PHIL DAVF: STUDY OF PHIL® EMBOLIC SYSTEM IN THE TREATMENT OF INTRACRANIAL DURAL ARTERIOVENOUS FISTULAS

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Statistical Analysis Plan

PHIL DAVF: STUDY OF PHIL® EMBOLIC SYSTEM IN THE TREATMENT OF INTRACRANIAL DURAL ARTERIOVENOUS FISTULAS

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1. Revision History

Revision	Description	Date
A	Original release	04/26/2021
B	Removed Section 8.2 Timing of Analyses, as all patients enrolled in the study will be included in the final analysis. Provided detailed definition of duration variables in Section 8.5. Added detailed description on handling of missing data in Section 8.6	02/21/2023

2. Abbreviations and Definitions

CSR	Clinical Study Report
CT	Computerized Tomography
dAVF	Dural Arteriovenous Fistulas
DMSO	Dimethyl Sulfoxide
DSA	Digital Subtraction Angiography/Angiogram
eCRFs	Electronic Case Report Forms
FAS	Full Analysis Set
IFU	Instructions For Use
INR	International Normalized Ratio
IRB	Institutional Review Board
MRA	Magnetic Resonance Angiography/Angiogram
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
nBCA	N-Butyl-Cyanoacrylate
NIHSS	NIH Stroke Scale
PHIL	Precipitating Hydrophobic Injectable Liquid
QOL	Quality of Life
SAP	Statistical Analysis Protocol

3. Introduction

This document describes the planned statistical analyses for the clinical study titled as “PHIL DAVF: Study of PHIL® Embolic System in The Treatment of Intracranial Dural Arteriovenous Fistulas” (protocol number: CL11005). This analysis plan is meant to supplement the study protocol. Any deviations from this analysis plan will be described in the clinical study report (CSR).

4. Study Design

The proposed study is a prospective, multicenter, single-arm, clinical study evaluating outcomes in subjects with intracranial dural arteriovenous fistulas (dAVF) treated with PHIL® device. The purpose of this study is to evaluate the safety and probable benefit of PHIL® device for the treatment of intracranial dAVF.

4.1 Primary Measured Outcomes

The following outcomes will be measured:

- Safety: The proportion of subjects with neurological death or ipsilateral stroke within the first 30 days following completion of the first PHIL treatment procedure.
- Probable benefit: Angiographic occlusion of the pre-specified target vessel intended for treatment at procedure following completion of the first PHIL treatment procedure.

Neurologic death is subject death reported as having resulted from a neurologic cause. Stroke is defined as a new focal neurological deficit in a defined vascular distribution of abrupt onset with symptoms persisting for >24 hours AND a neuro-imaging study or other quantitative study that does not indicate a different etiology. This includes ischemic and hemorrhagic strokes.

Angiographic occlusion of the pre-specified target vessel is defined as cessation of flow at the point of embolic agent administration at the target vessel.

4.2 Secondary Measured Outcomes

The following outcomes will be measured:

- The proportion of subjects with neurological death or ipsilateral stroke within the first 30 days following completion of all PHIL treatments
- Angiographic occlusion of the pre-specified target vessel intended for treatment at procedure following completion of all PHIL treatments

- New-onset or worsening of permanent morbidity at 6 month follow-up
- New-onset intracranial hemorrhage at 6 month follow-up
- New-onset of cranial nerve palsy at 6 month follow-up
- Clinically significant technical events during the PHIL embolization procedure(s) including but not limited to reflux of embolic material, migration of the embolic material, catheter entrapment or damage, and vessel dissection.
- Device-related adverse events at procedure and within 30 days
- Device-related mortality at procedure and within 30 days
- Procedure related adverse events including complications of arterial puncture, contrast induced nephropathy, radiation-induced injuries, renal and anesthesia-related complications.
- New-onset of device/procedure-related neurological adverse event or worsening of previous neurological deficit unresolved at 6 month follow-up.

Permanent morbidity is defined as a worsening of mRS score at 6 month follow-up compared to the baseline mRS score of:

- ≥1 point in subjects experiencing a stroke
- ≥2 points in subjects experiencing neurological adverse events.

