AAV-GAD

as part of the long-term follow-up study (pending regulatory approval) and will be followed for 5 years of assessments consistent with those participants who received AAV-GAD in study MGT-GAD-025.

Number of participants (planned): Approximately 14

Diagnosis and main criteria for inclusion:

The study population will consist of participants with Parkinson's disease not adequately controlled with appropriate anti-Parkinsonian medications. Participants must meet established clinical criteria for Parkinson's disease and meet ^{18}F-deoxyglucose (FDG)-positron emission tomography (PET) criteria for idiopathic Parkinson's disease; have a history of having experienced levodopa responsiveness for at least 12 months; and must have a threshold level of Parkinsonian disability as indicated by a score of ≥25 on the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part 3 (motor examination) while in the "off" state (without the benefit of medication).

In order to qualify for entry into the study, eligible participants must be willing to not receive DBS (or initiate other anti-PD treatments) for the 6-month duration of the study.

Duration of participation:

After informed consent is obtained, screening assessments should be conducted within the 40 days preceding surgery (AAV-GAD treatment or sham). After surgery, participants will be followed for 6 months in this study. The duration of individual participation will be approximately 7 months.

Investigational product, dosage and mode of administration:

AAV-GAD will be administered bilaterally via stereotactic infusion into each STN (1 infusion per hemisphere: 2 infusions in total). Each STN will be infused with either 35 μL of 1×10^{12} vg/mL AAV-GAD, for a dose of 3.5×10^{10} vg/STN or 50 μL of 2.09×10^{12} vg/mL AAV-GAD, for a dose of 10.45×10^{10} vg/STN. The total dose per participant will be 7.0×10^{10} vg or 20.9×10^{10} vg. AAV-GAD will be infused at a rate of approximately 0.23 μL/min.

AAV-GAD is formulated in a buffered solution of KH_2PO_4, Na_2HPO_4, NaCl, and $MgCl_2$, with pH 7.4. The AAV-GAD formulation will be diluted to a concentration of $1x10^{12}$ vg/mL (low dose) or used at the undiluted concentration of 2.09×10^{12} vg/mL (high dose).

Reference therapy, dosage and mode of administration:

Sham surgery.

Partial-thickness burr holes will be generated to eliminate the risk of intracranial hemorrhage, followed by sham physiological mapping of the STN and then saline infusion through catheters inserted into each partial-thickness burr hole (no brain infusion). The volume of saline will be 35 μL on each side (combined total of 70 μL).

Criteria for evaluation:

Safety:

Safety will be evaluated by vital signs, neurological examinations, physical examinations, electrocardiograms, radiographic imaging of the head (CT and MRI), clinical laboratory evaluations, descriptive analysis of AEs (including incidence, severity, seriousness, and relatedness), immune response, and the Columbia-Suicide Severity Rating Scale over the duration of the study.

Exploratory activity assessments:

Assessments of potential activity of AAV-GAD will include the MDS-UPDRS, Parkinson's disease-related pattern (PDRP), glutamic acid decarboxylase-related pattern (GADRP), MDS-Unified Dyskinesia Rating Scale, Montreal Cognitive Assessment, Parkinson's Disease Sleep Scale-2, Hauser Patient Diary,

Parkinson's Disease Questionnaire-39 Scale, EuroQol-5 Dimensions-5 Levels Survey, Clinical Global Impression-Severity, Clinical Global Impression-Improvement, Beck Depression Inventory-II, Beck Anxiety Inventory, Revised Hopkins Verbal Learning Test (HVLT-R), Stroop Color and Word Test (DKEFS version), Trail Making Test (TMT), Verbal fluency Test (DKEFS version), Digit Span Test, and levodopa dose and levodopa equivalent daily dose.

Statistical methods:

Details for all analyses will be described in a Statistical Analysis Plan (SAP).

Data summaries will be presented for all endpoints and will include descriptive statistics to summarize continuous variables (number of participants, mean, median, standard deviation, minimum, maximum, and quartiles). Categorical endpoints will be summarized by counts and percentages.

Safety analyses will be performed using the Safety Population, defined as all participants who are randomized and received treatment (AAV-GAD or sham). Efficacy analyses will be performed using the Intention-to-Treat (ITT) Population, defined as all participants who are randomized.

Sample size determination:

This is a Phase 1/2 study to establish safety and tolerability of AAV-GAD. While no formal sample size calculation was performed, it is believed that inclusion of approximately 14 participants (5 participants receiving AAV-GAD at a dose of 3.5×10^{10} vg/STN, 5 participants receiving AAVGAD at a dose of 10.45×10^{10} vg/STN and 4 participants undergoing sham surgery) will be sufficient to meet the study objectives.

Safety analyses:

Adverse events will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA; latest version) system organ classification and preferred term.

Descriptive summaries of vital signs, clinical laboratory evaluations, ECGs, physical examinations, neurological examinations, CT, and MRI (including changes from baseline) will be presented by study visit. Numbers and percentages of participants with abnormalities, according to predefined criteria where appropriate, will be tabulated.

The number of participants with a positive immune response will be summarized.

Exploratory endpoint analyses:

The exploratory endpoint analyses will be performed on data collected at the Week 12 and Week 26 visits.

Descriptive statistics will be presented for activity endpoints. Differences between the individual and pooled (when appropriate) AAV-GAD groups and the sham group in mean change from baseline to Weeks 12 and 26 will be compared for each of the endpoints.

[redacted]

SCHEDULE OF ACTIVITIES

Table 1: Schedule of Activities

Study Day/Month	Screening		Surgery/ Hospital		UV	Day 15 ±2 days	Day 29 ±3 days	Week 12 ±7 days	Week 19[a] ±7 days	Week 26/EW ±7 days
	Day -40 to Day -8	Day -7 to Day -3	Day 1	Day 2						
Informed consent	X[b]									
MRI of head [c]	X									X
^{18}FDG-PET of head [c]	X									X
CT or MRI for presurgical planning	X[d]									
UK Parkinson's Disease Society Brain Bank criteria	X[b]									
Inclusion/exclusion criteria [e]	X[b]									
Demographics [f]	X[b]									
Medical/surgical history	X[b]									
Prior and concomitant medications[g]	———	———	———	———	———	———	———	———	———	——— ▶
AE assessment[h]	———	———	———	———	———	———	———	———	———	——— ▶
MDS-UPDRS Part 3 "off" state[i]	X[b]						X	X		X
MDS-UPDRS Part 3 "on" state repeated [j]	X[b]						X	X		X
Montreal Cognitive Assessment (MoCA)	X[b]							X		X
Beck Depression Inventory-II	X[b]							X		X
Physical examination	X[b]		X[k]		X					X
Vital sign measurements	X[b]		X[l]	X	X	X	X	X		X
Complete neurological examination	X[b]			X	X	X	X	X		X
12-lead ECG	X[b]				X	X				
Clinical laboratory evaluations (chemistry, hematology, coagulation, and urinalysis)	X[b]	X		X[m]	X	X[m]	X[m]	X[m]		X[m]
Serum pregnancy test (WOCBP only)	X[b]	X			X[n]					
Training and validation of Hauser Patient Diary[o]	X[b]									
Distribution of Hauser Patient Diary	X[b]			X			X	X		
Revised Hopkins Verbal Learning Test (HVLT R)	X[p]									X
Trail Making Test (TMT)	X[p]									X
Stroop Color and Word Test (DKEFS version)	X[p]									X
Verbal fluency Test (DKEFS version)	X[p]									X

Study Day/Month	Screening		Surgery/ Hospital		UV	Day 15 ±2 days	Day 29 ±3 days	Week 12 ±7 days	Week 19[a] ±7 days	Week 26/EW ±7 days
	Day -40 to Day -8	Day -7 to Day -3	Day 1	Day 2						
Digit Span	X[p]									X
MDS-UPDRS Part 1 (Non-Motor Experiences of Daily Living)	X[p]						X	X		X
MDS-UPDRS Part 2 (ADL)	X[p]						X	X		X
MDS-UPDRS Part 4 (Complications)	X[p]						X	X		X
Beck Anxiety Inventory	X[p]									X
Unified Dyskinesia Rating Scale	X[p]							X		X
Parkinson's Disease Questionnaire-39 Scale	X[p]									X
Parkinson's Disease Sleep Scale-2	X[p]									X
Columbia-Suicide Severity Rating Scale	X[p]						X	X		X
EuroQol-5 Dimensions-5 Levels Survey	X[p]									X
Clinical Global Impression-Severity	X[p]									X
Clinical Global Impression-Improvement										X
Randomization	X[q]									
Surgery and related procedures			X							
Stereotactic imaging following frame placement (CT or MRI)			X							
Limited-cut CT at catheter tip to confirm localization following infusion (AAV-GAD groups only)			X							
Non-contrast CT of head within 24 hours after catheter removal (AAV-GAD groups only)				X						
Sham limited-cut CT at catheter tip to confirm localization following infusion (SHAM group only)			X							
Sham non-contrast CT of head within 24 hours after catheter removal (SHAM group only)				X						
Study drug administration			X							
Removal of catheter			X							
Removal of sutures and burr hole site assessment						X				
Anti-GAD and anti-AAV2 antibody evaluation (humoral immune response)		X					X	X		X

Study Day/Month	Screening		Surgery/ Hospital		UV	Day 15 ±2 days	Day 29 ±3 days	Week 12 ±7 days	Week 19[a] ±7 days	Week 26/EW ±7 days
	Day -40 to Day -8	Day -7 to Day -3	Day 1	Day 2						
Hauser Patient Diary review		X				X[r]		X[r]		X[r]
Check on control of Parkinsonism, and other neurological events									X	

Note: If, despite all efforts to encourage the participant to continue in the study, the participant withdraws consent after Day 1, every effort should be made to complete the full panel of assessments scheduled for the Week 26 visit.
During visits that include the MDS-UPDRS assessment, the MDS-UPDRS Part 3 "off" state assessment should preferably be performed before any other assessments or questionnaires.

a. Telephone visit. Participants will be contacted by telephone for assessment of AEs, changes in control of Parkinsonism, and other neurological events.
b. Assessments preferably to be performed between Day -40 and Day -21.
c. MRI and ^{18}FDG-PET scans done for surgical screening will be used as baseline assessments. Due to the retention of the nylon/titanium cranial anchor base above the skull as a burr hole cover following removal of the infusion system, the specific MRI conditions detailed in the IFU must be taken into account for all post-surgical MRI scans.
d. If an MRI of the head is done at screening, the MRI for presurgical planning does not need to be done.
e. The diagnosis of idiopathic PD will be made before any other screening procedure will take place.
f. Demographics will include sex, age, race and ethnicity.
g. Prior and concomitant medications will be recorded from date of informed consent form (ICF) signature till the final study visit on electronic case report form (eCRF). Changes in concomitant medications should be recorded before and after surgery.
h. Participants will be contacted by telephone on Day 7 or 8 (6 or 7 days after study drug administration) for assessment of AEs.
i. "Off" state scores will be obtained after at least 12 hours of holding dopaminergic medication.
j. Participants may take additional levodopa (in addition to their usual dose) if needed to achieve the "on" state.
k. Prior to the surgery
l. Vital sign measurements: temperature, heart rate, respiratory rate, and blood pressure will be recorded before surgery, approximately every 30 minutes for at least the first 4 hours after start of infusion (this can be prolonged in 30-minute intervals if the infusion takes longer than 4 hours), and then at approximately 8 and 12 hours after the start of infusion. Of note, the participant may be transferred to an inpatient hospital service for the assessment of vital signs between 4 hours and 12 hours after start of infusion. Height will be measured at screening, whereas weight will be measured at both screening and Week 26 visits.
m. Coagulation parameters will not be evaluated.
n. Serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.
o. Inform the participant that the Hauser Patient Diary should be completed twice per week (on 2 non-sequential days) for 3 consecutive weeks prior to the second screening visit (i.e., the Day -7 to Day -3 visit). After baseline, the participant should complete the Hauser Patient Diary on 2 non-sequential days in the week prior to Day 15, and Week 12, and Week 26.
p. Assessment only to be performed after the participant has qualified to enroll in the study.
q. Randomization will occur after all inclusion and exclusion criteria have been met and surgery is scheduled.
r. Participants will be contacted by telephone approximately 1 week prior to their scheduled visits on Day 15, Week 12, and Week 26 to remind them to complete the Hauser Patient Diary on 2 non-sequential days during the week prior to their visit.

