STATISTICAL ANALYSIS PLAN
Protocol AHE-05
Pharyngeal Electrical Stimulation Evaluatio for Dysphagia after Stroke

(PhEED)

Protocol Number: **(Version Date)**	AHE-05 26JAN2018
Name of Investigational Device:	Phagenesis Phagenyx System
Methodology:	Prospective, multi-center, randomized, sham-controlled, patient-masked, outcome assessor-blinded clinical study
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SIGNATURE PAGE

Protocol Title:	Pharyngeal Electrical Stimulation Evaluatio for Dysphagia after Stroke (PhEED)
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Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatory:
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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse events
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
DMC	Data monitoring committee
eCRF	Electronic case report form
FDA	Food and Drug Administration
HR	Heart Rate
ICH	International Conference on Harmonisation
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
SAP	Statistical analysis plan
SAE	Serious adverse event
SOC	System organ class
SOP	Standard operating procedure
US	United States

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

Dysphagia is common in the post-stroke setting. It is associated with increased incidence of in-hospital pneumonia, worse outcome and greater resource utilization. The actual incidence and the timing in the resolution of dysphagia are both very difficult to estimate. Effective treatments focused on facilitating the recovery of swallowing could provide an overall economic benefit to society.

Despite dysphagia imparting both patient-specific and social-economic burden, there is very little standardization with respect to dysphagia treatments or even evidence-based recommendations for treatment. Foley et. al.,[10] intended to update Martino et al.,'s earlier work[1] with a follow-on report including data up to Aug 2007, and specifically considering targeted treatments and their associated outcomes for post-stroke dysphagia. The published findings demonstrate very heterogeneous results, and pooled analyses were not possible. Descriptive findings anecdotally suggest that dysphagia treatment is associated with reduced pneumonia risk in the acute post-stroke setting.

1.2. Objectives of Statistical Analysis

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objectives.

Primary Objective:

- To evaluate the efficacy of Phagenyx® treatment in reducing the severity of unsafe swallows.

Secondary Objectives:

- To evaluate the efficacy of Phagenyx® treatment in improving nutritional management.

Exploratory Objectives:

- To further characterize the efficacy of Phagenyx® treatment in reducing the severity of unsafe swallows.
- To further characterize the efficacy of Phagenyx® treatment on nutritional management changes.
- To evaluate the efficacy of Phagenyx® treatment on improving quality of life.
- To evaluate the efficacy of Phagenyx® treatment on general stroke health outcomes.

Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

2. STUDY DESIGN

2.1. Synopsis of Study Design

This is randomized, sham-controlled, patient-masked, outcome assessor-blinded, prospective, multi-center study designed to support a *de novo* submission and FDA clearance for the Phagenesis Phagenyx® System for treatment of oropharyngeal dysphagia following a stroke. The study will follow an adaptive group sequential design with unblinded sample size re-assessment. To ensure 180 evaluable patients with 7-day data and assuming a 20% dropout rate, 225 patients will be enrolled initially. An interim analysis for futility will occur after the first 60 patients complete their 7-day visit and another interim analysis will be performed for efficacy after 120 patients complete their 7-day visit. The total sample size may be increased up to 338 patients after the second interim analysis to ensure 270 evaluable patients. Up to 15 investigational centers across the US and Europe will participate in this study. The enrollment period is expected to be approximately 24 months and patient participation will last for approximately 11 weeks. Patients will be assessed at the following intervals: baseline, within 48 hours of treatment, 7 days, 14 days or at discharge, whichever is first, and 11 weeks after completion of study treatments.

All enrolled patients will have the Phagenyx® Catheter placed and will receive either an active treatment with Pharyngeal Electrical Stimulation or a sham treatment by a HCP who is un-blinded to the treatment assignment.

Randomization will use stratification based on site and baseline PAS. Minimization may also be included to ensure group balance for study site and additional baseline covariates.

