Allegheny Health Network
30 Isabella Street, Suite 300
Pittsburgh, PA 15212
ahn.org

Study Title:	**Burst-Type Deep Brain Stimulation of the Subthalamic Nucleus in Parkinson's Disease: A Pilot Study of Tolerability and Efficacy**
Sponsor:	**Boston Scientific Corporation** 25155 Rye Canyon Loop Valencia, CA 91355
Device Information:	Boston Scientific Neuromodulation
Device Name:	Versise Gevia™ or Genus™ DBS Systems
Protocol Version:	Protocol Version 4: 19 Feb 2024
Principal Investigator:	Nestor D. Tomycz, MD, FAANS **Department of Neurosurgery** AHN Allegheny General Hospital 420 E North Avenue, Suite 302 Pittsburgh, PA 15212 Nestor.tomycz@ahn.org Phone: 412-359-6200 (24 Hours)
Site Co-Investigator:	Donald Whiting, M.D., M.S., F.A.C.S. **Department of Neurosurgery** AHN Allegheny General Hospital 420 E North Avenue, Suite 302 Pittsburgh, PA 15212 Donald.Whiting@ahn.org Phone: Phone: 412-359-6200 (24 Hours)

Table of Contents

Abbreviations and Definitions of Terms

ADE	Adverse Device Effect
AE	Adverse Event
DBS	Deep Brain Stimulation
IPG	Implantable Pulse Generator
SAE	Serious Adverse Event
UPDRS	United Parkinson's Disease Rating Scale

Protocol Synopsis

Abstract

Deep brain stimulation (DBS) has become an evidence-based treatment for movement disorders such as Parkinson's disease. Recent animal studies of DBS suggest that neuronal subpopulations may be specifically activated by burst-type DBS and that this type of electrical stimulation programming may improve the efficacy and durability of DBS. Burst-type DBS is defined as a novel stimulation protocol in which intermittent bursts of traditional high-frequency rectangular wave stimulation are delivered. Implanted pulse generators (IPGs) have the capability to deliver such stimulation by setting specific "on" and "off" times, however there is no published human data on the results of such programming in patients undergoing DBS for movement disorders such as PD.

Primary Objective

The primary objective is to determine change in the UPDRS-III motor score in the medication OFF state with burst-type DBS programming in the acute setting (after 30 minutes) and then after 6 months and 12 months for patients with bilateral subthalamic nucleus DBS for Parkinson's disease.

Study Design:

Randomized, double-blind cross-over study with N= 5 patients implanted with bilateral subthalamic nucleus DBS.

Study Site:

Allegheny General Hospital
Neuroscience Institute
420 E. North Avenue
Pittsburgh, PA 15212

Study Population

Patients for this study (N= 5) should have bilateral STN-DBS (with Boston scientific Gevia or Genus technology) implanted for Parkinson's disease. The patients should be on stable DBS programming settings and stable medication regimens defined as no DBS programming changes or Parkinson's disease medication changes over past 2 weeks. The DBS implantation should have been performed by either Dr. Nestor D. Tomycz, MD or Dr. Donald M. Whiting, MD at Allegheny General Hospital and implantation surgery must have occurred a minimum of 6 months prior to the day of enrollment.

Recruitment Strategy

Subjects will be recruited from the DBS practice of investigator neurosurgeons Dr. Nestor D. Tomycz MD and Dr. Donald M. Whiting MD. Patients will be identified by the neurosurgeons as well as by DBS nurse Cindy Angle RN and physician assistant Amanda Webb PA-C.

Recruitment will stop when approximately 5 subjects are enrolled. It is expected that approximately 15 subjects will be enrolled to produce 5 evaluable subjects.

Subject Replacement

In the event that consented subjects are unable to complete study procedures for any reason (e.g. unable to attend visits, adverse reaction to burst programming, or other concerns determined by primary investigator), subjects will be withdrawn from the study and primary investigator may screen and enroll replacement subjects(s) to ensure the number of completed subjects equals 5.