Abbreviations: AAV2 = adeno-associated virus serotype 2; ADL = activities of daily living; AE = adverse events; CT = computed tomography; DKEFS = Delis–Kaplan Executive Function System; ECG = electrocardiogram; EW = early withdrawal ^{18}FDG = ^{18}fluorodeoxyglucose; GAD = glutamic acid decarboxylase; HVLT-R = Revised Hopkins Verbal Learning Test; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; PD = Parkinson's disease; PET = positron emission tomography; TMT = Trail Making Test; UK = United Kingdom; UPDRS = Unified Parkinson's Disease Rating Scale; UV = unscheduled visit; WOCBP = women of childbearing potential.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AAV	adeno-associated virus
AAV2	adeno-associated virus serotype 2
AAV-GAD	The investigational product: Two recombinant adeno-associated virus (AAV) serotype 2-glutamic acid decarboxylase (GAD) vectors, GAD65 and GAD67, mixed in a 1:1 ratio (AAV-GAD)
ADL	activities of daily living
ADR	adverse drug/device reaction
AE	adverse event
AR	Adverse Reaction
CI	confidence interval
CMO	Contract Manufacturing Organization
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
CT	computed tomography
DBS	deep brain stimulation
DKEFS	Delis–Kaplan Executive Function System
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EW	early withdrawal
FDA	Food and Drug Administration
FDG	^{18}fluorodeoxyglucose
GABA	gamma-aminobutyric acid
GAD	glutamic acid decarboxylase
GADRP	glutamic acid decarboxylase-related pattern
GCP	Good Clinical Practice
GPi	globus pallidus internal segment
HVLT-R	Revised Hopkins Verbal Learning Test
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IFU	Instructions for Use
IND	Investigational New Drug

Abbreviation	Definition
INR	international normalized ratio
IRB/IEC	institutional review board/independent ethics committee
ITT	Intention-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MoCA	Montreal Cognitive Assessment
MP	Monitoring Plan
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
MSA	multiple system atrophy
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHP	nonhuman primate
NOAEL	No Observed Adverse Effect Level
PDRP	Parkinson's disease-related pattern
PET	positron emission tomography
PSP	progressive supranuclear palsy
PTT	partial thromboplastin time
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	serious adverse reaction (device or drug)
SNpc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
SoA	Schedule of Activities
STN	subthalamic nuclei(us)
SUSAR	suspected unexpected serious adverse reaction
TMT	Trail Making Test
UK	United Kingdom
ULN	upper limit of normal
UPDRS	Unified Parkinson's Disease Rating Scale
MDS-UPDRS	Movement Disorder Society-Sponsored Revision of the UPDRS
US	United States
UV	Unscheduled visit
WOCBP	women of childbearing potential

1 INTRODUCTION AND BACKGROUND INFORMATION

This is a Phase 1/2, randomized, double-blind, sham-controlled study to evaluate the safety and tolerability of AAV-GAD delivered bilaterally to the subthalamic nucleus (STN) in participants with Parkinson's disease.

Parkinson's disease is a neurodegenerative disorder with characteristic impairments of motor function such as slowed movement, impaired dexterity, gait disturbance, tremors, and rigidity of muscles. These clinical features are associated with progressive loss of neurons in the midbrain, particularly the substantia nigra pars compacta (SNpc). The net effect is a disruption of basal ganglia activity and downstream brain networks that control movement and possibly other neurological functions, including cognitive function and autonomic regulation.

The loss of dopamine signaling in Parkinson's disease leads to dysregulation of the STN due to a reduction in GABA inputs to this structure, resulting in excessive STN mediated activation of GPi/SNpr outflow, which increases the inhibitory brake on the thalamus. Loss of dopamine also leads to a decrease in GABA-mediated inhibition of GPi/SNr, further exacerbating the excessive basal ganglia outflow inhibition of the thalamus. This inhibition of the thalamus underlies the motor symptoms characteristic of Parkinson's disease.

Early in the course of Parkinson's disease, dopaminergic replacement therapy and other medications are sufficient for marked symptomatic improvement of the motor deficits, which are the major source of disability for these patients. Facilitation of dopaminergic neurotransmission benefits most patients early in the disease, but generally requires both increasing drug doses and a move to more complex polytherapy, yet still targeting the dopaminergic pathway. As the disorder advances and brain physiology changes in response to chronic medication exposure, drug-related complications develop and often cause significant disability, such as disabling dyskinesias and motor fluctuations. Thus, almost all Parkinson's disease patients reach a stage sometime after the initiation of treatment where their symptoms cannot be adequately controlled with current therapy. The development of these complications, among other factors, are among the primary reasons why patients with moderate to advanced Parkinson's disease and their physicians consider surgical intervention to reduce symptoms and improve function.

Gene therapy, consisting of the adeno-associated virus (AAV)-mediated delivery of the glutamic acid decarboxylase (GAD) 65/67 complementary DNAs into the intrinsic neurons of the STN, provides a therapeutic strategy to restore normal outflow of the basal ganglia to improve motor function. Glutamic acid decarboxylase is the rate-limiting enzyme for GABA production with inhibitory neurons expressing both GAD65 and GAD67 isoforms that serve complementary and synergistic roles in regulation of brain excitability. AAV-GAD comprises 2 recombinant AAV-GAD vectors, GAD65 and GAD67, mixed in a 1:1 ratio.

AAV-GAD drives expression of GAD in the transduced cells of the STN, which catalyzes the enzymatic conversion of glutamate to GABA. This restores the more normal glutamate/GABA balance in both the STN and its efferent targets, the GPi/SNr. Nonclinical evidence suggests that

increased STN activity (more abnormal activity) leads to increased GABA release to regulate this circuitry. As a result, the activity of downstream thalamocortical networks is normalized in an autoregulatory fashion, leading to improved motor function.

1.1 OVERVIEW OF NONCLINICAL STUDIES

Pharmacology and toxicology studies utilizing behavioral, electrophysiological, immunohistochemical, and imaging endpoints demonstrated that AAV-GAD injections into the STN of both rats and rhesus monkeys provided benefit in traditional Parkinson's disease models, consistent with the proposed mechanism of action. The original development and characterization of AAV-GAD in nonclinical models was carried out in 6-hydroxydopamine–lesioned Parkinsonian rats and demonstrated both phenotypic correction of motor deficits and neuroprotection of dopamine neurons (Luo et al. 2002). This study also demonstrated that more abnormally increased STN activity resulted in increased GABA release to the basal ganglia outflow nuclei, suggesting an autoregulatory component to this gene therapy. The approach was then generalized to a study in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated Parkinsonian nonhuman primates (NHPs), i.e., rhesus monkeys (Emborg et al. 2007), that provided further proof of concept and supported clinical translation. These MPTP-treated Parkinsonian NHPs received 20 µL of 6×10^{12} vg/mL AAV-GAD into the STN. This dose represents, based on the relative STN neuronal numbers in rhesus monkeys (approximately 150,000 neurons) versus the human STN (560,000 neurons) (Hamani et al. 2004), a 12-fold multiple of the dose used in the subsequent Phase 2 study discussed below, and a 12-fold or 4-fold multiple of the low and high doses to be administered in this study, respectively. This dose was well tolerated, and no acute or long-term toxicity was observed. The monkeys remained in good health throughout the 12-month duration of the study, and there was no evidence of any inflammatory responses on postmortem analysis.

1.2 OVERVIEW OF CLINICAL STUDIES

Following the successful proof of concept of STN administration of AAV-GAD in the nonclinical models, a Phase 1, first-in-human, unilateral treatment, dose escalation study was conducted (Kaplitt et al. 2007). In this open-label study, 12 participants with advanced Parkinson's disease had AAV-GAD in a final volume of 50 µL delivered to one STN. This allowed the untreated side to serve as a control. Participants were divided into 3 equal groups, with the low dose group receiving a total of $3.5x10^9$ vg, the middle dose group receiving $1.05x10^{10}$ vg and the high dose group receiving $3.5x10^{10}$ vg. Data from this Phase 1 study showed treatment with AAV-GAD to be well tolerated and safe, with improved motor function contralateral to the treated hemisphere. ^{18}F-deoxyglucose-positron emission tomography (^{18}FDG-PET), performed by an Investigator blinded to the side that was treated, demonstrated improvement in abnormal thalamic metabolism only in the treated hemisphere, thereby providing objective biological support for the clinical efficacy observations (Feigin et al. 2007).

Following completion of the Phase 1 study, a randomized, double-blinded, sham surgery, controlled, multicenter, Phase 2 study was conducted. In this study, 22 participants were randomized to treatment with 35 µL AAV-GAD (1×10^{12} vg/mL concentration) per hemisphere for a dose of 3.5×10^{10} vg (7.0×10^{10} vg total dose to the participant), and 23 participants were randomized to a sham surgery procedure. Of the 23 sham participants, 14 participants subsequently received AAV-GAD in the open-label phase of the study prior to premature discontinuation of the study and IND inactivation (LeWitt et al. 2011).

Data from the Phase 1 and 2 studies confirmed that treatment with AAV-GAD was both well tolerated and safe, with no serious adverse events (SAEs) related to the gene transfer or to the surgical procedure (Kaplitt et al. 2007, LeWitt et al. 2011, Niethammer et al. 2017).

In both the Phase 1 and Phase 2 studies, treatment with AAV-GAD led to statistically significant improvements in the primary efficacy endpoint, the Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 (motor examination) score in the "off" state. Improvement was observed at 3 months and continued for the duration of the study (12 months). In the Phase 2 study, the mean improvement in the "off" state UPDRS Part 3 (motor examination) scores was statistically significantly greater than that achieved in the sham surgery group at the primary blinded endpoint of 6 months and continued through 12 months (LeWitt et al. 2011, Niethammer et al. 2017). There was also a significantly greater percentage of clinically meaningful responders, defined as 9 points or greater in UPDRS Part 3 improvement, in the AAV-GAD group compared with the sham group at both 6 and 12 months (Niethammer et al. 2017). The Phase 2 study also noted improvements in the amount of time spent dyskinetic as well as ON time per day throughout the 12-month follow-up (Niethammer et al. 2017).

The Phase 2 study further identified a unique ^{18}FDG-PET brain network pattern associated with response to AAV-GAD therapy, involving the generation of new polysynaptic functional pathways linking the STN to the motor cortical regions (Niethammer et al. 2018). This new ^{18}FDG-PET metabolic network is termed the GAD-related pattern (GADRP) and is quantified using a *z*-scale unit score. This network was defined in an unbiased fashion while the data were blinded, using mathematical modeling to identify patterns which might distinguish AAV-GAD from sham. While AAV-GAD-treated participants showed significant and substantial changes in the GADRP at both 6 and 12 months, the sham-treated participants showed no significant changes in GADRP at either timepoint. Additionally, there was a strong positive correlation between the change in UPDRS Part 3 score and the change in GADRP. These data indicate that GADRP is an objective biomarker of Parkinson's disease brain network changes that is both specific to AAV-GAD-treated participants and reflective of clinical improvement.

Following identification of the GADRP in the Phase 2 study imaging data, the GADRP was also retrospectively quantified using the ^{18}FDG-PET data from the Phase 1 study, blinded to treatment dose. The ^{18}FDG-PET pattern unique to AAV-GAD treatment in the Phase 2 study was confirmed in the Phase 1 high-dose participants (same dose used in each STN in the Phase 2 study) but not in the lower-dose cohorts. These results help to both confirm the validity of the GADRP, since it

was found to be present in Phase 1 participants treated long before the GADRP was first identified, and demonstrates the robustness of the GADRP, since it was present in 2 different clinical studies of AAV-GAD performed years apart at different clinical centers using different stocks of AAV-GAD.

In summary, Phase 1 and Phase 2 clinical studies have demonstrated safety and efficacy of AAV-GAD treatment in participants with Parkinson's disease (Feigin et al. 2007, Kaplitt et al. 2007, LeWitt et al. 2011, Niethammer et al. 2017). Efficacy was determined by a significant reduction in the UPDRS Part 3 (motor examination) score in the "off" state. In addition, treatment with AAV-GAD therapy was associated with a unique brain network defined by ^{18}FDG-PET (Niethammer et al. 2018). There was a strongly positive correlation between the change in UPDRS score and the change in this AAV-GAD -induced ^{18}FDG-PET pattern (GADRP). This pattern was not observed in the sham surgery control group.

1.3 STUDY RATIONALE

Based on the encouraging findings from nonclinical and Phase 1 and 2 clinical studies, MeiraGTx is proposing to conduct a new Phase 1/2 clinical study (MGT-GAD-025) of AAV-GAD infusion into human Parkinson's disease participants with inadequate medication responses. This study will use AAV-GAD manufactured using new optimized processes that meet current FDA standards. As a result, it is necessary to first evaluate the safety and tolerability of AAV-GAD produced with this new method prior to conducting any further studies. This new process will use the same vector used in the prior Phase 1 and 2 studies and participants treated with the low dose will receive the same dose used in the prior Phase 2 study. Data from NHPs and other nonclinical toxicology studies established a no observed adverse effect level (NOAEL) with a safety margin of >4 to 5-fold the high dose in this current MGT-GAD-025 study.

1.3.1 ^{18}FDG-PET as a Potential Biomarker of AAV-GAD Treatment Effect

^{18}FDG-PET will be used in the screening process to exclude participants with atypical forms of Parkinson's disease most commonly misdiagnosed as idiopathic Parkinson's disease, i.e., those with multiple system atrophy (MSA) or progressive supranuclear palsy (PSP) (Tang et al. 2010). ^{18}FDG-PET measures the uptake of radiolabeled, peripherally administered glucose in brain tissue, providing an index of the relative activity of neurons within a region or in a network of regions. Therefore, the abnormalities in brain network activity can be evaluated with this imaging technique, and biological changes in brain function can be objectively measured following interventions.