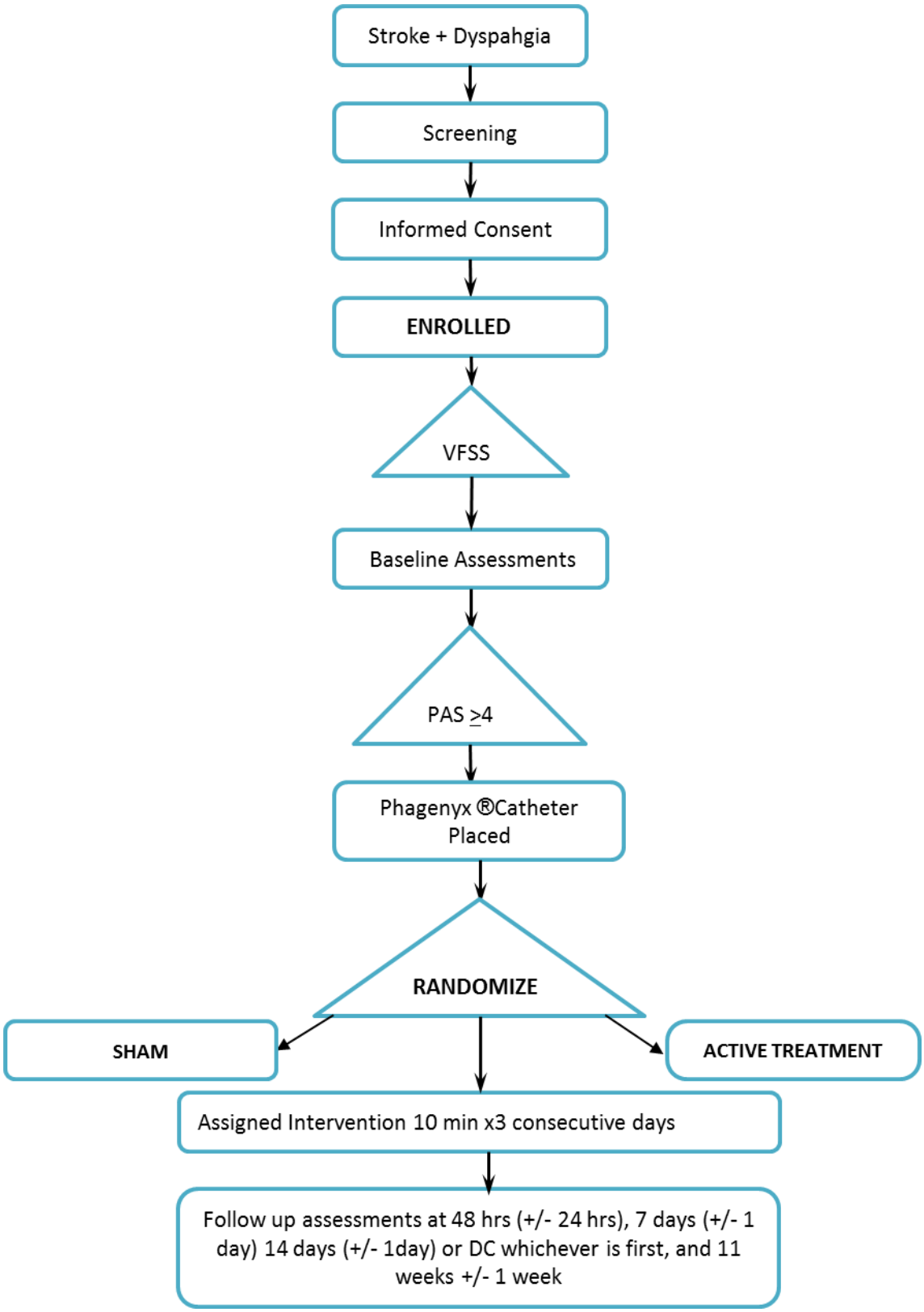
Administration of all protocol-specific assessments, other than PES or sham treatments, will be conducted by personnel who are blinded to the treatment assignment, including speech pathologists providing standard dysphagia care (excluding VitalStim and e-Stim). The standard dysphagia care data will be collected on the eCRF.

A core laboratory will be established for analysis of all procedural VFSS. The VFSS core lab will provide standardized baseline and follow-up analyses of the primary endpoint as well as VFSS-related tertiary endpoints. Personnel at the VFSS core lab will also be blinded to patient treatment assignment.

Up to three unblinded, active treatment roll-in patients will first be enrolled at each site in the US. Roll-in patients will be analyzed independently from the primary analysis population but will not contribute to the sample size cap.

Dysphagic patients enrolled into the study will continue to receive enteral or oral nutrition via the same manner as prior to study entry and will also have the Phagenyx® Catheter placed as part of the study. In the US, patients may receive feeding through the Phagenyx® Catheter for up to 2 weeks as needed. In Europe, patients may receive feeding through the Phagenyx Catheter for up to 30 days.

