A Prospective, Multicenter Study of the AERin Medical Vivaer® ARC Stylus for Nasal AirWAY Obstruction (AERWAY)

Statistical Analysis Plan

Study: A Prospective, Multicenter Study of the Aerin Medical Vivaer® ARC Stylus for Nasal Airway Obstruction (AERWAY)
(Protocol #TP900 / Rev E 16 May 2022)

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Product: Vivaer® ARC Stylus

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TABLE OF CONTENTS

1 ABBREVIATIONS

AE – Adverse event

CSR – Clinical study report

FAS – Full Analysis Set

NAO – Nasal airway obstruction

NOSE – Nasal Obstruction Symptom Evaluation

PPS– Per-Protocol Eligible Set

SAP – Statistical analysis plan

VAS – visual analog scale

2 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to prespecify statistical analysis methods for supporting completion of publications and clinical study report (CSR) of TP900 (AERWAY) for the Vivaer product.

The AERWAY postmarket study was primarily designed to generate additional effectiveness evaluations through observational reporting of outcomes measures defined in the protocol. No specific hypotheses or hypothesis tests were defined in the study protocol. This SAP outlines the data summaries, statistical techniques, and analyses that will be used to evaluate the effectiveness and safety measures and to propose subgroup analyses of interest.

Results of analyses performed under this SAP may be included in regulatory submissions, clinical study reports and/or manuscripts. Additional exploratory analyses, which are not defined in this SAP, may be performed to further support the clinical development program. Those additional analyses will be detailed in an amendment to this plan and/or documented in the CSR.

3 STUDY DESIGN

This is a single-arm, nonrandomized, prospective, multicenter postmarket study initiated in 2020 to collect longer-term data up to 36-months postprocedure on the effectiveness of the Vivaer procedure for treatment of nasal airway obstruction (NAO). Planned enrollment was 125 participants at up to 20 sites.

All participants were evaluated in-office prior to treatment and following treatment 3 months. Extended follow-up evaluations have been, or will be conducted remotely by phone at 6, 12, 24, and 36 months.

4 STUDY OBJECTIVES AND ENDPOINTS

The primary objective of this study is to continue to evaluate the effectiveness of the Vivaer ARC Stylus for treating the nasal valve area to improve symptoms in those diagnosed with NAO. Effectiveness is assessed through several outcome measures and endpoints as described in Table 1. Outcome measures are further described in Section 8.

Table 1. Objectives and endpoints.

Objective	Outcome measures and Endpoints
Evaluate effectiveness through symptom improvement.	Nasal Obstruction Symptom Evaluation (NOSE) Scale score: • Mean and mean change from baseline at the 3-, 6-, 12-, 24-, and 36-month follow-up evaluations. • Distribution of NOSE Scale score severity categories (mild, moderate, severe, extreme) at the 3-, 6-, 12-, 24-, and 36-month follow-up evaluations. • Mean, change from baseline in mean, and response distribution of the 5 components of the NOSE Scale score (nasal congestion, nasal blockage, trouble breathing, trouble sleeping, and getting enough air during exercise) at the 3-, 6-, 12-, 24-, and 36-month follow-up evaluations. • Proportion of responders based on improvement in NOSE Scale score at the 3-, 6-, 12-, 24-, and 36-month follow-up evaluations.
Evaluate effectiveness through participant quality of life (QoL) questionnaire feedback.	QoL questionnaire • Item response distributions and means where appropriate, at the 3-, 6-, 12-, 24-, and 36-month follow-up evaluations.
Evaluate safety through the safety profile.	Adverse events • Frequency of device-related and procedure-related serious adverse events through the 3-month evaluation • Incidence (type, severity, relatedness) of adverse events overall and by follow-up interval.
Evaluate Other Exploratory Outcome Measures	Nasal Assessment • Item response distributions prior to the procedure, immediately after the procedure, and at 3 months after the procedure. Visual analog scale (VAS) for pain • VAS pain score assessed at 3 months. Medications Updates to current medications or any new or changed medications at the 3-, 6-, 12-, 24-, and 36-month follow-up evaluations.