Baseline ^{18}FDG-PET scans will be assessed using an automated differential diagnosis algorithm based on previously identified disease-specific brain networks diagnostic of idiopathic PD to exclude participants with "lookalike" disorders such as multiple system atrophy and progressive supranuclear palsy (Tang et al. 2010, Tripathi et al. 2016, Rus et al. 2020). Scans will also be evaluated for GADRP in a double-blind fashion at baseline and at 6 months after study drug administration as an exploratory evaluation for potential correlates of efficacy.

1.4 BENEFIT/RISK

1.4.1 Potential Benefits of AAV-GAD

Early in the course of Parkinson's disease, medications enhancing dopaminergic neurotransmission are sufficient for achieving symptomatic improvement of most clinical features. Facilitation of dopaminergic signaling continues to benefit most patients, but as the disorder advances, higher and/or more frequent doses of dopaminergic drugs are required, as well as increased numbers of medications, and there is an increasing chance for patients to develop drug-related complications such as involuntary movements (dyskinesias), increased off times and motor fluctuations. As a result, Parkinson's disease usually progresses, and patients typically worsen and become less responsive to dopaminergic medication while developing adverse effects of medical therapy. When patients have disabling motor symptoms that no longer respond adequately to medical therapy and/or have complications of medical therapy, such as dyskinesias or motor fluctuations, medical options are limited.

Surgical options for these more advanced patients include destructive lesioning of the STN (i.e., subthalamotomy) or deep brain stimulation (DBS) of the STN to reduce excessive excitatory glutamatergic drive from STN projection neurons. However, subthalamotomy is permanent and can adversely affect critical nearby white matter connections. It is often not well tolerated when administered bilaterally, which is usually required for most patients. Deep brain stimulation is better tolerated than subthalamotomy as it modulates STN activity rather than destroying STN neurons. However, electrical stimulation from DBS is not specific to STN neurons and can also influence nearby white matter connections, leading to dose-limiting adverse effects such as speech and swallowing problems, sensory changes, and gait dysfunction.

Although DBS is effective and the current standard of care for patients who do not respond adequately to medications, the procedure has many limitations which complicate the patient's experience and limit access to therapy. Since DBS requires installation of electrodes into the brain and an implanted electrical stimulator, there is risk of inflammation, hardware-related infections, wound breakdown or skin erosion and pain from scarring, or skin sensitivity from the subcutaneous hardware. Patients must undergo 2 surgeries, the first to implant the brain electrode and a second to implant the pulse generator, with the second procedure usually performed under general anesthesia to facilitate tunneling of lead extensions. Patients must live in reasonable proximity to a DBS center, since most require frequent visits to reprogram and optimize DBS therapy for several months after surgery and periodic follow-ups indefinitely after the initial programming period. The DBS pulse generators also have a limited life span and must be replaced after some time. Finally, DBS is a local therapy that is designed to influence only the target structure and does not directly influence the basal ganglia circuitry, which controls movement beyond local effects on the STN.

The AAV-GAD gene therapy described in this protocol offers a method to increase GAD activity in the STN, enhance GABA production within the STN to reduce abnormal activity and release GABA downstream through STN projections to GPi/SNr. This improves the neurochemistry and

neuronal activity of all these structures, normalizing basal ganglia outflow and restoring motor function. Furthermore, AAV-GAD has the potential to overcome many of the limitations of DBS. Unlike DBS, AAV-GAD treatment requires only one routine stereotactic surgery, carried out under local anesthesia with no need for general anesthesia. No equipment is required to be permanently implanted in the brain, and there is no need for burdensome and lengthy post-surgical optimization of therapy. AAV-GAD treatment therefore avoids the potential risk of indwelling hardware-related infections. In both the Phase 1 and 2 studies, AAV-GAD led to clinical benefits in motor function without the need for ongoing management or adjustment of the therapy, and it was confirmed that AAV-GAD was both well tolerated and safe, with no SAEs related to the gene transfer. AAV-GAD is also infused into the STN, which is the most common target for Parkinson's disease surgery, so the procedure to identify and insert an infusion catheter into the STN is standard and has been utilized for decades in surgery for Parkinson's disease.

1.4.2 Potential Risks of AAV-GAD

Most of the participants in this study will be candidates for bilateral STN DBS. The bilateral administration of AAV-GAD into the STN is not expected to preclude any other Parkinson's disease treatment option if it fails to achieve clinically meaningful improvements. Yet it is theoretically possible that the passage of the infusion catheter into the STN could induce scar tissue that could jeopardize future DBS electrode positioning in that structure. However, there is prior experience of carrying out repeated DBS electrode placement in the same location. For example, a DBS system is sometimes removed due to refractory infection and reinserted several months later, after the infection clears. This is analogous to removal of the catheter followed by implantation of a DBS system in the future. The results from these experiences do not indicate that the second procedure poses an increased risk of complications. Three of 12 participants in the Phase 1 study experienced suboptimal long-term responses to unilateral gene therapy and progression of disease in the untreated hemisphere and subsequently underwent bilateral DBS-STN approximately 18 months later with no reported adverse events (AEs).

The risks associated with placement of the infusion catheter are similar to those that occur with the placement of depth electrodes for DBS. Implanting the infusion catheter carries the following risks also associated with other brain surgery procedures: paralysis, coma, and/or death; stroke; cerebrospinal fluid leakage; seizures; allergic response to implanted materials; reaction to anesthetic agents; nausea and/or vomiting; temporary or permanent neurological complications; confusion or attention deficits; pain or swelling at surgical sites; and headache/migraine. The DBS technique has a complication rate of approximately 1% for hemorrhage locally in the path of the electrodes. The risk for an operation-related infection is also possible; however, removal of all introduced equipment following gene therapy infusion is expected to reduce the possibility of hardware-related infections and other wound complications that occur with permanently implanted hardware. The acute delivery system for infusion of AAV-GAD is investigational. There are potential risks of catheter migration leading to off-target infusion and pump or other unexpected system malfunction that could lead to delivery of less or more AAV-GAD than the intended delivery volume. Appropriate risk control measures were implemented to mitigate these risks and

their effectiveness verified through engineering tests. These measures include the use of a breakaway connector to avoid accidental catheter movement and the use of a preset torque screwdriver to ensure a leak-free connection with the syringe. Patency checks are to be performed before and after each infusion to provide confirmation of the functionality of each infusion device that is used.

Adverse events reported during the Phase 1 study included headache (4 participants), nausea (1 participant), fatigue (1 participant), pain at the site of incision (1 participant), and subdural fluid collection (1 participant). These AEs were reported as unrelated to AAV-GAD. There were no deaths in the study. Three participants had SAEs (i.e., a hospitalization for a freezing episode in the off state after discontinuing entacapone, a COPD exacerbation, and arthroscopic knee surgery), which were reported as unrelated to AAV-GAD or procedures and resolved. Additionally, there were no clinically significant laboratory abnormalities, and there were no measured changes in antibody titers to either the virus or transgene in any participant.

Adverse events reported during the 12-month duration of the Phase 2 study included headache (7 AAV-GAD and 2 sham participants), nausea (6 AAV-GAD, 2 sham), depression (4 AAV-GAD, 2 sham), and worsening of Parkinsonism (8 sham participants). Other AEs reported in at least 2 participants in either group were influenza, sinusitis, incision site complication, muscular weakness, hypoesthesia, insomnia, and rash. The AEs were mostly mild and resolved. During the 6-month blinded phase of the study, 1 SAE was reported (i.e., bowel obstruction in a participant in the AAV-GAD treatment group). This event resolved and was classified as unrelated to AAV-GAD or the surgical procedure.

Nonetheless, there remains the possibility of an unanticipated reaction to the vector produced using the new method despite all the prior human safety data, which is the justification for this new Phase 1/2 study. Similarly, even though AAV-GAD was well tolerated previously, there is still the possibility of an unanticipated response to GAD expression within the STN, which might be controlled by medication adjustment or, in an extreme situation, DBS or even subthalamotomy to remove the source of GAD production. It is possible that even these may not be fully effective at resolving any unexpected AE, particularly if this is due to an inadvertent off-target infusion of AAV-GAD. The risk of permanent complication from off-target surgery is common to any gene therapy, cell therapy, or lesioning procedure and is not unique to AAV-GAD, although in both animal and human studies, there has been no evidence of SAEs related to off-target infusion of AAV-GAD other than inadequate therapeutic responses.

2 STUDY OBJECTIVES

All objectives and endpoints are listed in the table below.

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of AAV-GAD delivered to the STN in participants with PD	• Number of participants with adverse events and serious adverse events
Secondary	
• Not applicable	
Exploratory	
• [redacted]	[redacted]
• [redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
• [redacted]	[redacted]

3 STUDY DESCRIPTION

3.1 SUMMARY OF STUDY DESIGN

This is a Phase 1/2, randomized, double-blind, sham-controlled study designed to assess the safety and tolerability of AAV-GAD administered bilaterally into the STN in participants with Parkinson's disease not adequately controlled with appropriate anti-Parkinsonian medications.

The study will be carried out in the US at approximately 5 sites with established and highly experienced surgical programs for DBS treatment of Parkinson's disease. The principal investigators will be neurosurgeons or neurologists with expertise in the assessment and treatment of participants with Parkinson's disease and with strong backgrounds in clinical research. Each site will also have support personnel knowledgeable in the care of participants with this disorder.

Approximately 14 eligible participants will be randomized to receive 1 of 2 doses of AAV-GAD infused bilaterally into the STN (5 participants per dose group) or sham surgery (bilateral partial-thickness burr hole procedure) (4 participants) and followed for 6 months.

After discussion of the study risks and possible benefits with the Investigator, participants will provide written informed consent and be considered eligible for the study if they satisfy all inclusion and exclusion criteria. Day 1 will be defined as the day of AAV-GAD or sham treatment.

Safety and tolerability of AAV-GAD gene transfer will be assessed by AEs, vital sign measurements, neurological examinations, physical examinations, radiographic imaging of the head (computed tomography [CT] and magnetic resonance imaging [MRI]), clinical laboratory evaluations, electrocardiograms (ECGs), immune response, and the Columbia-Suicide Severity Rating Scale.

A Data and Safety Monitoring Board (DSMB) will be established for this study to provide expert input on safety of the investigational product, surgical procedure, and related issues.

Participants will also be assessed for potential clinical responses of AAV-GAD on Parkinson's disease signs, symptoms, and disabilities using assessments widely used in Parkinson's disease research for evaluating new medications and surgical procedures.

Upon completion of this study, participants randomized to receive AAV-GAD treatment will be asked to enter a long-term (4.5 year) safety follow-up study (MGT-GAD-026) in accordance with applicable regulatory agency guidance for surveillance of participants who receive gene therapy. Participants randomized to the sham group in this study will be offered bilateral, open-label AAV-GAD treatment as part of the long-term follow-up study (pending regulatory approval) and will be followed for 5 years of assessments consistent with those participants who received AAV-GAD in study MGT-GAD-025.

4 SELECTION AND WITHDRAWAL OF PARTICIPANTS

Participants who meet all inclusion criteria and none of the exclusion criteria will be eligible to participate in the study.

Individuals who do not meet the criteria for participation in this study (screen failure) or individuals who have not completed the screening assessments within the specified time period may be rescreened, after discussion with the Sponsor. Rescreened participants will be assigned a new participant number. Those tests that require repetition will be repeated, as needed, upon the agreement of the Sponsor.

4.1 INCLUSION CRITERIA

1. Male or female
2. Age 25 to 85 years, inclusive.
3. Must sign an informed consent form (ICF) (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for the study and is willing to participate in the study and consider participation in the long-term follow-up study.
4. Diagnosis of probable idiopathic Parkinson's disease by United Kingdom Parkinson's Disease Society Brain Bank criteria and no evidence of another Parkinsonian disorder.
5. Completed cranial MRI and ^{18}FDG-PET during Screening. MRI and ^{18}FDG-PET scans obtained during Screening will be used as baseline tests and will be reviewed to verify the diagnosis of Parkinson's disease.
6. Presence of typical features of Parkinson's disease and history of levodopa responsiveness demonstrated for at least 12 months prior to Screening.
7. Progressive Parkinsonian disability with demonstrated response from continued use of levodopa (or from other Parkinson's disease medications if part of the treatment regimen), but with insufficient response to medication (e.g., uncontrolled tremors, increased off-time, decreased on-time, motor fluctuations, dyskinesias, gait disturbance) or with intolerable side effects as judged by the Investigator.
8. Severe disability, which includes a practically defined "off" state MDS-UPDRS Part 3 (motor examination) score of ≥25 points after overnight omission of all Parkinson's disease medications.
9. Continued use of an unchanged stable anti-Parkinsonian drug regimen for ≥4 weeks prior to Screening.
10. Willingness to not add any new treatments for Parkinson's disease for the duration of the 6-month study period. Adjustments in the dose of dopaminergic medications are permitted when medically indicated.
11. Agrees not to participate in another interventional study until completion of this study and the long-term follow-up study.