Inclusion Criteria

1. Adult patients (male and female) ages 18-85
2. Bilateral DBS-STN (subthalamic nucleus) target for idiopathic Parkinson's disease implanted minimum 6 months prior to the day of study enrollment
3. Stable DBS programming settings and Parkinson's disease medications defined as no changes to either within past 2 weeks
4. Comfortable using DBS controller to turn off device prior to study visits
5. Able to provide informed consent and complete follow-up visits

Exclusion Criteria

1. DBS technology other than Boston scientific Genus/Gevia
2. Unable to complete follow-up visits
3. DBS brain targets other than STN (subthalamic nucleus)
4. Signs of progressive cognitive decline

Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, AEs, or due to medical illness which complicates follow-up. The Investigator or the Sponsor (if applicable) may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

The study duration per subject will be up to 365 days.

Description of Devices and Assessments

DBS System

Boston Scientific Neuromodulation (BSN) Vercise™ System: A neurostimulation device consisting of an implantable pulse generator (IPG), integrated rechargeable battery, two DBS leads, two DBS extensions, Burr Hole Cover, surgical tools, GUIDE XT Software and external devices (programming system, remote control, and charging system). The implanted pulse generator (IPG) for this study will be either the Gevia or Genus model.

UPRDS (United Parkinson's Disease Rating Scale)

The UPDRS is an assessment that can be utilized to follow the progression of PD and is completed by interviewing the patient. The UPDRS was developed in 1987 by neurologists as a gold standard to determine response to medications and has been heavily utilized to standardize the response to DBS. There are 4 sections of the test (I-IV), as follows:

(I) Mentation, Behavior, and Mood;
(II) Activities of Daily Living (ADL);
(III) Motor Examination;
(IV) Complications of Therapy.

This study will utilize only the Motor Examination (Section III) for study visits. Section III contains 14 items to evaluate overall motor disability, including the classic symptoms of PD. The questions in this section assess speech, facial expression, tremor at rest (for face, hands, and feet), action or postural tremor of hands, rigidity, finger taps, hand movements, rapid alternating movements of hands, leg agility, arising from chair, posture, gait, postural stability, and body bradykinesia and hypokinesia. Each item is scored on a scale from 0 (normal) to 4 (severe, marked, or unable), with the total possible score for the 14 items, including separate questions regarding symptoms present axially and in appendages, ranging from 0 to 108.

Summary of Study Visits

Screening

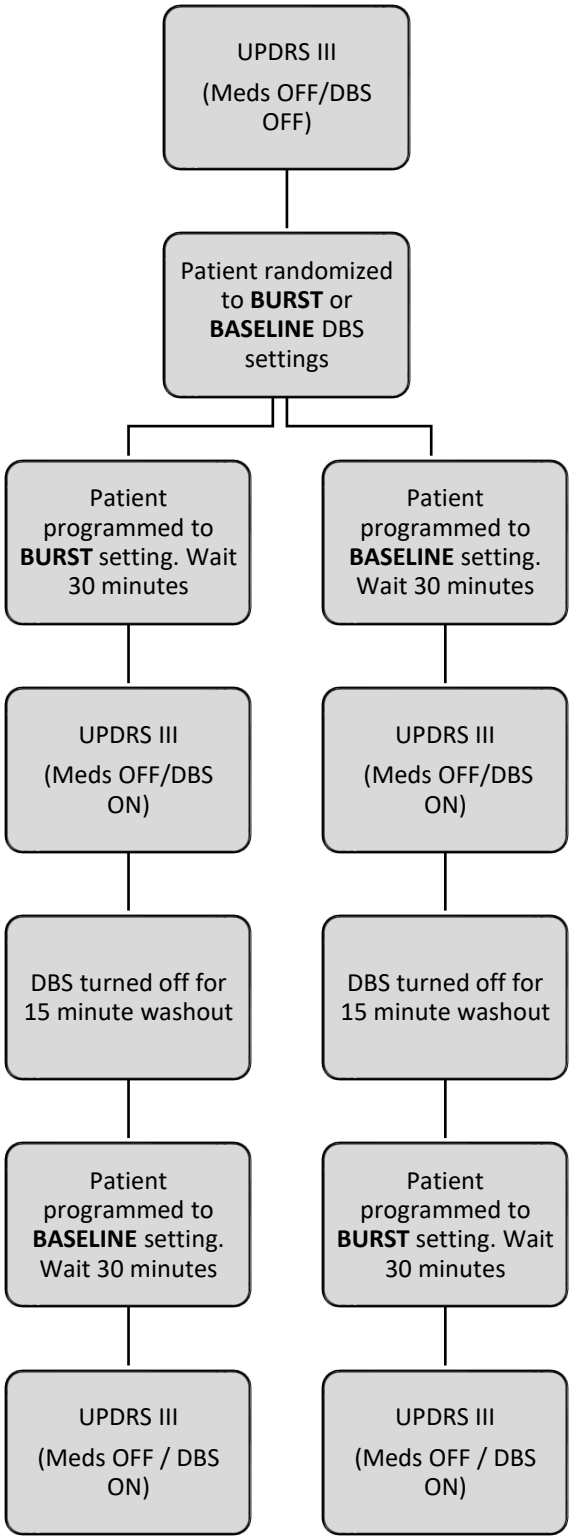
Patients will be approached for possible study participation during a routine, standard of care visit. All interested patients will undergo screening to determine eligibility into the study. Screening will including the following:

- Review and signing of informed consent document.
- Demographics: Date of birth, Gender, Ethnicity, Handedness
- Medical history*:* Surgical/Interventional Procedure History, Parkinson's Disease History (presence of symptoms required for eligibility will be documented), presence and in some cases severity of selected symptoms of either PD or PD medications that can also occur as a side effect of STN DBS dopamine dysregulation syndrome (DDS);
- Review of current Parkinson's disease medications*:* Dosage/frequency (Start Date, Stop Date)
- Review of concomitant medications

Visit One- Baseline (≤ 30 Days after Screening)

- Parkinson's disease dopaminergic medications will be withdrawn overnight to establish medication-OFF state and DBS will be turned OFF overnight for establishing DBS-OFF state. Examiner will establish a UPDRS-III baseline with medication-OFF, DBS-OFF state.
- Unblinded examiner will then turn the DBS ON to the patient's baseline DBS settings continuously ON or to burst DBS mode (baseline DBS settings for the patient with DBS set to 1 sec ON, 4 sec OFF), based on results of randomization. The patient will be blinded to this programming change and will be kept at this initial setting for 30 minutes.
- Next, a blinded examiner who did not perform the programming change will perform a UPDRS-III evaluation. Next, the DBS will be turned off for 15 minutes to permit for a washout period.
- Next, the DBS will be turned on by the unblinded examiner to the alternate setting (burst DBS in case that the patient first was turned on with their baseline DBS setting or baseline DBS setting in case that the patient was first turned on with burst DBS setting) and kept on this setting for 30 minutes.
- After 30 minutes, the blinded examiner will perform another UPDRS-III evaluation. Patients, who are blinded to the stimulation setting, will be asked if they preferred one stimulation mode over the other.
- If any adverse events occur with burst DBS mode, the unblinded examiner will decrease the amplitude of the DBS by 0.5mA increments until the adverse events abate. If there are not persistent adverse events with 30 minutes of burst DBS mode, the patient will be kept in burst DBS mode at the end of first visit and will be allowed to take their Parkinson's disease medications.

Figure 1. Visit 1 Assessment Schema



Randomization Procedure

Subjects will be randomized to determine which DBS setting is initially programmed during visit one. All subjects will be programmed to both settings over the course of the visit, but the order is randomized to ensure appropriate blinding of the UPDRS assessor. Subjects have a 50% chance of being randomized to the "burst" mode, and a 50% chance of being randomized to the "baseline" mode. Following the initial UPDRS assessment (Meds OFF/DBS OFF), the study coordinator or unblinded assessor will used a computerized randomization system to determine which DBS setting the subject receives first.

Visit Two (6 months +/- 30 Days)

- Parkinson's disease dopaminergic medications will be withdrawn overnight to establish medication-OFF state and DBS will be turned OFF overnight for establishing DBS-OFF state.
- Examiner will establish a UPDRS-III baseline with medication-OFF, DBS-OFF state. Examiner will then turn the DBS ON to the burst DBS state and keep ON for 30 minutes. After 30 minutes the examiner will perform another UPDRS-III evaluation and will ask about any adverse effects. Patients will then be allowed to take their Parkinson's disease medications and will be kept on the burst mode DBS state.
- Patients will be asked if they prefer the burst mode DBS state to their baseline settings before the study.