5 SAMPLE SIZE

The study was designed to enroll up to 125 participants at up to 20 sites. This was initially a registry-type study for collection of data from a substantial number of participants receiving the Vivaer procedure representing diverse clinics and geographical areas but was implemented as a postmarket single-arm study. No formal power analysis was performed; however, substantially smaller sample sizes were found to be sufficiently powerful in prior

studies to draw clinically and statistically meaningful conclusions regarding efficacy and safety of the procedure. The larger sample size in this postmarket study was used to potentially support exploratory subgroup analyses of interest.

6 RANDOMIZATION

This is a single-group, prospective, open-label study and therefore randomization is not applicable.

7 BLINDING

Neither the physicians nor participants were blinded as to treatment.

8 OUTCOME MEASURES

8.1 Nasal Assessment

The target nasal valve area within each nostril was visually examined just prior to the procedure, immediately after the procedure, and at 3 months after the procedure. Observations are categorized as not present, mild, moderate, or severe.

Assessments include:

- Saddle nose deformity
- Bruising around orbital area
- Soreness, pain
- Numbness.

Endoscope required for assessment of:

- Inflammation / generalized redness
- Swelling, edema
- Blanching (postprocedure only)
- Bleeding at anesthetic injection site (not requiring physician intervention)
- Bleeding at treatment site (not requiring physician intervention)
- Nasal obstruction from tissue edema
- Disruption of mucosal flow / crusting
- Evidence of increase in diameter of nasal valve (3 months only).

8.2 NOSE Scale Score

To evaluate the significance of a patient's nasal obstruction both before and after the procedure, this study used the well-known patient-reported NOSE Scale for determining the primary assessment of treatment effectiveness. The NOSE Scale is a validated disease-specific health status instrument used by clinicians to measure the outcome of patients treated for nasal obstruction.[1] The NOSE Scale consists of 5 items, each scored using a 5-point Likert scale 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.[2]

Treatment responder based on NOSE Scale improvement

Individual participant success (responder) is defined as at least 1 NOSE Scale class improvement, (eg, going from a score in the severe range (55-75) at baseline to a score in the moderate range (30-50) at the follow-up evaluation), or an improvement (decrease) in NOSE Scale score of 20% or more from baseline to the follow-up time point. Other levels of success (definitions of responder) may also be explored.

8.3 Visual Analog Scale (VAS) for Pain

Perception of pain associated with the procedure was measured using a horizontal 100 mm VAS[3] anchored on the left with the words "No Pain" (0) and on the right with the words "Worst Pain Imaginable" (10), was used to measure nasal pain associated with the procedure. Scores are obtained by measuring the distance in millimeters from the left origin of the line (0) to the point indicated with a vertical slash placed by the participant to indicate their current level of pain in and around the nose

8.4 Participant Quality of Life Assessment

The QoL questionnaire consists of 4 parts (Appendix A). The first part has 24 items and asks the participant to rate how much of a problem various symptoms and potential effects of their nasal obstruction present to their quality of life at the time of taking the survey relative to the time prior to having the Vivaer procedure. A 6-point ordered rating scale is used with descriptors:

- No Problem (0)
- Very Mild Problem (1)
- Mild or Slight Problem (2)
- Moderate Problem (3)
- Severe Problem (4)
- Problem as bad as it can be (5).

The second part has 3 questions related to frequency of use of medical products for nasal obstruction symptom relief now compared to before the procedure. Responses are on a 5-point ordered rating scale with descriptors:

- Much less frequently
- Less frequently
- About the same
- More frequently
- Much more frequently.

There is also a response of not applicable if a product was not being used prior to the procedure.

The third part has 3 questions. The first is a rating on a 10-point scale of satisfaction with symptom relief following the procedure where 1 represents symptoms have no effect on daily activity and 10 being symptoms completely prevent daily activity. The second question asks if the procedure would be recommended to a friend with similar symptoms (yes or no) and the third question asks if symptoms returned would you undergo the procedure again (yes/no).

The fourth section requests information on general health, including undergoing additional nasal surgery, significant changes in health, and changes to medication regimen.

8.5 Medications

Updates to current medications or any new or changed medications are requested at each evaluation. Medications because of intervention related to the study treatment are documented and will be correlated with reported adverse events.

8.6 Adverse Events

Participants are queried about any side effects or adverse experiences related to the Vivaer procedure that they may have experienced. Incidence (type, severity, relatedness) of adverse events overall and by follow-up interval were recorded according to definitions provided in the study protocol.