2.2. Study Schema


Stroke + Dyspahgia
Screening
Informed Consent
ENROLLED
VFSS
Baseline Assessments
PAS ≥4
Phagenyx ®Catheter Placed
RANDOMIZE
SHAM
ACTIVE TREATMENT
Assigned Intervention 10 min x3 consecutive days
Follow up assessments at 48 hrs (+/- 24 hrs), 7 days (+/- 1 day) 14 days (+/- 1day) or DC whichever is first, and 11 weeks +/- 1 week

2.3. Randomization Methodology

Randomization will be stratified by site and baseline PAS. Within each stratum a minimization approach with probabilistic allocation (Pocock and Simon, 1975) will be used to optimize balance between treatment groups on key prognostic factors including NIHSS, baseline PAS, and age. Randomization will occur via the study's EDC system. Administrative permission to access the randomization module and randomization eCRF will be limited to unblinded HCPs who will administer treatment and who will monitor study compliance.

2.4. Stopping Rules and Unblinding

The study will utilize a Data Monitoring Committee (DMC) with relevant clinical/medical experience with the product and/or indication/disease under clinical investigation. In order to oversee the safety of subjects as they are enrolled into the study, the DMC will establish a charter including a mission statement, operating procedures, and proposed monitoring criteria for the study, including any required interim analysis time points for assessing safety and proposed study stopping rules, if appropriate. The DMC will meet to ratify their operational charter within a reasonable timeframe relative to the enrollment of the first few subjects entering into the study.

The DMC may recommend that the sponsor modify or stop the study based on safety information. Written recommendations from the DMC will be provided to the study sponsor. The final decision regarding modification or stopping the study is the responsibility of the sponsor.

At the recommendation of the DMC the following actions may be taken at the second interim analysis:

- Stop the study for futility
- Stop the study for efficacy
- Increase the final sample size up to a maximum of 338 patients
- Continue the study as planned until reaching 225 patients

Details regarding the DMC's roles and responsibilities are detailed in the DMC Charter.

2.5. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in **Error! Reference source not found.**.

Table 1 Schedule of Assessments

	Screening	**Baseline**	**Phagenyx Treatment (10 minutes per day, 3 consecutive days)**	**48±24 Hour Follow-up**	**7±1 Days Follow-up**	**14-±1 days or discharge, whichever is first**	**11±1 Weeks Follow-up**
				Follow-up timing is based on last Phagenyx treatment.			
Medical History and Demographics	X						
Exam of nasopharynx		X[1]			X[1]	X	
Informed Consent	X						
ECG monitoring (for the first 20 patients randomized to active treatment)			X[2]				
Heart Rate and Blood Pressure Monitoring(for the first 20 patients randomized to active treatment)			X[2]				
NIHSS		X				X	X
Modified Rankin Score (mRS)		X				X	X
Barthel Index		X				X	X
FOIS		X			X	X	X
DSRS		X			X	X	X
EQ-5D, EQ-VAS		X					X
Pregnancy Test		X[3]					

VFSS		X[4]		X			
Pneumonia Assessment		X		X	X	X	
Adverse Event (AE) Assessment		X	X	X	X	X	X
Blinding Assessment						X	

[1] Assessment of nasopharynx at baseline, 1 week after catheter is in place and at catheter removal using flashlight or pen light. In the event of patient complaint or obvious symotoms, a fiberoptic exam is required and any adverse events are to be reported.
[2] Rhythm strip (30 seconds) printed at immediately prior to commencing PES treatment, 5 minutes into each of the three treatment sessions, and immediately post treatment. Continual ECG monitoring during PES to observe for any arrhythmias. Heart rate and Blood Pressure to be documented immediately prior to and after PES.
[3] Required only for females of child-bearing potential
[4] Baseline VFSS must meet the threshold criteria of demonstrating a PAS of ≥ 4, in three of the six boli (5 mL/1 tsp/bolus), during swallowing “thin liquid” barium media as assessed by the clinical staff administering the VFSS, unless its considered to be too high risk, then 2 swallows will qualify.