12. Willingness to not receive DBS or any other approved or experimental surgical therapy for PD during the 6-month study period.
13. Receiving stable doses of other medications for any other underlying medical conditions for ≥4 weeks prior to Screening.
14. Must demonstrate a full understanding of the Hauser Patient Diary rating criteria and demonstrate proficiency in completing the diary by reaching at least 66% of diary concordance with a site rater.
15. A woman must be:
    a. Not of childbearing potential or:
    b. Of childbearing potential and
        - Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method for at least 6 months after receiving the last dose of study intervention. The Investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are hormonal or barrier methods of contraceptive, or sexual abstinence.

    NOTE: Participants who are randomly assigned to sham surgery will also be required to adhere to this restriction to receive treatment in Study MGT-GAD-026.
16. If male, willing to use barrier and spermicide form of contraception or maintain sexual abstinence for at least 6 months following surgery.

    NOTE: Participants who are randomly assigned to sham surgery will also be required to adhere to this restriction to receive treatment in Study MGT-GAD-026.
17. Ability to discontinue use of aspirin, other antiplatelet drugs, or anti-coagulants at least 1 week prior to surgery and for 1 week following surgery.

4.2 EXCLUSION CRITERIA

1. Women who are pregnant or breastfeeding. Women of childbearing potential are required to have a negative serum pregnancy test at the Screening Visit and within approximately 1 week prior to surgery on Day 1. Participants are considered not of childbearing potential if they are surgically sterile (i.e., they have undergone a hysterectomy or bilateral oophorectomy), or are postmenopausal.
2. Any experimental therapy (drug or biologic) within 3 months prior to Screening.
3. Have a known allergy to any of the non-investigational drugs (e.g., antibiotics and local anesthesia) to be used in the study.
4. Known allergies, hypersensitivity, or intolerance to AAV-GAD excipients.
5. Any prior history of brain surgery for Parkinson's disease.
6. Ongoing treatment with dopamine receptor-blocking drugs.

7. History of any serious cerebral insult, such as head injury, or central nervous system infection, or uncontrolled seizures.
8. Mental retardation or impaired cognitive abilities, as judged by patient history or cognitive impairment as defined by Montreal Cognitive Assessment (MoCA) ≤20.
9. Focal or lateralized central nervous system (CNS) neurological deficits other than mild memory disturbance.
10. Neurological features suggestive of the diagnosis of a "Parkinson-plus" disorder (such as progressive supranuclear palsy, multiple system atrophy, corticobasal ganglionic degeneration, or "lower body" Parkinsonism) or normal pressure hydrocephalus.
11. Evidence of lesions or other significant abnormalities on cranial neuroimaging (either CT, MRI, or ^{18}FDG-PET) suggesting findings compatible with a probable diagnosis other than Parkinson's disease.
12. Alanine aminotransferase and/or aspartate aminotransferase >1.5 upper limit of normal (ULN) or alkaline phosphatase >1.5 ULN.
13. Clinically relevant abnormality on 12-lead ECG.
14. Administration of any live virus vaccine within 4 weeks of surgery.
15. Evidence of other significant medical or psychiatric disorders, such as psychosis, frequent occurrence of hallucinations, severe depression, significant cognitive decline in recent months, systemic organ failure, or bleeding diathesis, not attributable to adverse effects of anti-Parkinsonian medications.
16. Evidence of active impulse control disorder, or substance or alcohol abuse unrelated to use of dopaminergic medication.
17. Significant concurrent or recently diagnosed (≤2 months prior to the Screening Visit) medical condition that, in the opinion of the Investigator, could affect the participant's ability to tolerate or complete the study.
18. Current immunosuppressive therapy or underlying disorder associated with diminished immunocompetence.
19. Serum platelet count of <80,000/mm^3, international normalized ratio (INR) >1.3, or partial thromboplastin time (PTT) >40 seconds.
20. Score of ≥20 on the Beck Depression Inventory-II.
21. Acute or chronic systemic and/or local skin infections involving the scalp.
22. Criterion removed in protocol version 6.0.
23. Has any other condition that, at the consideration of the Investigator, makes them inappropriate for entry into the study.
24. Is an employee of MeiraGTx.
25. Is an employee of the Investigator or study site, with direct involvement in the proposed study or other studies under the direction of that Investigator or study site, as well as family members of the employees or the Investigator.

4.3 WITHDRAWAL CRITERIA

Participation in this clinical study may be discontinued for any of the following reasons:

- The participant withdraws consent or requests discontinuation from the study for any reason
- Occurrence of any medical condition or circumstance that exposes the participant to substantial risk and/or does not allow the participant to adhere to the requirements of the protocol
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the participant
- Requirement of prohibited concomitant medication
- Participant failure to comply with protocol requirements or study-related procedures
- Termination of the study by the sponsor or the regulatory authority

The reason for participant withdrawal must be documented in the electronic case report form (eCRF).

Participants who withdraw prior to surgery will be replaced. Participants who withdraw after surgery will not be replaced.

4.4 END OF STUDY

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last participant in the study. All participants who receive AAV-GAD will be followed in a subsequent long-term study in accordance with applicable regulatory agency guidance for the follow-up of participants who receive gene therapy. Additionally, participants randomized to the sham surgery group in this study will be offered bilateral, open-label AAV-GAD treatment as part of the long-term follow-up study.

5 STUDY TREATMENTS

5.1 TREATMENT GROUPS

Participants will be randomized to one of the three following groups:

- AAV-GAD at a dose of 3.5×10^{10} vg/STN, low dose group
- AAVGAD at a dose of 10.45×10^{10} vg/STN, high dose group
- Sham surgery

5.2 RATIONALE FOR DOSING

AAV-GAD will be administered bilaterally via stereotactic infusion into each STN (1 infusion per hemisphere: 2 infusions in total). Each STN will be infused with either 35 µL of 1×10^{12} vg/mL AAV-GAD, for a dose of 3.5×10^{10} vg/STN (low dose group) or 50 µL of 2.09×10^{12} vg/mL AAV-GAD, for a dose of 10.45×10^{10} vg/STN (high dose group). The total dose per participant will be 7.0×10^{10} vg or 20.9×10^{10} vg, in the low and high dose groups, respectively.

The doses are based on the safety demonstrated in MPTP-treated Parkinsonian NHPs and the prior Phase 1 and 2 studies, and safety data from other nonclinical studies evaluating AAV gene delivery into the brain. The high dose is >4-fold and the low dose is >12-fold less than the dose received by the NHPs (based on correcting for STN neuronal counts), which was well tolerated without any signs of toxicity (Hamani et al. 2004, Emborg et al. 2007).

Data from the prior Phase 1 study showed treatment with AAV-GAD to be well tolerated and safe with improved motor function contralateral to the treated hemisphere and consistent with improvement in thalamic metabolism based on ^{18}FDG-PET (Feigin et al. 2007, Kaplitt et al. 2007). All participants in the study received 50 µL of AAV-GAD infused into the STN, with the highest dose cohort receiving 3.5 $x10^{10}$ vg into the STN.

In the subsequent Phase 2 study, participants randomized to active treatment received AAV-GAD at a dose of 35 µL of 1×10^{12} vg/mL into each STN (i.e., the same total vg per STN as in the prior Phase 1 and the same as the low dose in the current study). The Phase 2 study confirmed that treatment with AAV-GAD was safe and well tolerated, and improved motor function.

A nonclinical GLP study evaluating the same AAV-GAD manufactured using new optimized processes delivered to the STN in rodents established a safe NOAEL that is >5-fold and >16-fold (based on correcting for STN volume) the high and low dose in this current MGT-GAD-025 study, respectively.

The safety and potential additional efficacy benefit of adding a higher dose group to this study are supported by previously observed safety as well as efficacy data.

- In the previous Phase 2 study, the same dose was delivered to each STN as the low dose in this current study. In one participant, however, due to mistargeting, the contralateral catheter was

inadvertently placed across the midline into the same STN that received the first catheter (LeWitt et al. 2011). This led to two catheters delivering the total viral load into a single STN, resulting in a doubling of the volume and dose to that STN in the one hemisphere (to a total volume of 70 µL). No adverse events resulted from this surgical error. Also, both the volume and titer of virus delivered to the brain in this study is in most cases orders of magnitude below the majority of completed or active human gene therapy studies approved by the FDA using AAV in the brain for a variety of disorders.

- While the safety data suggest that the higher dose would not be expected to pose an unacceptable risk, there is also justification for adding a higher dose based upon the potential for increasing efficacy of the gene therapy product. The low dose of AAV-GAD has demonstrated efficacy in previous Phase 1 and Phase 2 clinical studies conducted with AAV-GAD produced with an earlier method. In the Phase 2 study, the participant who inadvertently received a double dose to a single STN not only had no adverse effects but appeared to have a roughly 50% improvement compared to baseline in the primary outcome measure, which was the off-medication UPDRS part 3 score, despite only receiving treatment to one STN. This was also approximately double the average improvement observed in that cohort (in which all other participants received the intended dose per STN and received bilateral treatment).
- This suggestion of greater potential clinical improvement from a higher dose of AAV-GAD to the STN is also supported by functional imaging data. In the Phase 2 study, FDG-PET was used to evaluate brain network changes before and after gene therapy. From that data, the novel network GADRP was identified, which indicated a reorganization of dysfunctional brain circuits into more therapeutically beneficial circuits in response to AAV-GAD. The data demonstrated a highly significant change in this GADRP in treated participants, which correlated with the degree of clinical improvement, while this was not observed in the sham surgery group (Niethammer et al. 2018). This pattern was unknown at the time of the prior Phase 1 study, yet FDG-PET scans were obtained as a part of that study, thus a retrospective analysis of that data could be performed. In the prior Phase 1 study, participants were treated in 1 of 3 dose cohorts that escalated by approximately 3-fold between cohorts. The high dose in that Phase 1 study was equivalent to that used for the subsequent Phase 2 study on a per-hemisphere basis (and is the same as the low dose in the current study). FDG-PET analysis demonstrated consistent changes in GADRP, similar to the Phase 2 study but of a lower magnitude, and only in the highest dose cohort. The lower magnitude was expected since participants in the prior Phase 1 study were only treated in one hemisphere compared to bilateral treatment delivered in the Phase 2 study. This suggests that the highest dose from the prior Phase 1 study was potentially just above a therapeutic threshold and that a higher dose might further enhance GADRP, which would be expected to improve clinical scores based upon the correlation between the two in the Phase 2 data.

In summary, data from the previous Phase 1 and 2 studies demonstrated that treatment with the low dose that is included in the current study was safe and well tolerated, with no SAEs related to gene transfer, and with improvements in motor function. Clinical and functional imaging data suggest a potential for greater efficacy from delivery of a higher dose of AAV-GAD. Data from

NHP study and other nonclinical toxicology studies established a NOAEL with safety margins of >4-fold to >5-fold the high dose in this current MGT-GAD-025 study.

5.3 RANDOMIZATION AND BLINDING

Participants will be randomized to receive 1 of 2 doses of AAV-GAD (5 participants per dose group) or sham surgery (4 participants).

Randomization will occur after all inclusion and exclusion criteria have been met and surgery is scheduled.

Details of the randomization and randomization procedure will be provided in a randomization-specification document. The actual date/time of the randomization will be collected in the eCRF.

This study will be performed in a double-blinded manner, with Investigators, study staff, and participants unaware of treatment assignment. However, due to the requirement for surgical delivery of ATIMP in the operating room, surgeons, surgical staff, the pharmacist and the radiologist will be aware of treatment status in accordance with site-specific blinding/unblinding procedures. The surgical staff will perform the surgery and provide postoperative care; they will play no role in the evaluation of study participants.

5.4 BREAKING THE BLIND

After a participant completes the Week 26 Visit and that participant's data are considered clean in the MGT-GAD-025 study database, that participant's treatment assignment will be unblinded. Participants randomized to AAV-GAD treatment will be consented to enter the long-term follow-up study and participants randomized to sham surgery will be consented and offered AAV-GAD treatment in the long-term follow-up study (pending regulatory approval).

Emergency unblinding procedure

Code-breaking and unblinding in the event of medical emergencies can be done by the Investigator via physical code break envelopes stored at the site in accordance with the site's blinding/unblinding procedures.

Unblinding by the Investigator should occur only in the event of an AE/SAE for which it is necessary to know the treatment assignment to determine an appropriate course of therapy for the participant. The Investigator should first discuss options with the Sponsor, if possible, with due consideration of the safety of the participant.

Participants for whom the code has been broken by the Investigator will be encouraged to attend all post-treatment visits as indicated in the Schedule of Activities. Code breaking will be documented in the eCRF.

5.5 TREATMENT SUPPLIES

5.5.1 AAV-GAD

5.5.1.1 Formulation and Packaging

AAV-GAD is formulated in a buffered solution of KH_2PO_4, Na_2HPO_4, NaCl, and $MgCl_2$, with pH 7.4. The AAV-GAD formulation will be diluted to a concentration of $1x10^{12}$ vg/mL (low dose) or used at the undiluted concentration of 2.09×10^{12} vg/mL (high dose), as specified in the Pharmacy Manual.

The vehicle for the sham surgery procedure will be saline.

