Study Reference Number E7080

Statistical Analysis Plan for Protocol E7080: Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma

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Statistical Analysis Plan

Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma
PAS2

Study Reference Number E7080 (BSC), 10-02 (Asthmatx)

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PROTOCOL SUMMARY

Objective(s)	The objective of this study is to evaluate durability of treatment effect and to continue to evaluate the short-term and longer-term safety profile of the Alair System in the United States and Canada in the intended use population (patients 18 years and older with severe persistent asthma) following FDA approval.
Test Device	Alair System for Bronchial Thermoplasty
Control Device	None
Study Design	This will be an open-label, single arm study designed to demonstrate durability of the treatment effect and to evaluate the short-term and longer-term safety profile of the Alair System in the United States and Canada in the intended use population (patients 18 years and older with severe persistent asthma).
Planned Subjects/ Centers/ Countries	Up to 300 subjects (minimum of 250 subjects) will be enrolled to achieve at least 200 evaluable study subjects, accounting for a 20% drop-out rate over 5 years. The study will be conducted at a minimum of 15, and a maximum of 30, centers in the United States and Canada, limiting the number of subjects enrolled in Canada to no greater than 20%.
Primary Endpoints	The primary endpoint will be the proportion of subjects experiencing severe exacerbations during the subsequent 12 month (for Years 2, 3, 4, and 5) compared to the first 12 month after the Alair treatment.
Patient Success Criteria	The primary statistical objective is to demonstrate that the proportion of subjects who experience severe exacerbations in the subsequent 12-month follow-up (for Year 2, Year 3, Year 4 and Year 5 [in 12-month periods]) is not statistically worse when compared with the proportion of the first 12-months, which begins 6-weeks after the last Alair treatment. This objective will be met if the upper 95% confidence limit of the difference in proportions (i.e., the subsequent 12-month proportion minus the first 12-month proportion) is less than 20%.
Secondary Endpoints	The secondary endpoints will include the following additional safety endpoints which will be evaluated annually through Year 5 following treatment with the Alair System: • Rates of Severe exacerbations (exacerbations / subject / year) • Respiratory adverse events* (rates of respiratory adverse events, and proportion of subjects with respiratory adverse events)

	• Emergency room visits for respiratory symptoms (rates of emergency room visits and proportion of subjects with emergency room visits for respiratory symptoms) • Hospitalizations for respiratory symptoms (hospitalizations/ subject/ year and the proportion of subjects with hospitalizations for respiratory symptoms) • Respiratory Serious Adverse Events (detailed narratives will be provided for each event) • Pre- and post-bronchodilator FEV_1 * A respiratory adverse event is defined as any sign, symptom, illness, clinically significant abnormal laboratory value, or other adverse medical event associated with the "Respiratory System" that appears or worsens in a subject during a clinical study, regardless of whether or not it is considered related to the procedure used as part of the protocol.
Follow-up Schedule	A follow-up evaluation will be conducted at 6 weeks after the last treatment session. At this time, the 5 year follow-up phase will begin. Subjects will be contacted via phone every 3 months to solicit for adverse events and asthma status. An in-office follow-up evaluation will be performed annually starting after the 6 week evaluation.
Study Duration	Subjects treated with the Alair System will be followed for 5 years after the final procedure.

1 INTRODUCTION

This statistical plan addresses the planned analyses for the PAS2 Trial based on the protocol # 90889079. Specified analyses may be used for scientific presentations and/or manuscripts and may not all be provided to Regulatory Authorities.

2 ENDPOINT ANALYSIS

2.1 Primary Endpoint

The primary endpoint will be the proportion of subjects experiencing severe exacerbations during the subsequent 12-month period (for Years 2, 3, 4, and 5) compared to the first 12-month period after the Alair treatment.

Note: Severe exacerbation is defined as worsening of asthma symptoms requiring use of systemic corticosteroids (tablets, suspension, or injection). For subjects already taking oral corticosteroids on a daily or alternate day basis, a severe exacerbation will be defined as a worsening of asthma symptoms requiring any increase in daily dose of systemic corticosteroids. For consistency, courses of corticosteroids separated by 1 week or more will be treated as separate severe exacerbations.