2.6. Efficacy and Safety Variables

2.6.1. Efficacy Variables

The efficacy variables are as follows:

- Swallowing safety of a bolus based on PAS of each swallow, determined by a videofluoroscopic swallowing study (VFSS), converted to a trichotomized ordinal response of safe (PAS 1-3), penetration (PAS 4-5), or aspiration (PAS 6-8).
- The severity of unsafe swallows will be further evaluated via:
    - Physiologic measurement obtained using the Modified Barium Swallow Impairment Profile (MBSImP) metrics
    - PAS dichotomized as safe (PAS 1-3) or unsafe (PAS 4-8).
    - Mode of PAS: thin and nectar.
- Nutritional management changes will be evaluated via:
    - Time from baseline to removal of enteral feeding (i.e., removal of NG tube or PEG or transition to oral feeding).
    - Functional Oral Intake Scale (FOIS)
    - DSRS.
- Quality of life (QOL) will be assessed via the following instruments:
    - EuroQoL-5 Dimension Questionnaire (EQ-5D) and EuroQoL-Visual Analogue Scale (EQ-VAS).
- General stroke health outcomes assessed by:
    - Time to discharge from site in which treatment is received
    - Discharge destination
    - Patient location (home, institution)
    - Days on antibiotics during hospital stay
    - NIH Stroke Scale (NIHSS)
    - Modified Rankin Scale (mRS)
    - Barthel Index (BI)
    - New onset pneumonia, using a standardized definition adapted from the STROKE-INF study (Kalra et al., 2015).
    - Hospital readmission rate.
    - Number of CXR (related to suspect pneumonia).

2.6.2. Safety Variables

Safety assessments performed during the study included physical examinations, measurement of vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory evaluations including hematology, serum chemistry, and urinalysis, and monitoring of adverse events.

3. SUBJECT POPULATIONS

3.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- The **Roll-In (RI) population** will consist of all patients enrolled in a non-blinded roll-in manner and remained eligible to receive the Phagenyx treatment after initial pre-procedural VFSS testing is completed and the PAS is determined to meet entry criterion and no exclusions are found. All patients in whom treatment was attempted, regardless of procedural outcome, will be included in this analysis set.

- The **Safety Population** will consist of all patients that were enrolled in the study (including Roll-In patients) and underwent the pre-procedural VFSS with or without subsequent placement of the Phagenyx Catheter.

- The **Intent to Treat (ITT)** Population will consist of all patients that were randomized, irrespective of their protocol adherence and continued participation in the study.

- The **Per Protocol (PP) Population** will consist of all randomized patients who completed the full Phagenyx treatment regimen according to their randomization assignment and for whom completed primary endpoint data are also complete.

3.2. Protocol Violations

At the discretion of the sponsor, major protocol violations as determined by a review of the data prior to unblinding of the study results and the conduct of statistical analyses may result in the removal of a subject's data from the PP Populations. The sponsor, or designee, will be responsible for producing the final protocol violation file (formatted as a Microsoft Excel file), in collaboration with Cytel and the data monitoring group as applicable; this file will include a description of the protocol violation, and clearly identify whether or not this violation warrants exclusion from the PP Population. This file will be finalized prior to hard database lock.

All protocol violations will be presented in the data listings.

4. STATISTICAL METHODS

4.1. Statistical Hypotheses

The primary efficacy analysis is based on an ordinal logistic model of PAS (1-8 scale) of each bolus, determined by VFSS 48 hours following the last investigational treatment, and converted to a trichotomized response as follows: Safe (PAS 1-3), Penetration (PAS 4-5), or Aspiration (PAS 6-8). Hypothesis testing will be a superiority test performed on the main effect of treatment, β_{trt}, i.e., the difference in cumulative log odds between treatment groups, with $\beta_{trt} > 0$ indicating the PES group has higher odds of a safer responses than the control group.

- Primary Efficacy Endpoint: The null hypothesis is that $\beta_{trt} \leq 0$ (PES does not result in safer swallows than the control treatment), and the alternative hypothesis is that $\beta_{trt} > 0$ (PES results in safer swallows than the control treatment).

- If the primary endpoint meets statistical significance then formal testing and analysis for the secondary endpoint will be carried out.

The analysis of the secondary endpoint of FIOS is based on a Cochran-Mantel-Haenszel (CMH), stratified by site and baseline PAS, using the modified ridit score and test of "row mean scores different" to take into account the ordered nature of the response.

The analysis of the secondary endpoint of DSRS is based on an ANCOVA model of mean DSRS 48 hours after the last study treatment, adjusting for baseline. Hypothesis testing will be a superiority test performed on the main effect of treatment, δ, with $\delta \geq 0$ indicating the PES group has lower mean DSRS than the control group.

