Quality of Life Impact After Treatment of Nasal Airway Obstruction Using the Aerin Medical Vivaer® Stylus

Statistical Analysis Plan

Study: A Prospective, Multi-Center, Non-Randomized Study to Evaluate the Quality of Life Impact After Treatment of Nasal Airway Obstruction Using the Aerin Medical Vivaer Stylus (Protocol TP465 / Version Date: 25-Jan-2018)

Plan Date: 22 January 2019

Product: Aerin Medical Vivaer® Stylus

Sponsor: Aerin Medical, Inc.
232 E. Caribbean Drive
Sunnyvale, CA 94089

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1 INTRODUCTION

Aerin Medical believes that the benefits demonstrated with the Vivaer Stylus procedure in the Aerin Medical TP258 study, "A Prospective, Multi-Center, Non-Randomized Study to Evaluate Treatment of Nasal Airway Obstruction Using the Aerin Medical Device" may be durable beyond the initial six months of the study in terms of sustained quality of life impact. The TP258 study demonstrated the safety and effectiveness of the treatment procedure to the 26-week endpoint and was the clinical basis for 510(k) clearance of the device by the FDA (K172529 5 December 2017). This prospective follow-up study on a cohort of subjects from the TP258 study collected nasal obstruction symptom evaluations (NOSE) and responses to an Aerin Medical Quality of Life survey at 12, 18 and 24 months after the procedure.

The purpose of this statistical analysis plan is to outline the necessary statistical techniques required to evaluate the efficacy outcome parameters in the Final Report for Clinical Protocol (TP465).

2 OBJECTIVE

The objective of the study was to evaluate the long-term durability of benefits associated with the treatment procedure using the Vivaer Stylus for relief from nasal airway obstruction.

3 STUDY DESIGN

3.1 Overview

This investigation was a prospective extended follow-up study of subjects who had participated in the TP258 multicenter trial to evaluate the safety and efficacy of the Vivaer Stylus. Subjects were followed to the 26-week endpoint in that study. Subjects agreeing to participate in this follow-up study were to provide self-evaluation NOSE and quality of life measures at 12, 18, and 24 months after the treatment procedure. There was no concurrent control population or blinding in either the original TP258 study or in this extended follow-up study.

Self-administered evaluations were scheduled for 12, 18, and 24 months after the treatment procedure. Evaluations could occur in person with study personnel, by phone, or by mail.

3.2 Test Device

The Aerin Medical Vivaer® Stylus is a disposable handheld device capable of delivering bipolar radiofrequency energy to tissue and has been used to treat nasal airway obstruction. The device was cleared by the FDA (K172529 5 December 2017) with indication for use in otorhinolaryngology (ENT) surgery for the coagulation of soft tissue in the nasal airway, to treat nasal airway obstruction by shrinking submucosal tissue, including cartilage in the internal nasal valve area.

3.2 Population and Sample Size

Subjects who completed participation in the Aerin Medical TP258 study, "A Prospective, Multi-Center, Non-Randomized Study to Evaluate Treatment of Nasal Airway Obstruction Using the Aerin Medical Device" were eligible for inclusion and participation in this study. These subjects had exhibited significant symptoms of nasal obstruction attributed to internal nasal valve dysfunction prior to undergoing treatment with the Aerin Medical Vivaer Stylus and completing 26 weeks of follow-up in the Aerin Medical TP258 study.

The maximum sample size for this extended follow-up of the TP258 study was 49 subjects, the number that completed the TP258 study.

All eligible subjects who provided informed consent and completed at least 1 survey were included in the analysis population. A second nonenrolled population was defined as those subjects enrolled in the TP258 study that chose not to enroll in this extended follow-up study. The purpose of the nonenrolled population was to allow comparison of characteristics of subjects who self-selected to enroll in the follow-up study with those who chose not to enroll in the follow-up study.

4 OUTCOME MEASURES

4.1 Nasal Obstruction Symptom Evaluation (NOSE)

Nasal valve evaluation is based on clinical observations of signs and symptoms with no easily obtained, reproducible objective measurement techniques of the valve;[1] therefore, the Nasal Obstruction Symptom Evaluation (NOSE) questionnaire was used in the TP258 study as the primary outcome measure and was continued in this follow-up study. The NOSE questionnaire is a validated disease-specific health status instrument used by clinicians to measure the outcome of subjects treated for nasal obstruction.[2] The NOSE survey consists of 5 items, each scored using a 5-point (0 - 4) Likert scale. The 5 item scores are summed and then multiplied by 5 to make a total score range of 0 through 100, where higher scores indicate worse obstruction. Severity of symptoms can be classified as mild (range, 5-25), moderate (range, 30-50), severe (range, 55-75), or extreme (range, 80-100) nasal obstruction, based on responses to the NOSE survey.[3]

Treatment responders were defined in the TP258 study as subjects achieving a 15 point or greater improvement in the NOSE score compared to baseline.

4.2 Aerin Medical Quality of Life survey

A 21-item quality of life survey was developed to assess aspects of subjects' current quality of life compared to before the procedure that are typically associated with nasal obstruction and trouble breathing (Figure 1). The first 14 items addressed agreement or disagreement with statements concerning sleep, energy, productivity, emotions, activities, and work. Answers were provided on a 5-point Likert-type scale, Agree Strongly, Agree, Neither agree or disagree, Disagree, Disagree Strongly. The next 4 items addressed the occurrence of health-related symptoms

associated with nasal obstruction. The frequency of occurrence of headaches, sinus infections, sore throat, and post nasal drip were each assessed on a 5-point scale of Very Rarely/Never, Rarely, Occasionally, Frequently, Very Frequently. The last 3 items assess the frequency of use of medications and devices for nasal congestion. The 5-point response scale is Much less frequently, Less Frequently, About the Same, More Frequently, Much More Frequently.

