

Post Approval Study
Proposal #1

Endobronchial Valve for Emphysema
Palliation Trial Long Term
(VENT Long Term)
Follow-up Protocol

**Endobronchial Valve for Emphysema Palliation Trial Long Term
(VENT Long Term) Follow-up Protocol**

PROTOCOL NUMBER: 630-0008- A

IDE # G020230

PMA# P070025

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Contract Research Organization TBD

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Endobronchial Valve for Emphysema Palliation Trial Long Term (VENT Long Term) Follow-up Protocol

Protocol Summary

Title:	Endobronchial Valve for Emphysema Palliation Trial Long Term (VENT Long Term) Follow-up
Study Primary Investigator:	Frank C. Scirba, MD Associate Professor of Medicine and Education Division of Pulmonary, Allergy and Critical Care Medicine University of Pittsburgh
Study Design:	A multicenter, observational study evaluating subjects previously enrolled in the Endobronchial Valve for Emphysema Palliation Trial (VENT), a multi-center randomized prospective clinical trial.
Purpose:	The purpose of this study is to collect and report long-term safety and effectiveness data on the Emphasys Zephyr [®] Endobronchial Valve (EBV) in subjects with heterogeneous emphysema at three and four years post enrollment in the VENT study.
Subject Enrollment:	Up to 284 Subjects at up to 29 sites with follow-up at Year 4 and up to 129 of those Subjects with follow-up at Year 3 post VENT randomization.
Subject Population:	Surviving subjects previously enrolled in the VENT study (Protocol #630-0001 – J) and included in the modified Intent-To-Treat population.
Efficacy Outcomes:	FEV ₁ , FVC, 6MWT, SGRQ, mMRC and BODE
Safety Outcomes:	Adverse Events
Analysis Plan:	All outcomes will be reported with descriptive statistics.

Post Approval Study
Proposal #2

Zephyr[®] Endobronchial Valve
Post-Approval Study
(Zephyr EBV PAS)
Protocol

Zephyr[®] Endobronchial Valve Post-Approval Study (Zephyr EBV PAS) Protocol

Zephyr EBV PAS Protocol Summary

PMA #	P070025
Study Name and Number:	Zephyr Endobronchial Valve Post-Approval Study (Zephyr EBV PAS), Protocol # 630-0009- A
Study Objectives:	The objectives of this study are to evaluate the training effectiveness and longer-term safety and effectiveness of the Zephyr EBV when used in a real world cohort of subjects during commercial use by various physicians with a range of experience.
Study Design:	This is a prospective, observational, open-label, multi-center clinical trial designed to evaluate the training effectiveness and longer-term safety and effectiveness of the Zephyr EBV during commercial use in real world settings and in accordance with the labeling in subjects with heterogeneous emphysema.
Subject Population (subject Inclusion/Exclusion criteria):	<p><u>Inclusion</u></p> <ul style="list-style-type: none"> • The subject agrees to participate in this study by signing the Institutional Review Board approved informed consent form. • Subject selection in compliance with the indications for use and restrictions of the approved Instructions for use. <p><u>Exclusion</u></p> <ul style="list-style-type: none"> • The inability to obtain an informed consent. • Any condition deemed exclusionary in the judgment of the treating physician.
Sampling and Recruitment Strategy:	<p><u>Subject Sampling</u> Up to 200 subjects at up to 30 sites (maximum of 30 subjects per site) in the United States.</p> <p><u>Sample Size Justification</u> The variable of interest in the post approval study is the rate of valve expectoration or migration. In the VENT trial the observed rate of expectoration or migration was 7.9%. Emphasys has implemented device and training improvements and the expectation is that the rate will be in the 4-6% range in the hands of clinicians who are participating in the post approval trial. The sample size is based on statistical estimation, i.e., the half-width of a confidence interval is a function of the sample size. The confidence interval is computed by Clopper-Pearson methods and produce asymmetric confidence</p>

Zephyr EBV PAS Protocol Summary

	<p>bands. Since the interest is only on the upper limit, the sample size is based on restricting the upper one-sided confidence limit on the observed proportion. Of the expected range (4-6%), the largest variability will be for 6%. The target is to provide a sample size such that the upper one-sided 95% confidence limit is less than 10%, i.e., the observed rate, 6%, + 4%. A sample size of 200 patients treated with the Zephyr valve in the post approval study provides a 95% one-sided exact upper confidence limit of 9.54%. If the observed rate is 5% or 4%, the upper one-sided 95% confidence limits are 8.33% or 7.10%, respectively. Thus by choosing the largest of the estimated rates, we ensure that the upper one sided 95% confidence limit is less than the observed rate +4%.</p> <p><u>Subject Recruitment</u> All subjects evaluated for treatment with the Zephyr EBV at participating sites should be invited to participate in the study.</p>
<p>Definitions of Study Outcomes:</p>	<p><u>Training Effectiveness Outcomes</u></p> <ul style="list-style-type: none"> • Zephyr EBV migration and expectoration rates at 1,2 and 3 years post procedure in the Zephyr EBV PAS <p><u>Effectiveness Outcomes</u></p> <ul style="list-style-type: none"> • Post-bronchodilator spirometry at 1, 2 and 3 years post procedure in the Zephyr EBV PAS <p><u>Safety Outcomes</u></p> <ul style="list-style-type: none"> • Serious adverse event rates at 1, 2 and 3 years post procedure in the Zephyr EBV PAS
<p>Data Collection Techniques and Quality Assurance and Control:</p>	<ul style="list-style-type: none"> • Study-specific electronic Case Report Forms • Sponsor personnel or their designees will perform study site monitoring according to applicable U.S. FDA regulations, Good Clinical Practice, and Emphasys Medical, Inc.’s internal monitoring SOPs • Sponsor site audits, as necessary • Any evident pattern of non-compliance with respect to the protocol and/or any regulatory standards may result in the site being put on probation and required to halt further enrollment, if corrective actions are not subsequently undertaken to resolve the complaint issues, the site may be withdrawn from the study

