Galil Medical

Evaluating Cryoablation of Metastatic Lunch/Pleura Tumors in Patients – Safety and Efficacy (ECLIPSE)

Statistical Analysis Plan (SAP)

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Protocol Summary

Objective

The objective of this study is to assess the feasibility of cryoablation in local tumor control for tumors ≤3.5 cm in patients with pulmonary metastatic disease.

Study Design

This is a prospective single-arm feasibility study designed to determine the safety of Galil Medical's Cryoablation System and needles in cryoablation of lung tumors, as well as give an insight into the efficacy of the treatment. All comparisons will be qualitative in nature. Descriptive results of this feasibility study may be used to generate hypotheses for a pivotal study.

This study is to enroll at least 30, but up to 40, patients who will undergo cryoablation of at least 1 metastatic pulmonary tumor via a Galil Medical cryoablation system using Galil Medical cryoablation needles.

Patients will be screened within 6 weeks of the cryoablation procedure. After the cryoablation procedure visit date, follow-up visits will consist of within 1 Week of the cryoablation procedure and then 1, 3, 6, 12, 24, 36, 48 and 60 months post cryoablation procedure.

Sample Size Justification

Because estimates from this study will be used to power the pivotal study, this study must be able to provide such estimates. A sample size of at least 30 patients, but up to 40 patients, is considered clinically sufficient to give indications of both safety and potential efficacy. This data will be used to decide whether to proceed to a pivotal study, determine endpoints for such a study, and design the study to answer the proposed hypotheses. Up to approximately 10 additional patients may be enrolled to account for patients who do not meet inclusion/exclusion criteria. This study is not powered for formal statistical analysis.

General Analysis Methods

Data will be analyzed using descriptive statistics. Continuous variables (e.g., age) will be summarized by the number of patients, mean, standard deviation, median, interquartile range, minimum and maximum. Categorical variables (e.g., race) will be summarized by frequencies and percentages of patients in each category.

Analysis Populations

All analyses will be performed on the Intent-to-Treat (ITT) population consisting of all subjects treated with a Galil Medical Cryoablation System and needles as the attempted treatment. A per-protocol (PP) analysis may also be done, removing subjects who did not have a complete treatment and those that did not meet the study criteria but were enrolled.

Efficacy Endpoint Analysis

Efficacy Endpoint

The efficacy endpoint for this study is local tumor control in patients with pulmonary metastatic disease at 3, 6, 12, 24, 36, 48 and 60 months post cryoablation.

Analysis Methods

Patients may have up to five tumors so tumor control will be calculated on a per tumor level as well as a patient level. To be considered a success on a patient level all tumors treated during the baseline procedure must meet the tumor control criteria at that follow-up visit.

Post-treatment imaging including CT/MRI will be reported for baseline and follow-up visits. Tumor control for each time point will be determined by examining the change from baseline, and will be defined as:

Complete Response – Tumor disappearance or a $\geq 75\%$ decrease in the greatest trans-axial diameter (<25% of original size).

Partial Response – A <75% but $\geq 30\%$ decrease in the greatest trans-axial diameter.

Stable Disease – No change, allowing for a <30% decrease up to a <20% increase in the greatest trans-axial diameter.

Local Failure – A $\geq 20\%$ increase in the greatest trans-axial diameter.

Local Control – Local control will be defined as the absence of local failure. Tumors in complete response, partial response and stable disease will all be in local control.

Distant Failure – Distant failure (e.g. metastatic disease) will be defined as the appearance of distant cancer deposits consistent with metastatic spread of cancer outside the intended treatment area.

The local tumor control counts and rates will be presented along with the 95% two-sided confidence intervals for the rates. The rate at the each visit will be defined as the proportion of tumors/patients experiencing tumor control at a specific time point out of the number of patients who complete a follow-up visit at that time point.

Efficacy analyses will be performed on the ITT population. Analysis of the PP population may be done in support of the ITT analysis. No formal statistical hypothesis testing will be performed for efficacy endpoints.

Safety Endpoint Analysis

Safety Endpoint

The safety endpoint for this study is to assess the incidence and severity of cryoablation related adverse events.

Analysis Methods

Point estimates and two-sided Exact 95% confidence intervals will be generated for events related to the cryoablation procedure in the following categories:

- intra-operative events
- post-operative adverse events
- serious adverse events
- unanticipated adverse device effects

The safety analysis will be performed on the ITT population. No formal statistical hypothesis testing will be performed for safety endpoints.

Supportive Endpoint Analyses

Technically successful treatment

A technically successful treatment will be defined by an ablation volume encompassing the tumor with at least a 5 mm margin. Technical success will be calculated on a per tumor level as well as a patient level. To be considered a technical success on a patient level all tumors treated during the baseline procedure must meet the technical success criteria.