Note, worsening mRS scores associated with non-neurological causes, resulting in limitations to the subject's ability to walk or require assistance to attend to own bodily needs, will not be considered permanent morbidity. This includes medical events such as, bone fractures, muscle, ligament and tendon injuries, and other physical injuries.

4.3 Additional Measured Outcomes

The following outcomes will be measured:

- Improvement of neurological symptoms
- Number of procedures required to treat the fistula at 6 months follow-up
- Procedure time (defined as first to last fluoroscopic or digital subtraction angiographic acquisitions)
- Radiation exposure (dosage and time)
- Injected volume of PHIL
- Modified Rankin Scale (mRS) at 3 and 6 months

- Self-reported QOL questionnaire, EQ-5D at 6 months
- Unplanned adjunctive treatments

4.4 Safety Evaluation

All adverse events will be assessed in terms of the seriousness (SAE vs non-SAE) and relationship to the study device and procedure. Unanticipated adverse device effect will be collected as well.

5. Investigation Plan

The study is a prospective, multicenter, single-arm, clinical study evaluating outcomes in subjects with intracranial dural arteriovenous fistulas treated with PHIL® device. The purpose is to evaluate the safety and probable benefit of MicroVention, Inc. PHIL Liquid Embolic material for the treatment of intracranial dural arteriovenous fistulas.

The study will include up to 75 patients with an intracranial dAVF aged 22-80 years.

Subjects will undergo screening / baseline evaluation, the study procedure, supplemental embolization procedures as needed and clinical and angiographic follow-up up to 6 months.

The total subject duration is expected to be approximately 9 months.

Detailed investigational plan can be referred to the clinical study protocol (Protocol Number: CL11005).

6. Determination of Sample Size

This study will enroll up to seventy five (75) subjects in this study to obtain 6 month follow-up in 60 subjects. This assumes up to fifteen (15) subjects may be lost to follow-up. No statistical justification is established.

7. Study Subjects

□ Analysis Population

The analysis population will be comprised of the results from up to 75 treated subjects. Results will be presented based on one population:

Full Analysis Set (FAS): defined all enrolled subjects in whom the PHIL device was implanted.

8. Statistical Analysis Methodology

8.1 General Statistical Approach

Descriptive statistics (mean, standard deviation, frequency charts, etc.) for baseline participant characteristics, subject disposition and other relevant study parameters will be reported. Where applicable, a comparison to rates reported in the scientific literature will be performed.

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS. The statistical analyses will be based on data pooled across sites in aggregate. All subset summary tables and data listings will be sorted by site and subject. The pre-procedure observations will be used as the baseline value for calculating post-procedural changes from baseline.

Continuous demographic parameters, such as the age of the subject at the time of enrollment, will be summarized using descriptive statistics (N, mean, median, standard deviation, minimum and maximum value). Categorical demographic parameters, such as gender, will be summarized as a proportion of the population.

Data obtained during the neurological examination using the Modified Rankin and self-reported EQ-5D will be summarized at each time point using descriptive statistics.

Routine clinical chemistry and hematology will be assessed by the investigator as normal/abnormal and not clinically significant/clinically significant. The incidence of abnormal and clinically significant values will be summarized and reported in frequency tables for each visit at which the data are collected.

Subject counts will be tabulated for all adverse events for the population. Adverse events will also be tabulated for events that occurred from the start of the procedure to 6 month follow-up after last embolization. Tabulated subject counts will be presented as a proportion of the population.

All recorded data will be presented in the individual data listings.

8.2 Primary Measured Outcomes

- Safety

The measured safety outcome is the proportion of subjects with neurological death or ipsilateral stroke within the first 30 days following completion the first PHIL of treatment procedure. The descriptive analysis of this outcome will include the number of subjects with neurological death or ipsilateral stroke, the total number evaluated, the percent, and the Clopper-Pearson two-sided 95% confidence limits on the percent.

- Probable benefit
  The measured probable benefit outcome is the angiographic occlusion of the pre-specified target vessel intended for treatment at procedure following completion of the first PHIL treatment procedure. The descriptive analysis of this outcome will include the number of subjects with angiographic occlusion of treated vessel at procedure, the total number evaluated, the percent, and the Clopper-Pearson two-sided 95% confidence limits on the percent.