- Secondary Efficacy Endpoint of DSRS: The null hypothesis for the $\delta \leq 0$ (PES does not result in lower DSRS), and the alternative hypothesis is that $\delta > 0$ (PES results in lower DSRS).

4.2. Sample Size Justification

Sample size and power was determined through simulations. The study will follow an adaptive group sequential design with unblinded sample size re-assessment. In order to assure 180 evaluable patients with 7 day (+/- 1day) data and assuming a 20% dropout rate, approximately 225 patients will be enrolled initially. An interim analysis for futility (non-binding stop) will occur after the first 60 patients complete their 7 day visit, and another interim analysis will be performed for efficacy after 120 patients for futility stopping, early efficacy stopping on the primary endpoint and secondary endpoint, and sample size re-assessment (SSR). The total sample size may be increased up to approximately 338 patients after the second interim analysis to ensure up to 270 evaluable patients.

Based on prior feasibility studies (Bath et al., 2016) the primary endpoint is hypothesized to have an odds ratio of 2.23 favoring the PES group. For the secondary endpoint, the difference in mean DSRS between treatment groups is expected to be 1.75. A common standard deviation of 4 is assumed for DSRS in both treatment groups. With these effect sizes, the power is 95% for significance on the primary endpoint and 85% for significance on both endpoints. Additional simulation results under different assumptions are provided in the Simulation Report.

4.3. General Statistical Methods and Data Handling

4.3.1. General Methods

All output will be incorporated into Microsoft Excel or Word files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, median, standard deviation, minimum and maximum values will be presented. Time to event data will be summarized using Kaplan-Meier Methodology using 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% confidence intervals, as well as percent of censored observations.

Formal statistical hypothesis testing will be performed on the primary and secondary efficacy endpoints with all tests conducted at the 1-sided, 0.025 level of significance. Summary statistics will be presented, as well as confidence intervals on selected parameters, as described in the sections below.

For all analyses, baseline will be defined as the most recent measurement prior to the date and time of the administration of active treatment with Pharyngeal Electrical Stimulation or a sham treatment. Therefore, baseline may be on the same day as the start of study treatment, but prior to the administration of the study treatment.

4.3.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version X.X), unless otherwise noted. Medical History and adverse events will be coding using MedDRA version X.X. Concomitant medications will be coded using World Health Organization (WHO) Drug version X.X.

4.3.3. Methods of Pooling Data

Not applicable to the present study.

4.3.4. Adjustments for Covariates

No formal statistical analysis that adjusts for possible covariate effects is planned.

4.3.5. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a single primary efficacy endpoint.

4.3.6. Subpopulations

No analyses of subgroups of subjects are planned.

4.3.7. Withdrawals, Dropouts, Loss to Follow-up

Subjects who withdrew from the study were not to be replaced.

4.3.8. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the CRF will be included in data listings that will accompany the clinical study report.

4.3.9. Visit Windows

All data will be summarized by the scheduled visits. No visit windows will be applied. If multiple assessments are collected on one visit, the last assessment will be used in the analysis.

4.4. Interim Analyses

This study follows a 3-look adaptive group sequential design with sample size re-estimation. In order to assure 180 evaluable patients with 7 day(+/- 1day) data and assuming a 20% dropout rate, approximately 225 patients will be enrolled initially.

An interim analysis for futility (non-binding) will occur after the first 60 patients complete their 7 day visit, and a second interim analysis will be performed for efficacy after 120 patients complete their 7 day visit. At the recommendation of the Data Monitoring Committee (DMC) the following actions may be taken at this second interim analysis:

- Stop the study for futility of the primary endpoint (non-binding stop).
- Stop the study for efficacy of both the primary endpoint and secondary endpoint.
- Continue the study with initially planned sample size of 180 evaluable patients (no SSR; approximately 225 patients enrolled).
- Continue the trial and increase the sample size up to a maximum of 270 evaluable patients (approximately 338 patients enrolled).

The interim analyses will be performed by an unblinded Independent Statistical Center (ISC) and the recommendation for adaptation or early stopping will be made by the DMC. An electronic file exchange platform capable of secure storage of documents with audited access will be used to control flow of information during the study.