The primary statistical objective is to demonstrate that the proportion of subjects who experience severe exacerbations in the subsequent 12-month follow-up (for Year 2, Year 3, Year 4 and Year 5 [in 12-month periods]) is not statistically worse when compared with the proportion of the first 12-months, which begins 6 weeks after the last Alair treatment. This objective will be met if the upper 95% confidence limit of the difference in proportions (i.e., the subsequent 12-month proportion minus the first 12-month proportion) is less than 20%.

2.1.1 Hypotheses

The null and alternative hypotheses for the primary endpoint are as follows:

$$H_o : p_k - p_1 \geq 20\%$$

$$H_a : p_k - p_1 < 20\%$$

where p_1 is the proportion of patients with severe exacerbations at 1 year,
p_k is the proportion of patients with severe exacerbations at k years and
$k = 2, 3, 4,$ or 5.

2.1.2 Sample Size

Under the assumption that in the population of US subjects treated with the Alair System the proportion of patients that experience severe exacerbations will be 0.33 (33% of subjects) or less (based on data from AIR2 Trial - 30.9%, 95% CI 24.2%, 37.7%), a sample size of 200 is adequate to demonstrate durability of the treatment effect at 5 years post-Alair treatment. Up to 300 subjects (minimum of 250 subjects) will be enrolled to achieve at least 200 evaluable study subjects, accounting for a 20% drop-out rate over 5 years. To be counted as an evaluable subject, a subject must have either completed the 5-year visit no earlier than the start of the visit

window (1797 days) or have at least 1797 days of study follow-up (see Section 2.1.3) and have primary endpoint data at 5 years.

nQuery Advisor Version 7.0 was used to form a basis for the sample size estimation. The "Two group test of equivalence in proportions (large unequal n's)" procedure based on a one-sided test at alpha equal to 0.05 and a 20% delta was used to generate the powers presented in Table 1. A minimum of 80% power was achieved for all situations wherein the subsequent year's assumed proportion of subjects with severe exacerbations was 41% or less. The use of independent samples methodology provides a conservative (over-powered) sample size calculation for matched data on a single sample.

Table 1. Two group test of equivalence in proportions (large unequal n's) [from nQuery Advisor 7.0]

	1	2	3	4	5	6	7	8	9
Test significance level, α (one-sided)	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050
Standard proportion, π_S	0.330	0.330	0.330	0.330	0.330	0.330	0.330	0.330	0.330
Equivalence limit difference, $\pi_T - \pi_S$, Δ_0	0.200	0.200	0.200	0.200	0.200	0.200	0.200	0.200	0.200
Test expected proportion, π_T	0.330	0.340	0.350	0.360	0.370	0.380	0.390	0.400	0.410
Expected difference, $\pi_T - \pi_S$, Δ_1	0.000	0.010	0.020	0.030	0.040	0.050	0.060	0.070	0.080
Power (%)	99	99	99	98	97	95	92	88	83
n_s	250	250	250	250	250	250	250	250	250
n_T	200	200	200	200	200	200	200	200	200
Ratio: n_T / n_s	0.800	0.800	0.800	0.800	0.800	0.800	0.800	0.800	0.800
$N = n_s + n_T$	450	450	450	450	450	450	450	450	450

2.1.3 Statistical Methods

See Section 6.4 for how to identify severe exacerbations.

The proportions of patients with severe exacerbations at each year (p_k, k=1 to 5) will be calculated in two ways:

1. Complete Follow-up: using patients who complete the annual follow-up visit or have a follow-up visit (office or phone call) after the visit for that particular year if the annual visit is missed.
2. Complete/Partial Follow-up: using patients who complete the annual follow-up visit no earlier than the start of the follow-up window, have a follow-up visit (office or phone call) after the visit for that particular year if the annual visit is missed, have sufficient follow-up for the year, or had a severe exacerbation during the time period regardless of the amount of follow-up. Sufficient follow-up is having any follow-up visit (office or phone call), adverse event onset date, or hospitalization date that gives the patient at least the number of days of follow-up after the last BT procedure + 42 days given in Table 2.

Table 2. Days for sufficient follow-up by follow-up time

Time	Days for sufficient follow-up after the follow-up period starts*
1 Year	337 days
2 Years	702 days
3 Years	1067 days
4 Years	1432 days
5 Years	1797 days

* - the follow-up period starts at last BT procedure + 42 days. The number of days in this column represents the start of the follow-up window after the follow-up period starts and is calculated as # years times 365 days minus 28 days.