8.3 Secondary Measured Outcomes

The descriptive analysis of the following secondary measured outcomes will include the number of subjects with the outcomes of interest, the total number evaluated, the percent, and the Clopper-Pearson two-sided 95% confidence limits on the percent.

- The proportion of subjects with neurological death or ipsilateral stroke within the first 30 days following completion of all PHIL treatments
- Angiographic occlusion of the pre-specified target vessel intended for treatment at procedure following completion of all PHIL treatments
- New-onset or worsening of permanent morbidity at 6 month follow-up
- New-onset intracranial hemorrhage at 6 month follow-up
- New-onset of cranial nerve palsy at 6 month follow-up
- Clinically significant technical events during the PHIL embolization procedure(s) including but not limited to reflux of embolic material, migration of the embolic material, catheter entrapment or damage, and vessel dissection.
- Device-related adverse events at procedure and 30 days
- Device-related mortality at procedure and 30 days
- Procedure related adverse events including complications of arterial puncture, contrast-induced nephropathy, radiation-induced injuries, renal and anesthesia-related complications.

- New-onset of device/procedure-related neurological adverse event or worsening of previous neurological deficit unresolved at 6 month follow-up.

8.4 Additional Measured Outcomes

The descriptive analysis of the following additional measured outcomes will include the number of subjects with the outcomes of interest, the total number evaluated, the percent, and the Clopper-Pearson 95% confidence limits on the percent.

- Improvement of neurological symptoms
- Unplanned adjunctive treatments

The descriptive analysis of the following additional measured outcomes will include N, mean, median, standard deviation, minimum and maximum value.

- Procedure time (defined as first to last fluoroscopic or digital subtraction angiographic acquisitions)
- Radiation exposure (dosage and time)
- Injected volume of PHIL

The descriptive analysis of the following additional measured outcomes will include the number of subjects at each category and the percentage of each category.

- Number of procedures required to treat the fistula at 6 months follow-up
- Modified Rankin Scale (mRS) at 3 and 6 months
- Self-reported QOL questionnaire, EQ-5D at 6 months

8.5 Duration Variables

Study Day 1 is the day of study device deployment (index procedure). Study day will appear in the listings where applicable and is calculated relative to day 1 using the general formula:

Study Day = (Date of Event – Date of Study Device Deployment) +1, if event date is on or after Date of Study Device Deployment

Study Day = (Date of Event – Date of Study Device Deployment), if event date is before the Date of Study Device Deployment

Duration variables will be calculated using the general formula:

[(end date – start date)] +1

8.6 Handling of Missing Data

If there is missing data in primary and secondary outcome, sensitivity analysis will be performed on the imputed data.

Subjects whose data are not missing at random, such as those who exit the study due to a device-related primary safety event, will be considered a failure for the probable benefit endpoint and will be considered to have a primary safety event for the primary safety endpoint.

Subjects with missing data who exit the study due to a non-device-related primary safety event will be imputed by the multiple imputation methods; similarly, their missing probable benefit endpoint will also be imputed by the multiple imputation methods.

Subjects who are absent at post-procedure visits and can be assumed to be missing at random, will have their success or failure imputed for the primary safety and probable benefit endpoints. For example, if a study stops follow-up for reasons other than a device-related primary safety event, that subject will be imputed by the methods discussed below.

For multiple imputation methods, the assumption is that data from subjects undergoing imputation is missing at random (Little and Rubin (2000)). A comprehensive sensitivity analyses called the tipping point analysis will be done. In this analysis, one can start with either the worst-case analysis in which all missing at random data will be assigned a failure for the primary endpoint, or can be started with the best case scenario in which all missing at random subjects will be assigned a success for the primary endpoint. The tipping point analysis provides result for all possible outcomes from the imputation process and is thus comprehensive.

8.7 Software

All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows

(version 9.4, SAS Institute Inc. Cary, NC) .

9. Changes in Planned Analyses

Any deviations or changes from this SAP deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described with justification and rationale.