Zephyr EBV PAS Protocol Summary

Study Events and Subject Follow-up Schedule:	Study Events and Subject Follow-up Schedule*	
	Follow-up	Protocol (+/-) Window
	Screening Office Visit	n/a
	Enrollment	n/a
	Zephyr EBV Procedure	n/a
	Post Procedure 24-Hour Evaluation**	± 8 hours
	30 Day Office Visit	± 14 days
	180 Day Office Visit	± 90 days
	1 Year Office Visit	± 90 days
	1.5 Year Phone Contact	± 90 days
	2 Year Office Visit	± 90 days
	2.5 Year Phone Contact	± 90 days
	3 Year Office Visit	± 90 days
	<p>* Follow-up Evaluations/Office Visits/Phone Contacts based from date/time of Zephyr EBV Procedure.</p> <p>** All subjects will remain in hospital for at least one day post-procedure. If subject shows signs of atelectasis, it is recommended subject remains in hospital for a minimum of two days post-procedure.</p>	
Plan to Minimize Lost to Follow-up:	<ul style="list-style-type: none"> • Subject stipends • Subject travel reimbursements • Subject newsletters and informational pamphlets • Site incentives, as allowable per all applicable regulatory bodies and regulations • Regular interaction between Sponsor and Sites regarding study progress and potential enrollment/retention challenges 	
Analysis Plan:	<p>Analysis population for effectiveness outcomes is subjects that undergo the Zephyr EBV procedure and have minimum of one valve remaining implanted at the completion of the index procedure.</p> <p><u>Training Effectiveness</u> Descriptive statistics for all valve migrations and/or expectorations will be reported for all subjects meeting the analysis population definition.</p> <p><u>Effectiveness</u> Descriptive statistics for post-bronchodilator spirometry values will be reported for all subjects meeting the analysis population definition.</p> <p><u>Safety</u> Descriptive statistics for all serious adverse events will be reported for all subjects meeting the analysis population definition.</p>	

Zephyr EBV PAS Protocol Summary

	<p>Training effectiveness and longer-term safety and effectiveness data collection and reporting will occur annually up to 3 years post Zephyr EBV PAS enrollment.</p>																
<p>Reporting Requirements:</p>	<p>EMI will submit interim post-approval study status reports every 6 months for the first 2 years of the study and annually thereafter until the final report has been submitted according to “Guidance for Industry and FDA Staff: Procedures for Handling Post-Approval Studies Imposed by PMA Order”. All reports will be sent to:</p> <p>PMA Document Mail Center (HFZ-401) Center for Devices and Radiological Health Food and Drug Administration 9200 Corporate Boulevard Rockville, Maryland 20850</p> <p>The first interim report will be submitted 6 months after the date of the study approval letter from the FDA.</p>																
<p>Study Timeline:</p>	<p>Timeline of Study Events and Anticipated Dates</p> <table border="1" data-bbox="456 989 1273 1339"> <thead> <tr> <th data-bbox="462 995 997 1026">EVENT</th> <th data-bbox="997 995 1266 1026">DATE</th> </tr> </thead> <tbody> <tr> <td data-bbox="462 1026 997 1066">Study Initiation</td> <td data-bbox="997 1026 1266 1066">June 2009</td> </tr> <tr> <td colspan="2" data-bbox="462 1066 1266 1127">No. of IRB Approved Sites per Month: 2</td> </tr> <tr> <td data-bbox="462 1127 997 1167">Subject Enrollment Beginning</td> <td data-bbox="997 1127 1266 1167">August 2009</td> </tr> <tr> <td colspan="2" data-bbox="462 1167 1266 1228">No. of Subjects Enrolled per Month: 15</td> </tr> <tr> <td data-bbox="462 1228 997 1268">Study Enrollment Completion</td> <td data-bbox="997 1228 1266 1268">October 2010</td> </tr> <tr> <td data-bbox="462 1268 997 1308">Year 3 Visit Completion</td> <td data-bbox="997 1268 1266 1308">January 2014</td> </tr> <tr> <td data-bbox="462 1308 997 1339">Final Study Report</td> <td data-bbox="997 1308 1266 1339">April 2014</td> </tr> </tbody> </table>	EVENT	DATE	Study Initiation	June 2009	No. of IRB Approved Sites per Month: 2		Subject Enrollment Beginning	August 2009	No. of Subjects Enrolled per Month: 15		Study Enrollment Completion	October 2010	Year 3 Visit Completion	January 2014	Final Study Report	April 2014
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