9 STATISTICAL ANALYSIS

9.1 Analysis Populations

Full Analysis Set (FAS):
The FAS is comprised of all enrolled participants that underwent the study procedure and met eligibility criteria.

Per-Protocol Eligible Set (PPS):
The PPS is comprised of all participants who met enrollment eligibility criteria, underwent the study and no major protocol deviations.

Safety Analysis Set:
The safety analysis population is comprised of all enrolled participants that have received any study-specific procedure, including screening procedures (eg, nasal endoscopy) and any part of the Vivaer procedure, including anesthesia.

9.2 General Considerations and Statistical Methods

Summary descriptive statistics, including mean, median, standard deviation, minimum, maximum, and interquartile range for continuous measures, and frequencies and percentages for categorical outcomes will be presented for all variables of interest. Outcome measures will be presented by time. Confidence intervals will be included for means and medians where appropriate for the various outcome measures.

Informational and exploratory outcomes analyses will use $P<.05$ as a measure of statistical significance. Where feasible, longitudinal analyses of individual outcome

measures will incorporate *P*-value adjustment for comparisons of multiple time points. No adjustments will be made due to analyzing multiple outcome measures.

Analyses using repeated measures linear mixed models with multiple comparisons of time points are anticipated for outcome measures conventionally considered continuous data (NOSE). Components of the NOSE Scale score have also been treated as continuous but may also be analyzed using generalized linear models as outcomes represented by ordered categories.

Results will be presented using least square (adjusted) means where data are not complete across all time points.

Nonparametric analysis will be employed where gross violations of assumptions for parametric analyses are demonstrated.

Correlation analysis and regression modeling may be employed for exploratory analyses of relationships between and among various participant demographic and history characteristics and outcome measures, particularly NOSE Scale scores and components.

9.3 Data Pooling

All study data will be pooled across study sites.

9.4 Missing Values

Outcome measures will be analyzed by using available data only. No imputations are anticipated unless part of a subgroup analysis of interest.

9.5 Data Collection and Quality Assurance

Data are collected on electronic case report forms using the Medrio electronic data capture system and database. Qualified monitors review the data electronically and through site monitoring visits to assure that the investigator and staff are compliant with the protocol and applicable regulatory requirements in addition to assuring timely and accurate data collection.

9.6 Statistical Software

SAS 9.4 (SAS Institute, Cary, NC) will be used to create datasets from SAS data exports from the Medrio system 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).

9.7 Demographics and Baseline Characteristics

Demography and baseline characteristics will be summarized using frequencies and percentages for categorical factors and mean, standard deviation, minimum and maximum, median, and interquartile range for continuous factors.

9.8 Outcome Measures Analyses

Data collected at postprocedure evaluation time points conducted after a participant received additional ENT procedures outside of the study protocol will be excluded

from analysis of efficacy outcomes measures as these additional procedures would likely confound the effect of the original Vivaer treatment. For example, a participant who received a septoplasty after the 12-month evaluation will have any efficacy outcome measures that were collected after the septoplasty (24 months and 36 months) excluded from the analysis. Results after receiving additional treatments may be summarized separately.

Nasal Assessment - The visual physical and endoscopic assessment factors summarized to include frequency and percentage of responses in each category for each component of the nasal assessment at baseline, just prior to procedure, immediately after procedure, and 3 months after the procedure.

NOSE Scale score - Categorical responses and scores on the NOSE Scale and its individual components will be subject to multiple summary methods and analyses including the:

- Mean and mean change from baseline at the 3-, 6-, 12-, 24-, and 36-month follow-up evaluations.
- Distribution of NOSE Scale score severity categories (mild, moderate, severe, extreme) at the 3-, 6-, 12-, 24-, and 36-month follow-up evaluations displayed as number and percent.
- Mean, change from baseline in mean, and response distribution of the 5 components of the NOSE Scale score (nasal congestion, nasal blockage, trouble breathing, trouble sleeping, and getting enough air during exercise) at the 3-, 6-, 12-, 24-, and 36-month follow-up evaluations.
- Proportion (%) of responders based on improvement in NOSE Scale score at the 3-, 6-, 12-, 24-, and 36-month follow-up evaluations be displayed as number and percent.