4.5. Statistical Tests and Decisions at the Interim and Final Analyses

4.5.1. Test Statistics

For the primary endpoint, independent increments of the normally distributed Wald statistic $Z = \hat{\beta}_{trt}/\widehat{SE}(\hat{\beta}_{trt})$, calculated using the GEE method with a robust sandwich estimator, are used for hypothesis testing and conditional power (CP) calculations. For the secondary endpoint, independent increments of the normally distributed Wald statistic $Z = \hat{\delta}/\widehat{SE}(\hat{\delta})$ is calculated based on estimates of treatment effect and standard error from the ANCOVA model. Conditional power is defined as the probability of reaching statistical significance at the planned final analysis (N=180) conditional on the observed effect size, assuming the current observed effect size is the true effect size.

4.5.2. Procedure at the first interim analysis

The first interim analysis is planned for when 60 patients complete the 7 day visit. At this analysis, conditional power (CP) will be calculated for the primary endpoint. If CP < 5%, a non-binding recommendation will be made to stop for futility.

4.5.3. Procedure at the second interim analysis

The second interim analysis is planned for when for when 120 patients complete their 7 day visit.

Efficacy stopping: An early efficacy stopping boundary of Z > 2.5093 (one-sided $P < 0.0060$) will be used for all efficacy endpoints. This boundary is the group sequential boundary derived from the Lan-DeMets O'Brien Fleming spending function at 2/3 information fraction. Early stopping for efficacy will be recommended only if both the primary endpoint and secondary endpoint cross the same boundary. If the study continues, both endpoints will be tested against the group sequential boundary 1.9929 at the final analysis in a sequential manner -- the secondary endpoint is tested if the primary endpoint reaches statistical significance -- to preserve the study-wise type 1 error rate at one-sided level 0.025.

If the study is not stopped for efficacy, the interim results will be classified into different zones depending on estimation of the conditional power on the primary endpoint and, separately, on the secondary endpoint. Based on the interim zone, one of the following actions will be recommended:

- Stop the study for futility (non-binding stop).
- Continue the study until reaching the planned 180 evaluable patients (approximately 225 enrolled).
- Continue the study and increase the sample size up to a maximum of 270 evaluable patients (approximately 338 enrolled).

Details on the boundaries of these interim zones and specific actions to be taken within these zones are deferred to a restricted Simulation Report whose circulation is limited to a core study team to include the ISC and DMC in order to minimize the possibility of operational bias.

4.5.4. Procedure at the final analysis

At the time of the final analysis, hypothesis testing for the primary and secondary endpoints will be performed using a weighted combination statistic (Lehmacher and Wassmer 1999; Cui et al. 1999), whereby the Z-statistic from the first stage of the study (the first 120 patients, i.e., 2/3 of the planned information), Z_1, is combined with the independent Z-statistic from the remaining patients, Z_2, using pre-specified weights $w_1 = \sqrt{0.67}$ and $w_2 = \sqrt{0.33}$ to form a combination statistic $Z^* = w_1 Z_1 + w_2 Z_2$. These weights are used regardless of whether the sample size is increased beyond 180. If $Z^* > 2.5093$, statistical significance is achieved for that endpoint.

4.5.5. Type 1 Error Control

To see that Type 1 error is theoretically controlled even though sample size may be modified in a data-dependent manner, note that under the null hypothesis for the primary endpoint, the incremental statistics for the 2 stages, are independent with asymptotic N(0,1) distribution, regardless of final sample size.

Therefore the final test statistic is normal with mean 0 and variance $w_1^2 + w_2^2 = 1$. It follows that the joint distribution of $w_1 Z_1 + w_2 Z_2$ is the same as for the standard group sequential test with correlation w_1 at interim, as shown by Cui, Hung and Wang (1999). Because the pre-specified fixed weights w_1 and w_2 are used regardless of whether the sample size is modified based on interim data, the combination statistic with standard group sequential efficacy boundaries properly controls type 1 error. The same principles apply to the secondary endpoint.

Results of simulations performed under various null scenarios confirming type 1 error control are summarized in the Simulation Report.

4.6. Subject Disposition

A tabulation of subject disposition will be tabulated, including the number screened, the number received active treatment of PES, the number received a sham treatment, the number in each subject population for analysis, the number that withdrew prior to completing the study, and reasons for withdrawal.

A by-subject listing of study completion information, including the reason for premature study withdrawal, if applicable, will be presented.

4.7. Demographic and Baseline Characteristics

Baseline, demographic and medical history information will be summarized for the Roll-in, Safety, ITT, and PP populations using descriptive statistics. Summaries will be provided by treatment group, stratification factors, and other key baseline parameters when applicable. No formal statistical testing will be performed.

Demographic, Baseline and medical history data will be provided in data listings.