All analyses will be done for patients with Complete and Complete/Partial Follow-up. Point estimates and 95% confidence intervals for the proportion of subjects experiencing severe exacerbations during each of the 12-month evaluation periods will be provided. Additionally, the exact upper 95% confidence limit for the difference between the subsequent 12-month proportions and the first 12-month proportion will be calculated, based on methods assuming paired samples; in this analysis, each subsequent 12-month proportion would represent comparisons between the first-year proportion and the second-, third-, fourth-, and fifth-year proportions.

An exact upper 95% confidence limit of the difference between the subsequent 12-month proportions (for Years 2, 3, 4, and 5) compared to the first 12-month proportion for patients with data at both year 1 and year k that is less than 20% will reject the null hypothesis in favor of the alternative hypothesis and demonstrate that the proportions are not substantially worse during each of the subsequent evaluation periods.

Final conclusions regarding the durability of effectiveness (beyond 1 year) will be based on completing the 5 year follow-up of all subjects who are still in the study at that time.

A sensitivity analysis (tipping-point analysis) will be performed to assess the impact of patients with inadequate follow-up on the evaluations of the primary endpoint. The tipping-point analysis will be on the primary endpoint using matched pairs and will be performed as follows: assuming no loss to follow-up and given the observed number of patients evaluated at 1 year and k years, for all combinations of success/failure for patients with missing data, the primary endpoint will be evaluated until the point at which the conclusion of the study changes.

2.2 Secondary Endpoints

The secondary endpoints will include the following additional safety endpoints which will be evaluated annually through Year 5 following treatment with the Alair System:

- Rates of Severe exacerbations (exacerbations / subject / year)
- Respiratory adverse events* (rates of respiratory adverse events, and proportion of subjects with respiratory adverse events)

- Emergency room visits for respiratory symptoms (rates of emergency room visits and proportion of subjects with emergency room visits for respiratory symptoms)
- Hospitalizations for respiratory symptoms (hospitalizations/ subject/ year and the proportion of subjects with hospitalizations for respiratory symptoms)
- Respiratory Serious Adverse Events (detailed narratives will be provided for each event)
- Pre- and post-bronchodilator FEV_1

* A respiratory adverse event is defined as any sign, symptom, illness, clinically significant abnormal laboratory value, or other adverse medical event associated with the "Respiratory System" that appears or worsens in a subject during a clinical study, regardless of whether or not it is considered related to the procedure used as part of the protocol.

2.2.1 Hypotheses

There is no formal hypothesis for the secondary endpoints.

2.2.2 Statistical Methods

Descriptive statistics will be used to summarize the secondary endpoints. For continuous variables, summaries will include the sample size (N), mean, standard deviation, minimum, and maximum. Proportions will be presented with 95% confidence intervals.

3 GENERAL STATISTICAL METHODS

3.1 Analysis Sets

The Intent-to-Treat (ITT) analysis set will consist of all subjects who have been administered at least one BT procedure. The modified Intent-to-Treat (mITT) analysis set will consist of all subjects who have been administered three BT procedures and have primary endpoint data at year 1 and year 2, 3, 4, or 5, as applicable. Analyses based on the ITT analysis set will be considered primary. Analyses based on the mITT analysis set will be considered supportive.

3.2 Control of Systematic Error/Bias

All subjects who have met the inclusion/exclusion criteria and have signed the ICF will be eligible for enrollment in the study. Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

3.3 Number of Subjects per Investigative Site

There is no minimum or maximum number of subjects to be enrolled at each center, however, centers in Canada will be limited to 20% of overall enrollment.

4 ADDITIONAL DATA ANALYSES

4.1 Interim Analyses

No formal interim analyses are planned for the PAS2 Study for the purpose of stopping the study early for declaring effectiveness or for futility.

4.2 Subgroup Analyses

Inferential analysis of the subset of subjects enrolled at sites in the United States or in Canada may lack the statistical power to demonstrate that the proportions are not substantially worse during each of the subsequent evaluation periods. Descriptive statistics for the point estimates introduced above will be presented for each subset, however, the primary endpoint analysis of the upper 95% confidence limit of the difference between the subsequent 12-month proportions (for Years 2, 3, 4, and 5) compared to the first 12-month proportion will not be required for the subsets.

Descriptive statistics for the subset of subjects enrolled at sites in the United States or in Canada alone will be provided for each of the secondary endpoints, although no conclusions can be drawn from either subset because of the smaller sample sizes.