5.5.1.2 Study Drug Preparation and Dispensing

AAV-GAD will be supplied in vials with a coded label. The label will contain all information as per local requirements/regulations.

5.5.2 Acute Delivery System

Instructions for use (IFU) and maintenance of the Acute Delivery System will be provided to each site.

5.5.2.1 Acute Delivery System Description

The following devices are used as part of the procedure:

1. Infusion Catheter Kit: Sterile, disposable, single-patient, single-use infusion catheter system consisting of a parenchymal catheter and extension set (including a breakaway connector).
2. Cranial Anchor Kit: Sterile, disposable, single-patient, single-use Cranial Anchor kit
3. Transfer Guard and Syringe Kit: Sterile, disposable, single-patient, single-use syringe and sterile, disposable, single-patient, single-use syringe transfer guard
4. Accessory kit
5. Reusable pump

These components facilitate infusion by connecting the syringe containing the therapeutic agent(s) to the parenchymal catheter via the extension set. This system includes a breakaway connector to preclude accidental movement of the parenchymal catheter during infusion.

The infusion catheter kit, cranial anchor kit, transfer guard and syringe kit, and accessory kit will be manufactured by a qualified contract manufacturing organization (CMO). The pump is manufactured by Harvard Biosciences and the final product is provided to MeiraGTx for use in the clinical study. Neither MeiraGTx nor its qualified CMO will be reprocessing the syringe or the pump. Please refer to the IFU for further details.

All the components listed above will be provided by MeiraGTx to the site.

5.5.2.2 Device Packaging

The single-use disposable infusion catheter kit, anchor kit, and transfer guard and syringe kit (1 per hemisphere for each kit) will each be packaged and distributed in sterile packaging. The reusable accessory kit will be packaged in sterile packaging. The pump will be distributed in the packaging provided by the manufacturer.

5.5.3 AAV-GAD Administration and Surgery Procedure

On the day of AAV-GAD administration, participants will be taken to the operating room. Intravenous antibiotics will be given prior to skin incision. The neurosurgeon will make a frontal burr hole at a standard entry site normally used for the placement of STN DBS electrodes. Local anesthesia will be used unless general anesthesia is necessary for participant safety. This entry site is usually at or just anterior to the coronal suture in the mid-pupillary line; however, the entry site can be adjusted for optimal safety and accuracy depending upon the assessment of the participant's presurgical CT or MRI. The brain parenchymal infusion catheters will be placed in each STN bilaterally using standard stereotactic procedures.

Details of syringe and catheter infusion system preparation, insertion of the catheter, infusion, removal of the catheter, and intraoperative and post-operative imaging will be outlined in the IFU for the Acute Delivery System.

Briefly, standard stereotactic systems for the insertion of STN DBS electrodes will be used to target each STN. After a plan is created for trajectories from the frontal burr hole to the STN target, a burr hole will be generated centered over the planned entry site. The base of a specially designed burr hole cover used to secure the catheter will then be fixed to the skull. The trajectory plan and/or coordinates are to be confirmed prior to insertion of the cannula guide for each catheter placement. The surgeon will read the settings of the stereotactic frame or the plan in a frameless system while an assistant confirms and documents in the source documents that these match the plan written prior to the start of surgery. Standard methods for localizing the STN at the site will then be performed to confirm the proper location of the center of the STN. Once the dorsal and ventral limits of the STN are mapped along an optimal trajectory, the rigid cannula guide will be inserted to a depth of 10 mm above the intended target. The intended target will be the middle of the STN (based upon the intraoperative mapping).

Prior to thawing the study drug vial, the code will be confirmed to match the code provided by the sponsor. Prior to infusion, the vial will be thawed at room temperature and the AAV-GAD formulation will be prepared as specified in the Pharmacy Manual. An excess of 100 µL AAV-GAD will be drawn into the infusion syringe under sterile conditions. The neurosurgeon will then connect the syringe to the infusion catheter. Prior to inserting the catheter, the neurosurgeon will take the sterile syringe filled with the AAV-GAD solution and will prime the catheter system with the solution to flush air and confirm flow.

The catheter will then be disconnected from the infusion system and will be inserted to a predetermined depth through the cannula guide to place the tip of the infusion catheter within the center of the STN. Confirmation of the location of the catheter tip will be obtained using standard procedures for localizing DBS electrodes at the site. The cannula guide will be partially withdrawn to expose the catheter, and then the second stage of the locking mechanism (cranial anchor disk) will be inserted securely into the cranial anchor base that was previously fixed to the skull. The ancillary surgical supplies, forceps and standard Rhoton dissector will be used to close the locking mechanism and secure the catheter. The catheter and the release ripcord for the locking cap will both be externalized through the skin flap by using an IV needle and the incision will then be sutured. The catheter will then be reattached to the infusion system.

Prior to inserting the contralateral catheter, the surgeon will verbally confirm the coordinates or localization plan for the catheter tip in the contralateral hemisphere and this will be recorded in the source documents to document that they completed this prior to insertion of the contralateral cannula guide. The contralateral catheter will then be inserted in the same manner as the first catheter. Following completion of second catheter insertion, the infusion will commence, and the frame or fiducials will be removed. Confirmation of the location of this second catheter tip will be obtained using standard procedures for localizing DBS electrodes at the site.

In preparation for the infusion, ensure that the pump (pump head and controller) is at approximately the same level as the infusion site. Ensure that the pump is maintained at the same height for the duration of the infusion. To begin infusion, the syringe will be placed into the pump that will be programmed to infuse either 35 µL or 50 µL of AAV-GAD, depending upon the dose assignment, at a rate of approximately 0.23 µL/min. After completion of AAV-GAD infusion, a non-contrast CT of the head will be performed to document the catheter position upon completion of the infusion. The catheter will then be removed in its entirety by removing the release ripcord to open the locking mechanism followed by withdrawal of the catheter. A non-contrast CT of the head will be performed within 24 hours following removal of the catheter to evaluate any new bleeding or retained catheter fragment.

5.5.4 Saline Administration and Sham Surgery Procedure

The same surgical procedure described for AAV-GAD administration will occur for the participants randomized to sham surgery; however, the burr holes will be of partial-thickness and neither the inner table of the skull nor the dura will be penetrated, thereby minimizing the risk of intracranial injury, hemorrhage, or infection. Of note, surgeons need to carefully select where they create burr holes for the sham surgery, as these holes will be used for the administration of AAV-GAD in Study MGT-GAD-026. A sham procedure to simulate mapping of the STN will be performed per the site's standard practice, with electrophysiological recordings made from a routine case played as part of a mock mapping procedure for sites using this method to target the STN. The distal ~10 cm of the catheter will be cut, unbeknownst to the participant, and the truncated catheter will be inserted into the partial-thickness burr hole and fixed in place with the locking burr hole cover in identical fashion to the penetrating catheters for the AAV-GAD groups.

The release ripcord and catheter will be externalized in the same fashion as for AAV-GAD participants and then saline infusion will be performed through catheters inserted into each partial-thickness burr hole (no brain infusion). The volume of saline will be 35 µL on each side (combined total of 70 µL). A sham non-contrast CT of the head will be performed within 24 hours following removal of the catheter.

5.5.5 Treatment Compliance

Study drug will be administered under the supervision of the treating neurosurgeon as outlined in the IFU manual. Administration of study drug will be recorded in the eCRF.

5.5.6 Labeling, Storage, and Accountability

5.5.6.1 AAV-GAD Study Drug

The study drug will be labeled in accordance with the relevant current Good Clinical Practice (GCP) guidelines and MeiraGTx procedures and will include the statement "Caution: New Drug-Limited by Federal (or United States) law to Investigational Use." The study drug should be stored in the pharmacy at ≤-70ºC as specified on the label.

Health hazards related to the preparation and administration of AAV-GAD by health care workers are not anticipated. Recombinant AAV serotype 2 vectors, such as AAV-GAD, are considered to be the lowest risk group (Risk Group 1) for recombinant DNA agents and can be manipulated under the lowest biosafety level (Biosafety Level 1) according to the April 2019 National Institutes of Health Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. Nevertheless, waste generated during the preparation and administration of AAV-GAD should be properly disposed of in accordance with applicable Federal, state, and institutional policies regarding disposal of hazardous biological materials and medical waste.

All vials of study drug must be accounted for by the pharmacy. All used and unused vials will be destroyed at the site per institutional policies. Used vials are defined as the following: 1) vials that were thawed and product was infused, or 2) vials that were thawed and product was not infused.

5.5.6.2 Medical Devices

The Investigator or designee will record the receipt and disposition of the infusion catheter kits, cranial anchor kits, transfer guard and syringe kits, accessory kits, and the pumps. As used in this study, the infusion catheter kits, cranial anchor kits, transfer guard and syringe kits, and accessory kits are investigational, and all medical devices must be tracked. Shipping receipts must be retained with the study records. Details (e.g., serial number, lot number) of implants and other devices used for the surgery will be documented in the eCRF. After completion of the study, any unused infusion catheter kits, cranial anchor kits, transfer guard and syringe kits (or parts of those devices), accessory kits, and pumps must be available to be returned to MeiraGTx or designee. Final accountability and reconciliation will be completed.

The infusion catheter kits, cranial anchor kits, transfer guard and syringe kits, and accessory kits, pump(s) must be kept in a storage area that is physically separate from commercial device inventory at the clinical site. The investigational medical devices should be stored according to their respective labeling. The investigational devices or their immediate package will bear a label with the following information:

- The name and place of business of the manufacturer or distributor
- The quantity of the contents, if appropriate
- The following statement: "CAUTION - Investigational Device. Limited by Federal (or United States) Law to Investigational Use."

Following implant and administration of AAV-GAD, the parenchymal catheter system, transfer guard and syringe kit components, and accessory kit should be packaged in a sealed biohazard bag and stored until the end of the study when they will either be returned to MeiraGTx or designee or allowed to be destroyed.

All sterilized components must be used before the predetermined number of months from the date of sterilization as indicated by the "use by date" on the label.

5.6 PRIOR AND CONCOMITANT MEDICATIONS AND/OR PROCEDURES

5.6.1 Excluded Medications and/or Procedures

The following medications and procedures will be prohibited:

- Deep brain stimulation
- Other brain surgery for Parkinson's disease
- Other experimental therapy (drug or biologic) within 3 months prior to Screening and throughout participation in the study
- Dopamine receptor-blocking drugs
- Live virus vaccine within 4 weeks of surgery
- Immunosuppressive therapy
- New treatment for Parkinson's disease.

Note: Adjustments in the dose of dopaminergic medications are allowed when medically indicated.

5.6.2 Restricted Medications and/or Procedures

The following medications and procedures will be restricted:

- Aspirin, other antiplatelet drugs, or anticoagulants from 1 week prior to surgery through 1 week following surgery

Note: Participants receiving anticoagulation therapy must be able to maintain, with acceptable risk, a normal INR and PTT for at least 1 week prior to surgery and 1 week following surgery as determined by the participant's primary care physician.

5.6.3 Allowed Medications and/or Procedures

Participants will continue to receive any medications that they were receiving at study entry for underlying medical conditions. Participants should be on an unchanged, stable anti-Parkinsonian drug regimen and on stable doses of medications for any other underlying medical conditions for ≥4 weeks prior to Screening.

5.6.4 Documentation of Prior and Concomitant Medication Use

All concomitant medications (including prescription medications and over-the-counter preparations) used by the participant from date of ICF signing, during the study, and at the final study visit will be documented and recorded in the eCRF.

6 STUDY PROCEDURES AND VISITS

6.1 INFORMED CONSENT

Written informed consent must be obtained from participants by the Investigator or delegated clinician/staff member before any study-specific procedures are performed. See Section 12.2 for details on consent.

6.2 STUDY PROCEDURES

The Schedule of Activities (SoA) summarizes the frequency and timing of efficacy, safety, and immunogenicity assessments applicable to this study.

The diagnosis of idiopathic PD will be made before any other screening procedure takes place. During screening, assessments that are not part of the study entry criteria will be performed after the participant has qualified to enroll in the study (as per footnote "p" of the SoA [Table 1]).

All participants will be provided with an emergency card on enrollment to the study to enable 24-hour contact with study Investigators.

Participants randomly assigned to immediate treatment with AAV-GAD will be scheduled for surgery and complete the full battery of visits through the Week 26 visit (as described in the SoA), and then enter the long-term follow-up MGT-GAD-026 study.

Participants randomly assigned to sham surgery will follow the same visit schedule during the first 6 months, and then enroll in the long-term follow-up MGT-GAD-026 study, in which these participants will be offered treatment with AAV-GAD. The Week 26 visit of this study will serve as the Baseline visit of MGT-GAD-026.

Any medical condition already present at Screening should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at screening change in severity, frequency, or seriousness at any time during the study. In such a case, it should be reported as an AE.

The Week 19 visit is a telephone visit for assessment of AEs, changes in control of Parkinsonism, and other neurological events. The following actions must be taken if a participant fails to answer or return phone calls:

- The study-site personnel must attempt to contact the participant to reschedule the missed telephone visit as soon as possible.
- The Investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, emails, fax).
- Should the participant continue to be unreachable, they will be considered to have missed the telephone visit.