4.8. Efficacy Evaluation

4.6.1 Primary Efficacy Analysis

The primary endpoint is trichotomized PAS on each bolus, determined by VFSS 48 hours (+/- 24 hours) after completion of PES treatment. The three ordinal PAS categories are defined as Safe (PAS 1-3), Penetration (PAS 4-5), and Aspiration (PAS 6-8). Each patient contributes 12 measurements to the primary endpoint, of which six are from boli of a thin consistency and 6 are from boli of a nectar consistency.

The ITT population will be used for the primary analysis.

A cumulative logistic model will be used to analyze the primary endpoint, and a sandwich variance estimator via a generalized estimating equations approach will be used to account for correlated PAS outcomes within each patient.

The statistical model for the primary analysis will include treatment, bolus consistency, baseline maximum PAS, and treatment by consistency interaction as predictors. The response of individual i on bolus t is coded as $y_{it} = 1$ for a safe swallow, $y_{it} = 2$ for a swallow resulting in penetration, and $y_{it} = 3$ for a swallow resulting in aspiration. The log odds of a swallow with response $\leq j$ conditional on predictors x_{it} is modeled as

$$logit\big(P(y_{it} \leq j | x_{it})\big) = \beta_j + \beta_{base} * base_{it} + \beta_{trt} * trt_i + \beta_{nectar} * nectar_t + \beta_{trt*nectar} trt_i * nectar_t$$

with ordered intercept terms $\beta_1 < \beta_2$, a treatment indicator trt_i (1=PES, 0=control), and a consistency indicator $nectar_i$ (1=nectar, 0=thin). The maximum PAS (1-8) of individual i across all pre-treatment swallows of a given consistency at baseline is denoted $base_{it}$. The GEE approach with robust sandwich estimator is used to account for within subject correlation.

Missing PAS data will be imputed in the primary analysis. PAS values that are missing due to application of VFSS stopping criteria will be assigned the worst (highest) post-treatment PAS value. For patients who have no post-treatment PAS data due to lost-to-follow-up or death, the post-treatment PAS values will be imputed from baseline PAS values and other patient baseline characteristics using multiple imputation. In addition, tipping point analysis will be performed as a sensitivity analysis.

The estimated treatment effect in the logistic model will be presented along with standard error. The treatment effect will also be presented as an odds ratio with 95% confidence interval.

Sensitivity analysis will be performed in which missing values are ignored. Analyses of the primary endpoint with and without imputation will also be performed on the per protocol population.

4.6.2 Secondary Efficacy Analysis

The secondary endpoints are FIOS and DSRS 7 days (+/- 1 day) after completion of investigational treatment.

The ordered categorical endpoint of FIOS will be analyzed by a Cochran-Mantel-Haenszel (CMH) test stratified by site and baseline PAS, using the modified ridit score and test of "row mean scores different" to take into account the ordered nature of the response.

The secondary endpoint of DSRS will be modeled by an ANCOVA model with treatment, center, baseline PAS and baseline DSRS as predictors, and will be tested for statistical significance provided the primary endpoint is found to be statistically significant. The ITT population will be used.

Missing data on the secondary endpoint will not be imputed for the purpose of significance testing.

4.6.3 Exploratory Efficacy Analysis

Exploratory endpoints are as follows:

- The severity of unsafe swallows will be further evaluated via:
    - PAS outcome by each consistency (thin and nectar)
    - Physiologic measurement obtained using the Modified Barium Swallow Impairment Profile (MBSImP) metrics will be extracted from the thin and nectar swallows by the core lab by using the baseline and follow up VFSS data. These validated and reliable metrics of critical swallowing movements will be explored for their relationship to the primary study endpoint (PAS).
    - PAS dichotomized as safe (PAS 1-3) or unsafe (PAS 4-8)
- Nutritional management changes will be evaluated via:

  - Dysphagia Severity Rating Scale (DSRS) at 14 days or discharge, whichever is first, and at 11 weeks following the last investigational treatment.
  - Time from baseline to removal of enteral feeding (i.e., removal of NG tube or PEG or transition to oral feeding, or first diet upgrade)
  - Functional Oral Intake Scale (FOIS) at 7 days, 14 days or discharge, whichever is first, and 11 weeks following the last investigational treatment
- Quality of life (QOL) will be assessed baseline and 11 weeks following the last investigational treatment via the following instruments
  - EuroQoL-5 Dimension Questionnaire (EQ-5D) and EuroQoL-Visual Analogue Scale (EQ-VAS).
- General stroke health outcomes assessed by:
  - Time to discharge from site in which treatment is received
  - Discharge destination from the site in which treatment is received
  - Patient location (home, institution) at 11 weeks
  - Days on antibiotics during hospital stay
  - NIH Stroke Scale (NIHSS) at baseline and 14 days or discharge, and 11-week follow up
  - Modified Rankin Scale (mRS) at baseline, 14 days, and 11 week follow up
  - Barthel Index (BI) at baseline, 14 days or discharge, and 11-week follow up
  - New onset pneumonia, using a standardized definition adapted from the STROKE-INF study[26] at baseline, 48 hrs, 7 days, and 14 days or discharge
  - Hospital readmission rate
  - Number of CXR (related to suspect pneumonia)

Exploratory endpoints will be summarized by treatment group, and may be analyzed using appropriate statistical models with adjustments for key prognostic covariates. No multiplicity adjustments will be made for exploratory analyses.

For time-to-event endpoints, Cox proportional hazards models which includes effects for treatment, center and baseline PAS will be used. In addition, the Kaplan-Meier estimates of time to first event will be presented for each treatment group. Kaplan-Meier plot of time to first event (survival function) will also be presented by treatment groups.

For continuous endpoints, ANCOVA models with the effects of treatment group, center, baseline PAS and the baseline value of that variable will be used.

For nominal categorical endpoints, a Cochran-Mantel-Haenszel (CMH) test stratified by site and baseline PAS will be used. The ordered categorical endpoint of mRS will be analyzed by a CMH test stratified by site and baseline PAS, using the modified ridit score and test of "row mean scores different" to take into account the ordered nature of the response.

For hospital readmission rate, a Poisson model with the effects of treatment group, center, baseline PAS and using patient-year as the offset will be used.

4.9. Safety Analyses

Safety analyses will be conducted using the Safety Population.

4.9.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term.

Analyses of adverse events will be performed for those events that are considered treatment emergent, where treatment emergent is defined as any adverse event with onset after the administration of study medication through the end of the study, i.e. 30 days after the surgery or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the investigator through the end of the study.

Adverse events are summarized by subject incidence rates, therefore, in any tabulation, a subject contributes only once to the count for a given adverse event (SOC or preferred term).

The number and percentage of subjects with any treatment-emergent adverse event, with any treatment-emergent adverse events assessed by the Investigator as related to treatment (definite, probable, or possible relationship), and with any serious adverse event will be summarized by treatment group and overall. In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

No formal hypothesis-testing analysis of adverse events incidence rates will be performed.

All adverse events occurring on study will be listed in subject data listings.

By-subject listings also will be provided for the following: subject deaths; serious adverse events; and adverse events leading to withdrawal.

4.9.2. Laboratory Data

Clinical laboratory values will be expressed using conventional units.

The actual value and change from Baseline to each on study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry. In the event of repeat values, the last non-missing value per study day/time will be used.

Subject incidences of clinical laboratory change in classification with respect to the laboratory normal ranges will be summarized as shift tables. Clinically significant laboratory abnormalities will be reported and included in the AE tabulations.

Shift from baseline tables will be provided for clinical laboratory measurements including hematology, chemistry and urinalysis by each on study evaluation using categories of low, normal, and high and summarized by descriptive statistics

All laboratory data will be provided in data listings.

A subset listing will be presented for all clinically significant laboratory abnormal laboratory values.

4.9.3. Vital Signs and Physical Examinations

The actual value and change from Baseline to each on study evaluation will be summarized for vital signs.

The percentage and number of patients with shift from baseline will be summarized by each on study evaluation. The actual value and change from Baseline to each on study evaluation (as average of the duplicate measurements) in all vital signs parameter will be calculated and summarized descriptively

By-subject listings of vital sign measurements will be presented in data listings.

All physical examination findings will be presented in a data listing.

4.9.4. Electrocardiogram

ECG results will be summarized descriptively, including the number and percent of subjects with normal, abnormal and clinically significant abnormal results at Baseline and each study visit.

All ECG data for each subject will be provided in data listings.

4.9.5. Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary. Results will be tabulated by Anatomic Therapeutic Class (ATC) and preferred term.

The use of concomitant medications will be included in by-subject data listing.

5. CHANGES TO PLANNED ANALYSES

As of this date, there have been no changes between the protocol-defined statistical analyses and those presented in this statistical plan.

6. REFERENCES

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