Disease recurrence or progression

Disease specific survival, overall survival, and time to disease recurrence or progression will be analyzed by Kaplan-Meier methodology. These measures are defined as:

Disease-specific survival will be analyzed as the time in days from cryoablation procedure to death due to lung cancer. Patients who are alive will be censored at the date of their last visit. Patients who have died from causes other than lung cancer will be censored at the time of death.

Overall survival will be analyzed as the time in days from cryoablation procedure to death. Patients who are alive will be censored at the date of the last visit.

Freedom from disease recurrence or progression will be analyzed as the time in days from cryoablation procedure to disease recurrence or progression, determined locally by evidence of an increase in tumor size and/or contrast enhancement. Patients without disease recurrence or progression will be censored at the date of their last visit or their date of death (due to any cause).

Intra-procedural data

Initial cryoablation procedure information will be summarized by descriptive statistics. These include but may not be limited to:

- Type of procedure
- Tumor size and number
- Cryoablation needle type
- Number of each type of needle used
- Freeze and thaw times
- Ice formation
- How ice formation encompasses the tumor
- Who performed the procedure
- Cryoablation system used
- Cryoablation completion
- Antibiotic administration
- Type of anesthesia used
- Procedure duration
- Location, reason, and duration of chest tube placement

Physical performance and quality of life

Physical performance and quality of life assessments will be made by examining the change in the baseline scores to those reported post-operatively. Physical function assessments will be measured using Eastern Cooperative Oncology Group (ECOG) and Karnofsky Performance Scale

(KPS), and will be measured at screening, Week 1 and Months 3, 6, 12, 24, 36, 48 and 60. Quality of life will be measured by the Short Form (SF)-12 generic measure at screening, Months 1, 3, 6, 12, 24, 36, 48 and 60. The ECOG scale, KPS scale and each of the eight SF-12 domains will be summarized at each time point by descriptive statistics. Percent change from baseline for each measure will also be summarized by descriptive statistics.

Additional Data Summaries

Demographics, disease status, imaging data, lung function, and protocol deviations will be assessed by mean, standard deviation, median, interquartile range, minimum and maximum for continuous measures, and frequencies and percentages of patients in each category for categorical measures. These measures include but may not be limited to:

Demographics
- Age
- Gender
- Race and ethnicity
- Height, weight, and BMI
- Comorbidities
- Smoking history
- Concomitant medications

Disease status
- Primary cancer diagnosis
- Stage
- Cell Type
- Number of tumors
- Locations of tumors
- Prior treatment(s) for lung metastases
- New treatments received during study
- Evidence of additional metastatic disease during study
- Baseline laboratory data

Imaging and lung function
- Number of tumors
- Number of new tumors (at follow-up)
- Number of tumors treated with cryoablation (at baseline)
- Number of tumors not treated with cryoablation (at baseline)
- Tumor response (per tumor)
- Tumor distribution
- Location (per tumor)
- Greatest trans-axial diameter (per tumor)
- FVC (observed)
- FEV_1 (observed, predicted and % predicted)
- DLCO/VA

All protocol deviations

Subject Disposition

Subject disposition will be presented as:

- Number of subjects enrolled
- Number of subjects completing each follow-up visit
- Number of subjects withdrawn or lost to follow-up
- Number of subject deaths
- Number of subjects evaluable for ITT and PP analyses

Randomization and Blinding

As this is a single arm study, no randomization or blinding will be performed. To minimize selection bias within the enrolled patient population, participation in the study is to be offered to all eligible patients on a consecutive basis as they present to the physician at the site.

Handling of Missing Data

Missing data will be prospectively minimized through training of the participating investigator and site staff, and through appropriate clinical trial management. Every effort will be made to collect all data points in the study. All patient data that is available on patients who drop out during the course of the study will be included where possible.

Subset Analyses

No subset analyses were pre-specified in the protocol.

Poolability Analyses

Though individual treatments may vary (needle used, number of needles used, and freeze/thaw times, etc.), it is expected that data will be poolable across study sites since all sites and investigators will follow a common protocol with identical inclusion/exclusion criteria (same population) and outcome assessment. The primary efficacy endpoint will be evaluated by study site.

Statistical Software

All statistical analyses will be produced using SAS software Version 9.1 or above (SAS Institute, Cary, NC.).

Version, Revision History, and Approvals

Current Version

Version 2.0 – Approval Date: Aug. 27, 2012

Revision History

Version	Approval Date	Key Changes
1.0	Sept. 27, 2011	Initial Release
2.0	Aug. 27, 2012	Revised Pooling section to reflect treatment variation between sites/subjects. Added the word "treated" to the Analysis Populations section. Changed "Alquest" to "NAMSA" on signature page to reflect company name change.

Approvals

Name	Study Role	Signature	Date
███████	Galil – Director, Clinical Research		
█████████	Galil – Director, Regulatory Affairs		
██████	NAMSA – Biostatistican		