Please indicate your level of agreement with the following statements:
Compared to before I had the Aerin Medical Nasal procedure, I have experienced

		Agree Strongly	Agree	Neither agree or disagree	Disagree	Disagree Strongly
1.	Less difficulty falling asleep					
2.	Less waking up at night					
3.	Better sleep throughout the night					
4.	Waking up feeling rested					
5.	Less fatigue during the day					
6.	Increased productivity					
7.	Increased energy					
8.	Increased ability to focus					
9.	Increased sense of overall well-being					
10.	Less feelings of frustration/restlessness/irritability					
11.	Less feelings of sadness					
12.	Less feelings of embarrassment or self-consciousness that I had to breathe through my mouth instead of my nose					
13.	Missing fewer activities with family and friends					
14.	Missing fewer days at work					

Compared to before you had the procedure, how often do you suffer from the following conditions?

		Very Rarely/ Never	Rarely	Occasionally	Frequently	Very Frequently
1.	Headaches					
2.	Sinus infections					
3.	Sore throat					
4.	Post nasal drip					

Compared to the time prior to when you had the procedure, how often have you used each of the following products to help you with nasal congestion/difficulty breathing through your nose?

		Much less frequently	Less frequently	About the same	More Frequently	Much More Frequently
1.	Oral medications (antihistamines, oral decongestants)					
2.	Nasal sprays (nasal steroids, inhaled decongestants)					
3.	Nasal breathing strips (for example, BreatheRight® Strips)					

Figure 1. Aerin Medical Quality of Life survey.

5 STATISTICAL ANALYSIS

Statistical methods are described within the outcome specific subsections that follow. Each subject served as their own control for comparison of preprocedure to postprocedure condition.

5.1 Analysis Populations

All eligible subjects who provided informed consent and completed at least 1 survey will be included in the analysis population. A second nonenrolled population will be defined as those subjects enrolled in the TP258 study that chose not to enroll in this extended follow-up study. The purpose of the nonenrolled population is to allow comparison of characteristics of subjects who self-selected to enroll in the follow-up study with those who chose not to enroll in the follow-up study.

5.2 Derived Variables

Appropriate derived variables will be created as needed for study data summary and reporting. These are discussed in the section describing the analysis of the variable.

5.3 Missing Values

Every effort will be made to obtain complete follow-up data for every subject; however, as these are point-in-time surveys completed by the subject, it will not be possible to retrieve responses to missed survey items. No imputation of missed items or surveys is planned for the primary analysis; however, sensitivity analysis involving imputation of missed values may be undertaken if warranted.

5.4 Data Collection and Quality Assurance

Completed NOSE and Quality of Life surveys on case report forms will be monitored for correct score calculation by qualified Aerin Medical personnel and qualified contract personnel. Data from the Case Report Forms will be entered and stored in an electronic database (Excel).

5.5 Statistical Software

SAS 9.4 (SAS Institute, Cary, NC) will be used to create datasets from the excel database for reporting and analysis. Analyses will be performed using SAS 9.4 (SAS Institute, Cary, NC) and SigmaPlot 14.0 (Systat Software, Inc., San Jose, CA).

5.6 Demographics and Baseline Characteristics

Demographic and baseline data are available from the TP258 study and will be summarized separately for the enrolled analysis population and the nonenrolled population and examined for potential differences between enrollees and nonenrollees. Discrete variables will be described as frequencies and percentages at each level of the categorical variable. Continuous variables will be summarized descriptively (n, mean, median, standard deviation, minimum, and maximum).

5.7 Primary Analysis

Mean NOSE scores at baseline and each follow-up evaluation will be calculated to show the time course progression of improvement. Repeated measures analysis of variance (ANOVA) will be used to test for differences from baseline to follow-up evaluations. The statistical significance level will be set at 5% (p-value < 0.05).

5.8 Secondary Analyses

Appropriate statistical techniques such as Student's t-test and ANOVA will be used for continuous outcome measures. Categorical and binomial outcomes will be examined using Fisher's exact test, χ^2, or binomial tests. All analyses of secondary outcomes measures are exploratory for informational purposes only. No adjustments for multiple comparisons will be applied.

Nasal Obstruction Symptom Evaluation (NOSE)

The number and proportion (percent) of treatment responders (≥15-point improvement (decrease) in NOSE score from baseline to each follow-up visit) will be calculated.

Mean percent improvement from baseline to each follow-up evaluation will be calculated.

NOSE scores will also be summarized as number of subjects and percentage falling in each category (mild, moderate, severe, extreme) at baseline and each follow-up evaluation.

Responses to individual questions of the NOSE will be summarized as number of subjects and percentage falling in each response category (Not a Problem, Very Mild Problem, Moderate problem, Fairly Bad Problem, Severe problem) at baseline and each follow-up evaluation.

Aerin Medical Quality of Life Survey

The number and percent distribution of responses for each of the 21 items will be presented.

5.9 Data Pooling

Data from the investigational sites will be pooled for the primary analysis but may be examined for site effect if warranted.

6 References

1. Rhee JS, Weaver EM, Park SS, Baker SR, Hilger PA, Kriet JD, Murakami C, Senior BA, Rosenfeld, RM, DiVittorio D. Clinical consensus statement: Diagnosis and management of nasal valve compromise. *Otolaryngol Head Neck Surg* 2010;143(1):48-59.
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3. Lipan MJ, Most SP. Development of a severity classification system for subjective nasal obstruction. *JAMA Facial Plast Surg* 2013;15(5):358-361.