Subgroup summaries may be performed for subgroups of interest (e.g. sex, age, etc.).

4.3 Justification of Pooling

The clinical study will be conducted under a common protocol for each investigational site with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each investigational site.

Pooling analyses will be performed to assess the homogeneity of various characteristics and outcomes (e.g. primary endpoint, baseline characteristics, etc.) across investigational sites. If needed, virtual sites will be formed by combining low enrolling investigational sites within geographical region (United States and Canada); low enrolling sites are defined as having <5 subjects. The combining of investigational sites within region will be accomplished by taking the investigational site with the smallest enrollment and combining it with the investigational site with the largest enrollment (of those not enrolling at least 5 subjects).

Consistency will be investigated across country and investigational sites (after combining low enrolling sites), using statistical tests appropriate to the variable and an alpha level of 0.15.

4.4 Multivariable Analyses

Multivariate analyses will be conducted to explore the impact of baseline characteristics on treatment effect, for both the treatment period and the post-treatment period, including changes from year 1 to year 2 through year 5.

4.5 Other Analyses

Demographic data including, but not limited to, age, race, gender and ethnicity, and baseline characteristics including, but not limited to, AQLQ (asthma quality of life questionnaire), maintenance asthma medication doses (see dose conversions in Section 6.5), pre- and post-bronchodilator forced expiratory volume in one second (FEV_1), prior 12 month history of severe exacerbations (use of systemic corticosteroids (tablets, suspension, or injection) for asthma

symptoms), and emergency room visits and hospitalizations for respiratory symptoms, will be reported for each subject. Procedural characteristics will also be summarized.

Demographic, baseline clinical information, and procedural characteristics will also be provided separately for the subsets of patients enrolled at sites in the United States and sites in Canada.

4.6 Safety Analyses

Adverse events will be reported for the short-term (treatment period) and for the long-term (post-treatment period). The treatment period will be defined as the day of 1st procedure bronchoscopy till 6 weeks (41 days) after the last procedure bronchoscopy. The post-treatment period will begin at the end of the treatment period (i.e. beginning at 6 weeks [42 days] after the last procedure bronchoscopy) for patients who have at least one post-treatment visit (i.e. 6-week visit or later). Patients who do not have a post-treatment visit will not be counted in post-treatment summaries. Annual summaries will be based on a 365-day period beginning at 6 weeks (42 days) after the last procedure bronchoscopy.

Verbatim terms will be classified to preferred terms and system organ classes using the MedDRA dictionary. The preferred terms and system organ classes will then be tabulated by the treatment period and each year of follow-up. All reported adverse events will be summarized by the number of subjects reporting adverse events, system organ class (SOC), preferred term, severity, seriousness, duration, and relationship to procedure. In the summary of MedDRA coded terms, for the preferred terms listed in Table 3, the system organ class will be changed to "Respiratory, thoracic and mediastinal disorders". The reason for the change in SOC is to conservatively report respiratory-related adverse events since the preferred terms in Table 3 represent events that could be related to respiratory function.

Table 3. Preferred Term that will have the system organ class (SOC) changed to "Respiratory, thoracic and mediastinal disorders" for summary tables

System Organ Class Code	System Organ Class	Preferred Term Code	Preferred Term
10005329	Blood and lymphatic system disorders	10020094	Hilar lymphadenopathy
10007541	Cardiac disorders	10007617	Cardio-respiratory arrest
10018065	General disorders and administration site conditions	10008469	Chest discomfort
		10008479	Chest pain
		10062501	Non-cardiac chest pain
10021881	Infections and infestations	10001076	Acute sinusitis
		10006451	Bronchitis
		10053160	Bronchitis viral
		10009137	Chronic sinusitis
		10022000	Influenza
		10023874	Laryngitis
		10067321	Laryngitis fungal
		10024968	Lower respiratory tract infection
		10025028	Lung abscess
		10028810	Nasopharyngitis