Visit Three (12 months +/- 30 days)

- Parkinson's disease dopaminergic medications will be withdrawn overnight to establish medication-OFF state and DBS will be turned OFF overnight for establishing DBS-OFF state.
- Examiner will establish a UPDRS-III baseline with medication-OFF, DBS-OFF state. Examiner will then turn the DBS ON to the burst DBS state and keep ON for 30 minutes. After 30 minutes the examiner will perform another UPDRS-III evaluation and will ask about any adverse effects. Patients will then be allowed to take their Parkinson's disease medications and will be kept on the burst mode DBS state.
- Patients will be asked if they prefer the burst mode DBS state to their baseline settings before the study. At the conclusion of the study, patients will be asked if they want to continue to use burst DBS state or if would prefer to be programmed back to their pre-study baseline DBS settings.

Phone Follow-Up Visits

Phone follow up calls will be completed by study personnel to determine subject's programming preference at 1 week, 1, 3 and 9 months post programming changes.

Table 1. Schedule of Study Events

Activities	Screening/ Enrollment	Visit 1 (Baseline)	Visit 2 Month 6 +/- 30 days	Visit 3 Month 12 +/- 30 days	Phone Follow-up[4]
Informed Consent	x				
Demographics	x				
Medical History	x				
Parkinson's Medications	x	x	x	x	x
Concomitant medications	x	x	x	x	x
Adverse Events		x	x	x	x
Serious Adverse Events		x	x	x	x
Adverse Device Effects		x	x	x	
UPDRS III (Meds OFF[1]/DBS OFF[2])		x	x	x	
UPDRS III (Meds OFF[1]/DBS ON-Burst)		x	x	x	
UPDRS III (Meds OFF[1]/DBS ON-Baseline[3])		x			

[1] Parkinson's disease dopaminergic medications should be withdrawn overnight to establish medication-OFF state
[2] DBS should be turned off overnight to establish DBS-OFF state
[3] DBS should be programmed to the baseline settings patient had before study entry
[4] Phone follow up calls to determine subject's programming preference will be completed by study personnel at 1 week, 1, 3 and 9 months post programming changes.

DBS Programming Procedure

Each time that programming is performed it will be conducted in the same manner as is done for DBS in movement disorders: each electrode will be systematically checked for impedance. The optimal electrodes will be used in either monopolar or bipolar mode to maximize the clinical benefit. At no time will charge densities above 30 microCouloumbs/ cm2 /phase be applied.

The parameters that may be are, the polarity of stimulation (off, negative, or positive), bipolar or monopolar stimulation, the amplitude (0-0.1 mA), the pulse width (10-450 msec), and the frequency of stimulation (2-225 Hz). Each programming session will be performed in the same manner: Beginning on the right side of the body, interrogate the stimulator with the Access Review device. Determine if the device has been on continuously since the last visit, and if there were any activations. The impedance of that device will then be measured (normal impedance 250–2,000 OHMs). In this protocol, subjects will be blinded to which electrodes will be active during each test period of stimulation.

Outcomes Being Measured

Adverse Events and Serious Adverse Events

An adverse event (AE) is any undesirable experience (sign, symptom, illness, or other medical event) occurring in the patient, regardless if it is associated with the investigational procedure that appears or worsens during the clinical study.

A serious adverse event (SAE) is one that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongs hospitalization
- Result in disability or permanent damage to the body's function or structure
- Results in a congenital anomaly or birth defect
- Required intervention to prevent permanent impairment or damage
- Or, is an important medical event - when the event does not fit the other outcomes, but may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

Adverse event information will be collected throughout the study, beginning once the patient is enrolled in the study and monitored until each event is adequately resolved or explained. An AE or SAE description (including the nature of the event, date and time of onset, determination of non-serious versus serious, intensity, duration, causality, and outcome of the event) will be recorded on the case report forms by the investigator or research coordinator. A summary report of all serious adverse events will be provided to the reviewing IRB annually. Serious adverse events will be reported within 5 days of the investigator learning of the event to the reviewing IRB.

Secondary Endpoints

Burst DBS may require less energy and therefore a secondary endpoint we will include is a calculation of IPG (implanted pulse generator) or battery longevity. Secondary endpoints will also patient preference for stimulation mode.

Statistical Methods

Statistics will be performed using Mann-Whitney-U test and p-value < 0.05 will be required for statistical significance.