During visits that include the UPDRS assessment, the MDS-UPDRS Part 3 "off" state assessment should preferably be performed before any other assessments or questionnaires. Site staff are to confirm that the last dose of dopaminergic medication(s) was taken by the participant at least 12 hours before performing the MDS-UPDRS Part 3 "off" state assessment (also see Section 7.2).

For the other assessment tools, the following order is recommended:

1. HVLT-R (10 min + 20-25 min delay*)
2. Trail Making Test (10 min)
3. Color-word interference (10 min)
4. Digit Span Test (5 min)
5. *HVLT-R delayed memory (continued from 1, above, after planned delay)
6. Verbal fluency test (10 min)
7. All other questionnaires

Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study. Similarly, unscheduled clinical chemistry examinations will be permitted as required to manage emerging issues.

6.3 EARLY TERMINATION VISIT AND WITHDRAWAL PROCEDURES

The end-of-treatment visit for participants completing the study is the Week 26 visit.

If a participant who received surgery withdraws early, they will be encouraged to maintain contact with the Investigator and allow reporting to the sponsor of follow-up MRI and clinical features related to Parkinson's disease and other neurological problems. Every effort should be made to complete the full panel of assessments scheduled for the Week 26 Visit.

If a participant discontinues (for any reason) the study after surgery on Day 1, all assessments scheduled for the Week 26 Visit should be completed.

In the case of a participant lost to follow-up, attempts to contact the participant must be made and documented in the participant's medical records.

7 EFFICACY ASSESSMENTS

7.1 ^{18}FDG-PET

^{18}FDG-PET scans will be performed per site standards to assess patient's eligibility and evaluate the abnormalities in brain network activity and biological changes in brain function.

Scans will also be evaluated for PDRP and GADRP at baseline and at 6 months after study drug administration as an exploratory evaluation for potential correlates of activity.

PDRP score is a z-scale unit score of ^{18}FDG-PET brain network pattern.

GADRP score is a z-scale unit score of ^{18}FDG-PET brain network pattern associated with response to AAV-GAD therapy, involving the generation of new polysynaptic functional pathways linking the STN to the motor cortical regions.

^{18}FDG-PET scans will be collected for centralized reading by an independent specialist.

7.2 QUESTIONNAIRES AND SCALES

The following assessment tools will be used in this study:

- Columbia Suicide severity rating scale: a measure assessed by the Investigator or a qualified member of her/his team (e.g., a neurologist), used to identify and assess individuals at risk for suicide.
- Beck Depression Inventory-II: a 21-item self-report inventory measuring the severity of depression in adolescents and adults
- Beck Anxiety Inventory: a 21-item self-report inventory measuring the severity of anxiety in adolescents and adults
- Clinical Global Impression-Severity: a 7-point scale completed by the Investigator or a qualified member of her/his team (e.g., a neurologist), to rate the severity of the participant's illness at the time of assessment, relative to her/his baseline state (prior to the surgery)
- Clinical Global Impression-Improvement: a 7-point scale completed by the Investigator or a qualified member of her/his team (e.g., a neurologist) to assess how much the participant's illness has improved or worsened relative to her/his baseline state (prior to the surgery)
- EuroQol-5 Dimensions-5 Levels Survey comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The participant is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state.

- Montreal Cognitive Assessment: a brief cognitive screening task assessment administered by the Investigator or a qualified member of her/his team (e.g., a neuropsychologist) of different cognitive abilities such as visuospatial skills, executive function, memory, language and attention.
- Parkinson's Disease Questionnaire-39 Scale: a 39-item questionnaire completed by participants that measures health status and quality of life
- Parkinson's Disease Sleep Scale-2: a 15-item scale completed by participants to self-rate and quantify the level of sleep disruption being experienced
- Unified Dyskinesia Rating Scale: a scale formatted as a questionnaire for the participant and completed by the Investigator or a qualified member of her/his team (e.g., a neurologist), used to evaluate the involuntary movements that can be associated with long-term treatment with dopaminergic medication
- MDS-Unified Parkinson's Disease Rating Scale Part 1 (Non-Motor Experiences of Daily Living), Part 2 (motor experiences of daily living), Part 3 (motor examination) and Part 4 (motor complications). Part 1 has two components: 1A concerns a number of behaviors that are assessed by the Investigator or a qualified member of her/his team (e.g., a neurologist) with all pertinent information from participants and caregivers, and 1B will be completed by the participant with or without the aid of the caregiver, but independently of the Investigator. Part 2 is designed to be a self-administered questionnaire like Part 1B. Part 3 will be completed by the Investigator or a qualified member of her/his team (e.g., a neurologist) and has instructions for the Investigator to give or demonstrate to the participant. Part 4 integrates patient-derived information with the Investigator's clinical observations and judgments and will be completed by the Investigator or a qualified member of her/his team (e.g., a neurologist).

  The MDS-UPDRS Part 3 will first be completed while in the "off" state. "Off" state scores will be obtained after at least 12 hours of holding dopaminergic medication. Once this assessment is completed, participants are to take their usual medications for Parkinson's disease. "On" state evaluations will be assessed when participants and Investigators agree that the participant is in a typical "on" state (as a guidance, the "on" state is expected to be achieved approximately 2 hours after taking medication(s) for Parkinson's disease). Participants may take additional levodopa (in addition to their usual dose) if needed to achieve the "on" state.
- Revised Hopkins Verbal Learning Test (HVLT-R) is a test administered by the Investigator or a qualified member of her/his team (e.g., a neuropsychologist), assessing verbal memory. Participants are presented with a list of words over repeated learning trials and are required to recall words from the list immediately and after a delay of 20-25 minutes and complete a yes-no delayed recognition task. The HVLT-R also provides 6 alternate forms in order to reduce the effects of practice and will be administered during each session.
- Stroop Color and Word Test (DKEFS version) is a test administered by the Investigator or a qualified member of her/his team (e.g., a neuropsychologist), measuring processing speed and

executive functioning. There are 4 parts. Participants are required to read printed color names as fast as possible (Part 1), and name color patches as fast as possible (Part 2). To assess executive functioning, and specifically cognitive inhibition, participants are then required to name the ink color of printed color names, avoiding the 'read' the printed work. In the 4th part, participants are required to do the same as in Part 3 unless the word is presented in a box, and in these instances, they must read the word instead of naming the color.

- Trail Making Test (TMT) (DKEFS version) is a paper-and-pencil test administered by the Investigator or a qualified member of her/his team (e.g., a neuropsychologist), measuring processing speed and executive functioning. There are 4 trials to complete including a cancellation task (i.e., cross-out targets as fast as possible), simple tracking tasks requiring participants to connect numbers with a line as fast as possible, connect letters in order, and lastly, a more complex task requiring them to alternate between numbers and letters in sequences.
- Verbal fluency Test (DKEFS version) is a verbal fluency test administered by the Investigator or a qualified member of her/his team (e.g., a neuropsychologist), measuring executive function and language abilities. Participants are required to generate as many words as possible aloud within a one-minute period following letter cues (3 trials) and category cues (3 trials).
- Digit Span test (part of Weschler Memory and Weschler scales) is a test administered by the Investigator or a qualified member of her/his team (e.g., a neuropsychologist), measuring attention and working memory span. Participants are required to repeat strings of digits of increasing length in the same order as well as in reverse order.

To the extent possible, all questionnaires to be used in repeated assessments should be administered by the same rater (Investigator, neuropsychologist, or neurologist, as applicable).

7.3 HAUSER PATIENT DIARY

The Hauser Patient Diary will be used to collect information on how much time a participant spends in the different Parkinson's disease states:

- ON - Good or practically normal mobility
- ON with Troubling Dyskinesia – participant is troubled by involuntary twisting, turning movements. These movements are different from the rhythmic "tremor" which is a symptom of Parkinson's disease itself
- OFF - stiffness, marked decrease in mobility, and/or immobility
- ASLEEP - time spent sleeping.

The diary is divided into 30-minute sections starting at midnight and ending at 11:30 PM.

Participation in the study requires that participants demonstrate full understanding of the rating criteria and proficiency in completing the diary. At the Screening Visit, participants will be taught

how to use the diary by a member of the study site staff. At the end of the training session, participants and a site staff rater will concurrently but separately complete diary entries for 3 half hour periods. Diary concordance of at least 66% will be required for the participant to qualify for the study.

Participants are to complete this 24-hour diary of their Parkinson's disease symptoms twice per week (on 2 nonsequential days) for 3 consecutive weeks prior to the second screening visit (i.e., the Day -7 to Day -3 visit) (baseline entries), and on 2 nonsequential days during the week prior to Day 15, and Weeks 12 and 26.

The change from baseline in absolute number of daily hours in the "on without troublesome dyskinesias" state to the weeks prior to Day 15, Week 12 and Week 26 will be compared.

8 SAFETY ASSESSMENTS

Safety will be evaluated by vital signs, neurological examinations, physical examinations, ECGs, radiographic imaging (CT and MRI), clinical laboratory evaluations, descriptive analysis of AEs (including incidence, severity, seriousness, and relatedness), immune response, and the Columbia-Suicide Severity Rating Scale over the 6-month duration of the study. Safety will continue to be assessed within the proposed separate long-term follow-up study, assuming regulatory approval.

8.1 DATA AND SAFETY MONITORING BOARD

A DSMB will be established to ensure the continuing safety of the participants enrolled in this study. This committee will consist of neurosurgeons and neurologists with expertise in the assessment and treatment of participants with Parkinson's disease and with backgrounds in clinical research. The committee will meet at predefined timepoints, or on an ad hoc basis at the request of the sponsor to provide expert consultation on specific issues as described in the DSMB charter.

8.2 ADVERSE EVENTS

Adverse event definitions are provided in Table 2.

Table 2: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this product.
Adverse Drug Reaction (ADR)/Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • Results in death • Is life threatening[a] • Requires hospitalization or prolongs existing hospitalization[b] • Results in persistent or significant disability or incapacity • Is a congenital anomaly or birth defect • Or is another important medical condition[c]
Unexpected Serious Adverse Drug Reaction	A SAR whose nature, severity or outcome is not consistent with the reference safety information (RSI). As AAV-GAD is an investigational medicinal product, the RSI is included in the IB for this study.

a: Life threatening refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g., a silent myocardial infarction).

b: Hospitalization is defined as an inpatient admission, regardless of length of stay. Hospitalization for an elective procedure for a pre-existing condition does not constitute an SAE.

c: Medical judgment should be exercised in deciding whether an AE or ADR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalization but may seriously jeopardize the participant by requiring intervention to prevent one of the other outcomes listed in the table (e.g., a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalization, or development of drug dependency).

Adverse events include:

- An exacerbation of a pre-existing illness
- An increase in the frequency or intensity of a pre-existing episodic event or condition
- A condition (regardless of whether PRESENT prior to the start of the study) that is DETECTED after study drug administration (or sham surgery). (This does not include pre-existing conditions recorded as such at screening.)
- Continuous persistent disease or a symptom present at baseline that worsens following administration of study drug (or sham surgery)
- Overdose of study drug

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is an AE
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalization where no untoward or unintended response has occurred, e.g., elective cosmetic surgery

8.2.1 Seriousness Assessment

When an AE or adverse drug/device reaction occurs, the Investigator responsible for the care of the participant must first assess whether the event is serious using the definition given in Table 2. If the event is classified as 'serious' then the sponsor/designee must be notified within 24 hours as outlined in Section 8.2.6.

8.2.2 Assessment of Severity

The Investigator will assess the severity of all AEs and/or adverse drug/device reactions (serious and nonserious) in this study as mild, moderate, or severe.

8.2.3 Assessment of Causality

For all AEs, the relationship of the AE to the administration of the study drug, the surgical procedure, and the devices is to be assessed and captured in the study-specific eCRF.

Relation to study drug is to be assessed according to the definitions in Table 3.

Table 3: Adverse Event Causality Definitions

Related	Description	Event Type
NO (unrelated, unlikely to be related)	The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship or another cause (concomitant drugs, therapies, complications, etc.) is suspected.	Unrelated AE or SAE
YES (possibly, probably, or definitely related)	The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) is more likely. The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.	AR or SAR

AE = adverse event; SAE = serious adverse event; AR= adverse reaction; SAR = serious adverse reaction.

8.2.4 Assessment of Expectedness

8.2.4.1 Unexpected Serious Adverse Reaction

If there is at least a reasonable possibility of a causal relationship between the event and the study drug, the Sponsor must assess the expectedness of the event. An unexpected serious adverse reaction (SAR) is one that is not reported in the current IB, or one that is more frequently reported or more severe than previously reported. In view of the limited clinical experience with the study drug, there are at present no events considered as expected. Therefore, any SAE that is assessed as related to study drug (i.e., considered a SAR) will be deemed an unexpected serious adverse reaction) and safety reporting guidelines will apply (Section 8.2.6).

8.2.5 Clinical Laboratory Abnormalities

It is the responsibility of the Investigator to assess the clinical significance of all abnormal laboratory values as defined by the appropriate reference range(s). All abnormal values assessed to be of clinical concern and at least possibly related to study drug or of uncertain causality should be repeated. Clinically significant abnormal laboratory values occurring during the clinical study are to be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE if intervention for management of the abnormality is required or at the discretion of the Investigator.