System Organ Class Code	System Organ Class	Preferred Term Code	Preferred Term
		10034835	Pharyngitis
		10034839	Pharyngitis streptococcal
		10035664	Pneumonia
		10035728	Pneumonia pneumococcal
		10035730	Pneumonia primary atypical
		10062352	Respiratory tract infection
		10060693	Respiratory tract infection bacterial
		10039083	Rhinitis
		10040753	Sinusitis
		10060841	Sinusitis bacterial
		10044008	Tonsillitis
		10046306	Upper respiratory tract infection
		10047473	Viral pharyngitis
		10051513	Viral sinusitis
		10047482	Viral upper respiratory tract infection
10022117	Injury, poisoning and procedural complications	10009913	Collapse of lung
		10069363	Traumatic lung injury
10028395	Musculoskeletal and connective tissue disorders	10050819	Musculoskeletal chest pain
10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10062042	Lung neoplasm
10029205	Nervous system disorders	10034018	Parosmia
		10040744	Sinus headache

In addition to the complete tabulation of adverse events for all subjects enrolled in the study, adverse events will also be tabulated separately for the subsets of subjects enrolled in sites in the United States and the sites in Canada.

4.7 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended statistical analysis plan approved before performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

5 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation.

6 PROGRAMMING CONSIDERATIONS

6.1 Statistical Software

Statistical data review will be performed by the sponsor. Statistical analyses will be performed using SAS System software, version 9.2 or later (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

6.2 Format of Output

Results of analysis will be output programmatically to Word documents from SAS with no manual intervention. All output for the final statistical report will be in the form of a Word document containing tables, figures, graphs, and listings, as appropriate.

6.3 Methods for Handling Missing Data

All patients who are enrolled will be eligible for evaluation, regardless of the treatment that ensues. The effect of missing data for the primary endpoint will be evaluated with a sensitivity (tipping-point) analysis (Section 2.1.3). Statistical models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes). Outlier values will be evaluated for their validity; all data will be included unless judged to be invalid.

When calculating rates of adverse events, missing and partial dates will be handled as shown below:

Partial Date Description	Action Taken
Entire onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1 will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

6.4 Identification of Severe Exacerbations (SE)

1. Filter the medication data (MEDS) to keep all courses of oral corticosteroids (CLASS3=OCS) and other medications that are intravenous uses of the same medications - identify those by looking for CLASS3='Other Specify' and lowcase(CLSSP) with values: 'intravenous corticosteriod' 'intravenous corticosteroid' 'cortcosteroid iv' 'corticosteroid iv'. Note there are spelling mistakes in the entered data.
2. Merge the medication data with the AE data by patient and AE related number (RELAENO) on the medication data with AENUM on the AE data.
3. Use the onset date and the resolution date of the AE to determine the length of the SE. If an AE has no resolution date, impute the date of the most recent follow-up (scheduled or

unscheduled) as the resolution date. For partial onset and resolution dates, impute dates as described in Section 6.3.

4. When an AE matches with a course of medication, the AE is considered to be an SE, however, when AEs that are SEs occur too close together, the combined AEs are one SE. If the resolution date of one AE selected as an SE is <=6 days before the onset date of another AE that is an SE, then combine the AEs into one SE. There could be more than two AE combined into a single SE.
5. SEs are classified in the time period where the onset date of the SE occurs regardless of the duration of the SE.
6. For each time period, count the number of SEs for each patient and whether the patient has an SE or not. Two types of summaries will be done for the SEs (also ER visits and hospitalization) to include the following patients: (1) patients with the follow-up visit or later visit for that time period, and (2) patients from (1) and patients with any SE in the time period.

6.5 Medication Dose Conversions

Table 4. Beclomethasone Equivalents

Drug	Conversion Factor
Budesonide	1.25
Fluticasone	2
QVAR	2.5
Mometasone	2.5
Triamcinolone	0.5
Flunisolide	0.5
Ciclesonide	2.5

Table 5. Salmeterol Equivalents

Drug	Conversion Factor
Formoterol	100/24
Formoterol Fumarate	100/24

7 REVISION HISTORY

Document Revision Number	Template Number and Version	Section	Change	Reason for Change
AA	NA	All	First version	
AB	90702621, AC	All	• Reorganized SAP to match the standard template (90702621) • Replaced sections 2-4 from version AA with a protocol summary • Changed the primary statistical analysis for the primary endpoint to be paired instead of a two-group test • Update the algorithm for identifying severe exacerbations to be more specific • Add Table 3 to describe the reassignment of SOCs	The original SAP was written by a CRO (QST) before BSC took over statistical support for this study; the SAP was re-written to conform to the current SAP template and to update statistical methods for the primary endpoint.