VAS for pain - Summary will include mean (median) VAS pain scores assessed postprocedure and at 3 months.

Participant QoL Questionnaire – Responses to questionnaire items will be summarized by response category (frequency and percent) and by mean (median) response where appropriate at the 3-, 6-, 12-, 24-, and 36-month follow-up evaluations.

Medications - Medications associated with relief or treatment of NAO symptoms or associated with the treatment of adverse events will be documented at baseline and updated as necessary at each evaluation or adverse event. Medications relevant to nasal obstruction may be categorized (eg, antihistamine, intranasal steroid, decongestant, anticholinergic, immunotherapy) for summarization and reporting purposes.

Change in medication use for nasal obstruction symptoms - Proportions of participants reporting increase, decrease, or no change in use for medication

categories will be summarized at the 3-, 6-, 12-, 24-, and 36-month follow-up evaluations.

9.9 Subgroup and Other Analyses and Summaries

Several subgroups of interest have been identified for further exploration in relation to the effect on NOSE Scale scores and responder proportions:

- valve collapse mechanism (dynamic, static, mixture)
- prior septoplasty or turbinate surgery
- presence/absence of septal deviation
- presence/absence of enlarged turbinates.

Other areas of interest include:

- Characteristics of treatment nonresponders.
- Substudy of endoscopic nasal assessment images of participants identified with septal deviation. The study will examine the feasibility of grading the degree of septal deviation and assess the potential for correlation with NOSE Scale scores.

9.10 Safety Analysis

All adverse events (AE) will be analyzed for all participants. Adverse events are coded using a custom Aerin Medical dictionary so that adverse events may be categorized for analysis at an appropriate level of detail. Listings will be provided to detail individual events. The number of participants, number of AEs, and the proportion of participants reporting each AE will be summarized. Multiple occurrences of the same AE for a participant will be noted but only counted once for reporting of AE incidence. Seriousness and severity of AEs and their relationship to the device and procedure will be summarized. A time course of adverse events will be presented. Any unanticipated adverse device experiences or adverse events that occur at an unexpectedly high incidence rate will receive detailed analyses. Narratives will be presented for all deaths, serious adverse events, unexpected adverse device experiences, and participants withdrawn due to an adverse event.

10 REFERENCES

1. Stewart MG, Witsell DL, Smith TL, et al. Development and validation of the Nasal Obstruction Symptom Evaluation (NOSE) scale. *Otolaryngol Head Neck Surg* 2004;130(2):157-163.
2. Lipan MJ, Most SP. Development of a severity classification system for subjective nasal obstruction. *JAMA Facial Plast Surg* 2013;15(5):358-361
3. Scott J, Huskisson EC. Graphic representation of pain. *Pain* 1976;2:175-184.

Appendix A - Quality of Life Assessment

Compared to before I had the Aerin Medical Nasal procedure

	No Problem (0)	Very Mild Problem (1)	Mild or Slight Problem (2)	Moderate Problem (3)	Severe Problem (4)	Problem as bad as it can be (5)
1. Nasal obstruction						
2. Need to blow nose						
3. Sneezing						
4. Runny nose						
5. Cough						
6. Post-nasal discharge						
7. Thick nasal discharge						
8. Decreased sense of smell or taste						
9. Difficulty falling asleep						
10. Wake up at night						
11. Lack of a good night's sleep						
12. Wake up tired						
13. Fatigue						
14. Reduced productivity						
15. Reduced concentration						
16. Frustrated/restless/irritable						
17. Sad						
18. Embarrassed						
19. Snoring						
20. Mouth breathing during exercise						
21. Reduced sports or exercise tolerance						
22. Shortness of breath during experience						
23. Headache						
24. Nasal Congestion						

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)					

Rate Your Satisfaction:											
1. How satisfied are you with the outcome (symptom relief) of your Vivaer Treatment (1-10)											
(1 being my symptoms have no effect on my daily activity)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10	(10 being symptoms which completely prevent me from my daily activity)
2. Would you recommend the treatment to a friend or relative who suffered from the same nasal symptoms you had?									☐ Yes	☐ No	
3. If your symptoms were to come back would you chose to undergo the same procedure again?									☐ Yes	☐ No	