8.2.6 Safety Reporting Requirements

All AEs, serious and non-serious, will be fully documented on the appropriate eCRF. For each AE, the Investigator must provide its duration (start and end dates or ongoing), severity, assessment of causality, and whether specific action or therapy was required.

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until the participant's last study visit.

8.2.6.1 Investigator Responsibilities Relating to Safety Reporting

The Investigator will assume overall responsibility for evaluating and reporting AEs. In urgent situations, a member of the study team may report on their behalf, while making every effort to discuss the event with them. All nonserious AEs and ARs, including all events observed following study drug administration, should be recorded in the participant's medical notes, and in the eCRF. Serious Adverse Events and SARs should be reported to the Sponsor or designee immediately once the Investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours) (see Section 8.2.6.2).

All AEs, which include clinical laboratory test results, that occur after the time of informed consent until the final visit are to be documented. Participants should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study drug. Once written informed consent is obtained, the Investigator should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Clinically significant abnormal laboratory or other examination findings (e.g., ECG) that are detected during the study or significantly worsen during the study should be reported as AEs. The Investigator is to exercise their medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study are to be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

8.2.6.2 Serious Adverse Event Reporting – Procedures for Investigators

All adverse events are to be recorded in the participant's medical notes and the CRF from the date of written informed consent until the last study visit. The Sponsor or designee must be notified of all SAEs within 24 hours of the Investigator becoming aware of the event during this period. The Investigator will respond to any SAE queries raised by the Sponsor or designee as soon as possible.

After the last visit, any SAE reported to the Investigator and considered causally related to study treatment should be reported as part of the follow-up study.

The SAE form must be completed by the Investigator (i.e., the individual named on the delegation of responsibilities list who is responsible for the participant's care) with attention paid to the severity, and causality of the event. In the absence of the Investigator, the SAE form should be completed and signed by a member of the site study team and emailed as appropriate within the required timeframe. The Investigator should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email to the Sponsor or designee (see Section 8.2.8). Systems will be in place at the site to enable the Investigator to check the form for clinical accuracy as soon as possible.

The minimum components required for reporting a SAE are the patient ID and year of birth, name of reporting Investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

For information on code-breaking and unblinding in the event of medical emergencies, please refer to Section 5.4.

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilized. Follow-up should continue after completion of the study if necessary. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to the Sponsor or designee (see Section 8.2.8) as further information becomes available. Additional information and/or copies of test results, etc. may be provided separately. The participant's name and full date of birth must not be used in any correspondence and must be blacked out and replaced with study identifiers on any test results, should they be provided.

8.2.6.3 Pregnancy Reporting

If a participant becomes pregnant prior to receiving treatment, the participant should not receive treatment and will be replaced. If a participant becomes pregnant after receiving treatment, the participant will continue the protocol-defined assessments. However, any assessment that in the opinion of the Investigator or primary physician would be deemed a risk to the pregnancy may be omitted or deferred.

In case a pregnancy occurs after study treatment is administered, the participant's general practitioner is to be notified that she is participating in a gene therapy study and that, although the risks involved are minimal, there is a chance of gene transfer to the unborn child.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to the Sponsor or designee using a pregnancy report form, within 24 hours of the Investigator becoming aware of the event.

If the female partner of a male participant becomes pregnant while the participant is receiving study drug or within the safety follow-up period defined in the protocol, the Investigator should notify the Sponsor or designee as described above.

After written informed consent is obtained from the female partner (via a pregnant partner consent form), the pregnancy should be followed until its outcome is known. Once the outcome of the pregnancy is known, the pregnancy report form should be completed and faxed/emailed to the Sponsor or designee (see Section 8.2.8). If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.2.6.4 Expedited Reporting

The Sponsor or designee will report all relevant information about serious and unexpected adverse reactions that are fatal or life-threatening as soon as possible to the relevant Competent Authorities, and, in any case, no later than 7 days after knowledge by the Sponsor or designee of such a case. Relevant follow-up information is to be communicated within an additional 8 days.

All other serious and unexpected adverse reactions will be reported to the relevant Competent Authorities as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor or designee.

The Sponsor or designee also will inform all Investigators of the SAE/SAR as required per local regulation.

8.2.7 Special Situation Reports

Special situation reports include reports of study treatment error and reports of adverse reactions associated with product complaints.

- Study treatment error: Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, participant, or consumer, respectively. The administration or consumption of the unassigned treatment, higher doses than planned and administration of an expired product are always reportable as study treatment errors.
- Product complaint: Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations report will only be completed if a complaint is associated with an adverse drug reaction. For more information, please refer to the Pharmacy Manual.

All special situation events as described above must be reported in the same time frame as SAEs (see Section 8.2.6.2). All AEs associated with these special situation reports should be reported as

AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

8.2.8 Safety Contact Information

SAE forms must be scanned and sent by email to [redacted].

8.3 PHYSICAL AND NEUROLOGICAL EXAMINATIONS

A standard/limited physical examination and neurological examination will be performed.

8.4 CLINICAL SAFETY LABORATORY EVALUATIONS

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the SoA (Table 1) for the timing and frequency of all sample collections.

Blood samples for hematology, chemistry, and coagulation panels and urine samples will be obtained for the tests outlined in Table 4, and testing will be performed at the participating institution.

Note that a serum pregnancy test must be performed for women of childbearing potential at Screening and within 1 week prior to the surgery.

Coronavirus Disease 2019 (COVID-19) testing and follow-up will be done as per institution protocol.

Screening results will be assessed by the Investigator for inclusion of participants in the study. Additionally, unscheduled clinical laboratory tests may be obtained at any time during the study at the Investigator's discretion. The diagnosis corresponding to any clinically significant abnormality or abnormality requiring treatment/intervention must be recorded as an AE.

Table 4: Clinical and Safety Related Laboratory Tests

Standard Safety Chemistry Panel	
Alanine aminotransferase	Albumin
Alkaline phosphatase	Aspartate aminotransferase
Blood urea nitrogen	Calcium
Chloride	Glucose
Creatinine	Inorganic phosphorus
Lactate dehydrogenase	Magnesium
Potassium	Sodium
Total and direct bilirubin	Total carbon dioxide
Total protein	Uric acid

Hematology	
Hematocrit	Hemoglobin
Mean corpuscular volume	Platelets
White blood cell count and differential [1]	
Coagulation	
Partial thromboplastin time	International normalized ratio
Prothrombin time	
Urinalysis	
Bilirubin	Glucose
Hemoglobin	Ketones
Microscopy [2]	pH
Protein	Specific gravity

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.
2. Microscopy is performed only as needed based on positive dipstick test results.

8.5 VITAL SIGN MEASUREMENTS

Vital sign measurements include oral or tympanic temperature (Celsius), heart rate (beats per minute), respiratory rate (breaths per minute), and blood pressure (mmHg). In addition, height will be measured at screening, whereas weight will be measured at both screening and Week 26 visits.

Note that on the day of surgery, temperature, heart rate, respiratory rate, and blood pressure are to be measured before surgery, approximately every 30 minutes for at least the first 4 hours after start of infusion (this can be prolonged in 30-minute intervals if the infusion takes longer than 4 hours), and then at approximately 8 and 12 hours after the start of infusion. Of note, the participant may be transferred to an inpatient hospital service for the assessment of vital signs between 4 hours and 12 hours after start of infusion.

8.6 ELECTROCARDIOGRAM

Standard 12-lead ECGs (ventricular rate, PR interval, QRS duration, and QT interval) is to be performed with the participant in a supine position having rested in this position for at least 5 minutes before each reading.

8.7 IMMUNE RESPONSE

Immune responses against AAV2 viral capsids and/or the AAV-GAD product will be assessed.

Blood samples will be obtained to evaluate for anti-GAD antibodies and anti-AAV2 antibodies.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified conditions, and where applicable, controlled-temperature conditions as indicated in the Laboratory Manual.

The immunological studies will be conducted at one or more central laboratories.

8.8 RADIOGRAPHIC IMAGING

Radiographic imaging of the head (CT or MRI) will be performed per site standard for assessments pre-, intra-, and post-operatively.

Due to the retention of the nylon/titanium cranial anchor base above the skull as a burr hole cover following removal of the infusion system, the specific MRI conditions detailed in the IFU must be taken into account for all post-surgical MRI scans. Participants will also be provided with a patient implant card (in addition to the emergency card), which will specify the need to perform MRI scans under specific conditions.

8.9 BLOOD VOLUME

The total blood volume collected for the study is approximately 58.5 mL (Table 5).

Table 5: Approximate Volume of Blood to be Collected

Type of Sample	Approximate Volume per Sample (mL)	No. of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Hematology	2.0	7	14.mL
Serum chemistry	3.5	7	24.5 mL
Coagulation (PT/PTT)	2.0	2	4 mL
Immunogenicity	4.0	4	16 mL
Approximate Total[b,c]			58.5 mL

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
c. Please refer to the Laboratory Manual for Sample Collection requirements

9 DATA COLLECTION AND MANAGEMENT

9.1 DATA COLLECTION, MANAGEMENT AND ENTRY

Electronic case report forms will be completed for each study participant. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the participant's eCRF. The eCRFs must be reviewed and electronically signed by the Investigator. Source documentation supporting the eCRF data should indicate the participant's participation in the study and should document the dates and details of study procedures, AEs, and participant status.

The Investigator, or designated representative, should complete the eCRF pages as soon as possible after information is collected, preferably on the same day that a study participant is seen or spoken to. Any outstanding entries must be completed immediately after the final visit. An explanation should be given for all missing data.

10 STATISTICAL ANALYSES

10.1 STATISTICAL METHODS

10.1.1 General Considerations

Details for all analyses will be described in a Statistical Analysis Plan (SAP).

Descriptive statistical methods will be used to summarize the data from this study with formal hypothesis testing performed for MDS-UPDRS Part 3 and GADRP. The descriptive methods used to summarize continuous variables will include the number of participants, mean, median, standard deviation, minimum, maximum, and quartiles. The descriptive methods used to summarize categorical data will include counts and percentages.

10.1.2 Analysis Populations

Safety analyses will be performed using the Safety Population, defined as all participants who are randomized and receive treatment (AAV-GAD or sham).

Efficacy analysis will be performed using the Intention-to-Treat (ITT) Population, defined as all participants who are randomized.

10.1.3 Analysis of Safety

10.1.3.1 Adverse Events

AEs will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA; latest version) system organ classification and preferred term.

10.1.3.2 Clinical Laboratory Evaluations

Descriptive summaries of clinical laboratory results, including changes from baseline, will be presented by study visit. Numbers and percentages of participants with abnormalities will be tabulated.

10.1.3.3 Vital Sign Measurements

Descriptive summaries of vital signs, including changes from baseline, will be presented by study visit. Numbers and percentages of participants with abnormalities, according to predefined criteria, will be tabulated.

10.1.3.4 Electrocardiograms

ECG results will be reviewed for clinically notable abnormalities according to predefined criteria.

10.1.3.5 Immunogenicity

The number of participants with a positive immune response will be summarized.

10.1.3.6 Columbia-Suicide Severity Rating Scale

Descriptive summaries of the Columbia-Suicide Severity Rating Scale will be presented by study visit.

10.1.3.7 Other

Descriptive summaries of findings on physical examination, neurological examination, CT, and MRI will be presented by study visit.

10.1.4 Analysis of Efficacy

10.1.4.1 Exploratory Efficacy Endpoints

The exploratory efficacy analyses will be performed at Weeks 12 and 26.

Descriptive statistics will be presented for efficacy endpoints. Differences between the individual and pooled (when appropriate) AAV-GAD groups and the sham group in mean change from baseline to Weeks 12 and 26 will be compared for each of the endpoints.

[redacted]

[redacted]

Additional sensitivity analyses will be described in the SAP.

[redacted]

10.1.5 Interim Analysis

There is no interim analysis planned for this study.

10.1.6 Sample Size Determination

This is a Phase 1/2 study to assess safety and tolerability of AAV-GAD produced using an updated production methodology, therefore, no formal sample size calculation was performed. Based upon experience with and data from the prior Phase 1 and 2 studies, it is estimated that inclusion of

approximately 14 participants (5 participants receiving AAV-GAD at a dose of 3.5×10^{10} vg/STN, 5 participants receiving AAV-GAD at a dose of 10.45×10^{10} vg/STN and 4 participants undergoing sham surgery) will be sufficient to determine safety and tolerability of AAV-GAD.

11 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1 STUDY MONITORING

Monitoring and auditing procedures developed by MeiraGTx/designee will be implemented to ensure compliance with the protocol, Declaration of Helsinki, ICH GCP, Directive 2001/20/EC, and the applicable regulatory requirements.

The frequency, type and intensity of routine and triggered on-site or central/remote monitoring will be detailed in the study Monitoring Plan (MP). The MP will also detail the procedures for review and sign-off of monitoring reports.