Regulatory and Ethical Considerations

Compliance Statement

This study will be conducted in full accordance all applicable Allegheny Health Network Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH). All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with the AHN IRB Policies IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

Risk Assessment

Risks of the study are minimal. Patients may experience a temporary worsening of motor symptoms when they stop medications the night before patient visits and may also experience a temporary worsening of motor symptoms when programmed into burst-type DBS. These motor symptom changes, if they do occur, would be reversible, and no patient will be required to continue using burst-type DBS after the first visit if they do not want to or if they find the motor symptom changes worse or bothersome. Patients may contact a member of the study team if they wish to exit the study or stop using burst-type DBS programming at any time.

Potential Benefits of Participation

The potential benefits of burst-type DBS include the potential of better motor symptom control including improved tremor, improved rigidity, and improved dyskinesias. An additional benefit may be that burst-type DBS may require lower energy for treatment and could therefore prolong DBS implanted pulse generator (IPG) life.

Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. All patient data will be de-identified and kept on a secure computer within the Neuroscience Research Department at Allegheny General Hospital.

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and

any recipient researchers (including others at AHN) before sharing a limited dataset (PHI limited to dates and zip codes).

Data Safety Monitoring

The research team, including the PI, will meet a minimum of every 12 months to review accruals, adverse events, potential breaches in confidentiality and any unanticipated problems related to this research. Any identified reportable events or breaches in confidentiality will be reported immediately to AHNRI IRB and AHN Privacy Department. Any events or changes in the risk/benefit ratio affecting decisions about study continuation will be submitted to the IRB immediately via a prompt report form.

Payment to Subjects

Study subjects will receive $50.00 US dollars stipend for their time/inconvenience for each completed visit for a possible total of $150.00 US dollars if all 3 visits are completed. Subjects will be provided with a debit card which will be used to deposit each stipend amount at the end of each visit.

Publication

Data analysis will occur for 3 months after study completion with a plan to publish the data in a peer-reviewed neurological journal.

References

Brocker, D.T., Swan, B.D., Turner, D.A., Gross, R.E., Tatter, S.B., Miller Koop, M., Bronte-Stewart, H., Grill, W.M., Koop, M.M., Bronte-Stewart, H., et al. (2013). Improved efficacy of temporally non-regular deep brain stimulation in Parkinson's disease. Exp. Neurol. *239*, 60-67

Eisinger, Robert S., et al. "A review of basal ganglis circuits and physiology: application to deep brain stimulation." Parkinsonism & related disorders 59 (2019): 9-20.

Grill, W.M. (2018). Temporal Pattern of Electrical Stimulation is a New Dimension of Therapeutic Innovation. Curr. Opin. Biomed. Eng. *8*, 1–6.

Mastro, K.J., Zitelli, K.T., Willard, A.M., Leblanc, K.H., Kravitz, A. V., and Gittis, A.H. (2017). Cell-specific pallidal intervention induces long-lasting motor recovery in dopamine-depleted mice. Nat. Neurosci. *20*, 815–823.

Spix, T. A., Nanivadekar, S., Toong, N., Kaplow, I. M., Isett, B. R., Goksen, Y., ... & Gittis, A. H. (2021). Population-specific neuromodulation prolongs therapeutic benefits of deep brain stimulation. *Science*, *374*(6564), 201-206.

Appendix A

Visit 1 Case Report Form

Subject # _____

Date _____ / _____ / _____
dd mmm yyyy

Last dose of Parkinson's medications: _____ am / pm

Time DBS device turned off: _____ am / pm

To be completed by unblinded examiner

Subject randomization for initial DBS setting (Circle): Burst / Baseline

	Left	Right
Active Contacts	_____	_____
Amplitude	_____	_____
Pulse Width	_____	_____
Frequency	_____	_____

Subject Programming Preference (Circle): Burst / Baseline / No preference

Comments:

_____

_____

_____

Appendix A

Visit 2 and 3 Case Report Form

Subject # _____

Date _____ / _____ / _____
dd mmm yyyy

Last dose of Parkinson's medications: _____ am / pm

Time DBS device turned off: _____ am / pm

	Left	Right
Active Contacts	_____	_____
Amplitude	_____	_____
Pulse Width	_____	_____
Frequency	_____	_____

Comments:

_____

_____

_____

_____