The sponsor's designated representative (the monitor) will contact the Investigator and conduct regular visits to the study site. The monitor will be expected and allowed to verify the Investigator's qualifications, to review study site facilities, and to inspect study records, including proof of Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review, with the stipulation that participant confidentiality will be maintained in accordance with local and Federal regulations, including Health Insurance Portability and Accountability Act requirements. The monitor will also be responsible for confirming adherence to the study protocol, reviewing eCRFs and source documents, and ensuring the integrity of the data. eCRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents, including laboratory test reports and other participant records. Instances of missing or uninterpretable data will be resolved in coordination with the Investigator.

The monitor will also follow up on any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The monitor will maintain contact with the site through frequent direct communications with the study site by email, telephone, facsimile, and mail. The Investigator and all other site personnel agree to cooperate fully with the monitor and will work in good faith with the monitor to resolve all questions raised, and difficulties detected by the monitor.

11.2 AUDITS AND INSPECTIONS

The Investigator understands that regulatory authorities, the IRB/IEC, and/or MeiraGTx Quality Assurance auditors or designees have the right to access all eCRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the study to at least 2 years after the last approval of a marketing application or for at least 2 years after clinical development of the study drug for the indication being studied has been discontinued. The Investigator is required to guarantee access to these documents and to cooperate with and support such audits and inspections. The Investigator and study-site personnel are responsible for being present and available for consultation during study-site audit visits conducted by the Sponsor or its designees.

In the event of a request for a study site inspection by any regulatory authority, MeiraGTx must be notified as soon as possible.

11.3 DIRECT ACCESS TO PARTICIPANT RECORDS

Participating Investigators must agree to allow study related monitoring, including audits, IRB/IEC review and regulatory inspections, by providing access to source data and other study-related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the study.

11.4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The IRB/IEC must be a properly constituted board or committee operating in accordance with 21 CFR Part 56, "Institutional Review Boards." This protocol, any protocol amendments, and the associated informed consent forms must be submitted to the IRB/IEC for review and approved before the enrollment of any participant in the study. The Investigator is responsible for sending a copy of the letter or certificate of approval from the IRB/IEC for the protocol and any protocol amendments to the sponsor.

All types of participant recruitment or advertising information must be submitted to MeiraGTx/designee and to the IRB/IEC for review and approval prior to implementation. IRB/IEC approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to eliminate a potential hazard to study participants. In such cases, the chair of the IRB/IEC should be notified immediately, and the amendment forwarded to the IRB/IEC for review and approval.

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator file. Copies of IRB/IEC approvals should be forwarded to MeiraGTx/designee.

11.5 TRIAL OVERSIGHT

Trial oversight is intended to preserve the integrity of the study by independently verifying a variety of processes and prompting corrective action and preventative actions where necessary. The processes reviewed relate to participant enrollment, consent, eligibility, and allocation to study groups; adherence to study interventions and policies to protect participants, including reporting of harms; and completeness, accuracy, and timeliness of data collection.

In multicenter studies, oversight is considered and described both overall and for each recruiting center by exploring the study dataset or performing site visits as described in the study Monitoring Plan.

12 ETHICS

12.1 ETHICAL CONDUCT OF THE STUDY

The Investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

12.2 WRITTEN INFORMED CONSENT

Written informed consent will be obtained from each participant by the Investigator or delegated clinician/staff member following appropriate explanation of the aims, methods, possible benefits, and risks of the study, allowing sufficient time for the potential participant to ask all questions s/he may have about the study. The Investigator or designee will explain that the participants are under no obligation to enter the study and that they can withdraw at any time during the study, without having to give a reason, and without their clinical care being affected. No clinical study-specified procedure will be conducted prior to obtaining consent from the participant.

If new safety information results in significant changes in the risk/benefit assessment, the ICF will be reviewed and updated if necessary, and participants will be re-consented as appropriate.

12.3 CONFIDENTIALITY

The Investigator must ensure that the participant's privacy is maintained. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or data will be released to any unauthorized third party without prior written approval of the sponsor.

12.4 PROTOCOL AMENDMENTS

All amendments to the protocol must be documented in writing, reviewed, and approved by the Investigator and the sponsor, and submitted to the IRB/EC/CEC for approval prior to initiation, except in cases where required for participant safety. Protocol amendments must be submitted to the relevant Competent Authorities in accordance with regulatory requirements. If the protocol amendment substantially alters the study design or potential risk to the participant, a new written ICF for continued participation in the study must be obtained from each participant or their legal representative.

13 DATA HANDLING AND RECORDKEEPING

13.1 INSPECTION OF RECORDS

The Investigator shall permit authorized representatives of the sponsor, regulatory authorities, and IRB/IECs to review the portion of the participant's medical record that is directly related to the study. As part of the required content of the ICF, the participant must be informed that their records will be reviewed in this manner.

13.2 RETENTION OF RECORDS

In compliance with the ICH/GCP guidelines, the Investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The Investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of retention of study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator/institution must permit access to such reports.

13.3 PUBLICATION OF STUDY DATA

Following completion of the study, the data may be considered for publication in a scientific journal and/or for reporting at a scientific meeting by the Sponsor and/or Investigators. However, the Sponsor shall have the right to the first publication of the study data, including as part of a joint, multi-center publication (Sponsor in conjunction with Investigators from all appropriate sites contributing data, analysis and comments). For other publications, the Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to delay publication until mutual agreement on the content, format, accuracy, interpretation of data in the manuscript, and journal selected for publication are achieved, as well as to protect

Sponsor's interests in its intellectual property (the publication is to be in accordance with the terms of the clinical trial agreement).

In addition, this clinical study must be registered with ClinicalTrials.gov, which will be done by the sponsor/designee.

14 REFERENCES

Emborg, M. E., M. Carbon, J. E. Holden, M. J. During, Y. Ma, C. Tang, J. Moirano, H. Fitzsimons, B. Z. Roitberg, E. Tuccar, A. Roberts, M. G. Kaplitt and D. Eidelberg (2007). "Subthalamic glutamic acid decarboxylase gene therapy: changes in motor function and cortical metabolism." J Cereb Blood Flow Metab 27(3): 501-509.

Feigin, A., M. G. Kaplitt, C. Tang, T. Lin, P. Mattis, V. Dhawan, M. J. During and D. Eidelberg (2007). "Modulation of metabolic brain networks after subthalamic gene therapy for Parkinson's disease." Proc Natl Acad Sci U S A 104(49): 19559-19564.

Hamani, C., J. A. Saint-Cyr, J. Fraser, M. Kaplitt and A. M. Lozano (2004). "The subthalamic nucleus in the context of movement disorders." Brain 127(Pt 1): 4-20.

Kaplitt, M. G., A. Feigin, C. Tang, H. L. Fitzsimons, P. Mattis, P. A. Lawlor, R. J. Bland, D. Young, K. Strybing, D. Eidelberg and M. J. During (2007). "Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson's disease: an open label, phase I trial." Lancet 369(9579): 2097-2105.

LeWitt, P. A., A. R. Rezai, M. A. Leehey, S. G. Ojemann, A. W. Flaherty, E. N. Eskandar, S. K. Kostyk, K. Thomas, A. Sarkar, M. S. Siddiqui, S. B. Tatter, J. M. Schwalb, K. L. Poston, J. M. Henderson, R. M. Kurlan, I. H. Richard, L. Van Meter, C. V. Sapan, M. J. During, M. G. Kaplitt and A. Feigin (2011). "AAV2-GAD gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomised trial." Lancet Neurol 10(4): 309-319.

Luo, J., M. G. Kaplitt, H. L. Fitzsimons, D. S. Zuzga, Y. Liu, M. L. Oshinsky and M. J. During (2002). "Subthalamic GAD gene therapy in a Parkinson's disease rat model." Science 298(5592): 425-429.

Niethammer, M., C. C. Tang, P. A. LeWitt, A. R. Rezai, M. A. Leehey, S. G. Ojemann, A. W. Flaherty, E. N. Eskandar, S. K. Kostyk, A. Sarkar, M. S. Siddiqui, S. B. Tatter, J. M. Schwalb, K. L. Poston, J. M. Henderson, R. M. Kurlan, I. H. Richard, C. V. Sapan, D. Eidelberg, M. J. During, M. G. Kaplitt and A. Feigin (2017). "Long-term follow-up of a randomized AAV2-GAD gene therapy trial for Parkinson's disease." JCI Insight 2(7): e90133.

Niethammer, M., C. C. Tang, A. Vo, N. Nguyen, P. Spetsieris, V. Dhawan, Y. Ma, M. Small, A. Feigin, M. J. During, M. G. Kaplitt and D. Eidelberg (2018). "Gene therapy reduces Parkinson's disease symptoms by reorganizing functional brain connectivity." Sci Transl Med 10(469).

Rus, T., P. Tomse, L. Jensterle, M. Grmek, Z. Pirtosek, D. Eidelberg, C. Tang and M. Trost (2020). "Differential diagnosis of parkinsonian syndromes: a comparison of clinical and automated - metabolic brain patterns' based approach." Eur J Nucl Med Mol Imaging 47(12): 2901-2910.

Tang, C. C., K. L. Poston, T. Eckert, A. Feigin, S. Frucht, M. Gudesblatt, V. Dhawan, M. Lesser, J. P. Vonsattel, S. Fahn and D. Eidelberg (2010). "Differential diagnosis of parkinsonism: a metabolic imaging study using pattern analysis." Lancet Neurol 9(2): 149-158.

Tripathi, M., C. C. Tang, A. Feigin, I. De Lucia, A. Nazem, V. Dhawan and D. Eidelberg (2016). "Automated Differential Diagnosis of Early Parkinsonism Using Metabolic Brain Networks: A Validation Study." J Nucl Med 57(1): 60-66.

APPENDIX: GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

The measures outlined in this Appendix are temporary, while access to sites is restricted during the COVID-19 pandemic. As restrictions are lifted, the decision to revert back to the protocol in effect prior to the pandemic should be discussed and agreed with the sponsor.

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the Investigator to protect the health and well-being of participants and site staff.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted after consultation between the participant and Investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form.

Scheduled visits that cannot be conducted in person at the study site will be performed remotely/virtually, and site-based evaluations may be delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy and safety endpoint assessments should be performed as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

The sponsor will continue to monitor the conduct and progress of the clinical study and any changes (e.g., delay or discontinuation in recruitment, site monitoring and audits) will be communicated to the sites and health authorities according to local guidance. If a participant has tested positive for COVID 19, the Investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

Each participant will be risk assessed on a case-by-case basis by the Investigator and his/her research team to decide the appropriate care for the participant.

Item no	Item	Management of Item
1	Missed assessments	Missed assessments will be captured as a deviation with the prefix COVID-19 RELATED.
2	Protocol Deviations	Any deviations to the study protocol due to COVID-19 pandemic will be captured with the prefix COVID-19 RELATED.
3	Participant missing any scheduled visits	If scheduled visits cannot be conducted within the visit window, the site can schedule an additional visit at the earliest opportunity the participant is able to travel,
4	Participants may be unable to attend study visit during visit window.	It is acknowledged that this is a global crisis and participants may be put at more risk attending hospital appointments due to route of travel to the research facility. If appropriate, the sponsor will offer expenses for taxi fares to avoid busy train or bus routes.
5	Participants visits conducted outside of visit window	Participants will be assessed individually by the sites on a case by case basis and phone interviews may be conducted by sites for all post-treatment visits up until at least 3 months post-surgery. Participants undergoing telephone assessment will be asked to provide information on any adverse events or other safety concerns.
6	Participants self-quarantined or government implemented quarantine.	If participants and/or their caregivers are under quarantine and unable to leave home, their cases will be assessed by medical monitors and PI as to risk of delayed appointment. (e.g., ongoing AEs, date of last appointment, less than 3 months since intervention).
7	Potential lack of reporting of symptoms due to delayed visits Delayed reporting of SAEs, SARs & SUSARs- Potential for events to not be reported within 24 hours of occurrence Delayed Participant reporting of Adverse Events	All participants are provided with emergency cards on enrollment to the study to enable 24-hour contact with study investigators. All serious adverse events should be reported by an Investigator (as assigned on the delegation log) or another member of the site team, in the Investigators absence and where delegated, within 24 hours of the event occurring. Reminder of importance to report any new AEs/symptoms to be communicated to participants by the sites during this time.
8	Emergencies during the study and the provision of emergency contact arrangements:	If a participant encounters difficulties in contacting the Trial Team in the event of emergencies, s/he has been provided with an alert card to inform other healthcare providers of their participation in the gene therapy trial. The Trial card includes the 24 hour/7-day contact number, participant's trial code, trial number, and brief details of the trial intervention.

9	Assessment results outside of window not true representation of protocol stated timepoints	Participant safety will be the most important factor to consider. Participants will complete visits as close to the visit window as possible and deviations will be recorded where applicable.
10	Clinician(s) and site research staff unavailable due to contraction of virus	Site to ensure appropriate staff are available and are documented on the delegation log to provide medical coverage if the Investigator is unavailable.
11	Monitor may not be allowed on site or may be quarantined and unable to visit.	Monitors will be encouraged to attend the sites where and when possible. If they are unable to do so, they will conduct remote monitoring as much as possible and arrange as many visits as required to get back on track once the site re-opens.