Galil Medical

CUC13-LNG079-02: Multi-center Study of Metastatic Lung Tumors Targeted by Interventional Cryoablation Evaluation (SOLSTICE)

Statistical Analysis Plan (SAP)

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Protocol Summary

Objective

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

Study Design

This is a Phase II multicenter, prospective, single arm. Target inclusion for this study is 226 lesions. It is estimated this study will enroll 150 patients in order to achieve the target lesion goal. Patients enrolled 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 8 weeks of the cryoablation procedure. After the cryoablation procedure visit date, protocol directed follow-up visits will consist of within 1 Week of the cryoablation procedure and then 1, 3, 6, 12, 18, and 24 months post cryoablation procedure.

Sample Size Justification

This is a prospective, single-arm study designed to determine the safety and efficacy of Galil Medical's Cryoablation System and needles in cryoablation of metastatic lung tumors.

The primary efficacy endpoint for the trial is 12-month local control. The papers shown below were used as reference for clinicians who determined a clinically relevant efficacy endpoint performance goal was 84% success at 12-months. This observed cryoablation group's local control rate will be tested against this performance goal.

Paper	Lesions	12-month Local Control Success	Lower 97.5% 1-sided Wilson CI
Okuneiff (2006)	125	91%	0.8469
Rusthoven (2009)	63	100%	0.9425
Baschnagel (2013)	47	97%	0.8757
Ricardi (2012)	77	94%	0.8632
Norihisa (2008)	43	94.50%	0.8337
Yoon (2006)	101	90%	0.8261

This test is accomplished by testing against the following hypotheses:

H_0: $C_{DEVICE} \leq 84.0\%$

H_a: $C_{DEVICE} > 84.0\%$

where C_{DEVICE} is the observed cryoablation local control rate at 12-months.

The null hypothesis will be rejected and the primary efficacy endpoint performance goal will be met if the lower bound of the one-sided 97.5% confidence interval for the 12-month tumor local control rate is greater than 84.0%.

PASS 12 was used to calculate the sample size needed. A sample size of 203 lesions achieves 85% power (and guarantees at least 80% power) to detect a difference (P1-P0) of 0.0700 using a one-sided binomial test. The target significance level is 0.0250. The actual significance level achieved by this test is 0.0239. These results assume that the population proportion under the null hypothesis is 0.8400.

Power Analysis of One Proportion
Numeric Results for testing H0: P = P0 versus H1: P > P0
Test Statistic: Exact Test

Power	N	Proportion Given H0 (P0)	Proportion Given H1 (P1)	Target Alpha	Actual Alpha	Beta	Reject H0 If R ≥ This
0.8501	203	0.8400	0.9100	0.0250	0.0239	0.1499	181

To account for up-to a 10% 12-month lesion attrition rate, the final sample size has been increased to 226 lesions.

Note that, for the purposes for sample size calculations, the observations are assumed to be independent. However, the primary analyses will account for within subject correlation, as described below.

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. 95% confidence intervals will be calculated as appropriate.

Analysis Populations

All primary analyses will be performed on all tumors with a Galil Medical Cryoablation System and needles as the intent-to-treat evaluable population. A supplemental per-protocol analysis

will be done for the primary endpoint, removing tumors that 1) did not have a complete treatment; and subjects who 2) did not meet the study criteria but were enrolled; or 3) had a deviation with high likelihood of affecting the study outcome (as determined by a review of all occurring deviations).

The intent-to-treat and per-protocol analyses will be compared for level of agreement. It is expected that the two populations will be similar; however, any substantial differences between the two will be analyzed appropriately to elucidate the cause of these differences. Missing data will be imputed for the primary analysis as outlined in section "Handling of Missing Data" section later in the SAP. Additional sensitivity analyses using alternate missing data imputation will be presented.

Efficacy Endpoint Analysis

Efficacy Endpoint

The primary efficacy endpoint for this study is assessment of cryoablation on local tumor control in patients with pulmonary metastatic disease at 12 months post cryoablation.

Analysis Methods

The primary efficacy endpoint for this study is defined as follows: local tumor control in patients with pulmonary metastatic disease at 12 months post cryoablation. Tumor control will be defined by the criteria defined in Section 9.7 of this protocol.

Patients are allowed up to 6 tumors and the primary efficacy endpoint (tumor control) will be calculated on a per tumor level.

The rate of local tumor control at 12-months will be analyzed using a random effects logistic regression model accounting for within subject correlation to account for multiple tumors per subject. The null hypothesis will be tested comparing the lower bound of the Wald 97.5% one-sided confidence interval for the estimated rate of local tumor control to the performance goal of 84.0%. If the lower bound is greater than 84.0%, the null hypothesis will be rejected and the endpoint will be considered met.

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

The safety endpoint for this study is to assess the incidence and severity of intra-operative events, post-operative adverse events, serious adverse events and unanticipated adverse device effects related to the cryoablation procedure.

No formal hypothesis test is being made on the safety endpoints. Point estimates and two-sided 95% confidence intervals will be generated for cryoablation related adverse events.

Supportive Endpoint Analyses

Tumor control (patient level & weighted average response)

The primary efficacy endpoint is on a lesion basis. Analysis on a patient level will also be conducted in two ways. 1) Patient level: A patient must exhibit tumor control on all lesions to be considered a success using logistic regression analysis to calculate success rate and Wald 95% CI. 2) Weighted average response: patient level response rate weighted by the number of lesions that are evaluated. This will be reported as a proportion (number of successful lesions over the total number of lesions) and a 95% exact CI.

Tumor control (pulmonary metastatic disease)

Efficacy of cryoablation on local tumor control in patients with pulmonary metastatic disease at 18 and 24 months post cryoablation using a random effects logistic regression model to account for the correlation among multiple tumors per subject.

Tumor control (additional cryoablation)

Patients may receive additional cryoablation treatment(s) to the index tumor(s) initially subjected to cryoablation while participating in the study protocol. This additional cryoablation may be performed on the index tumor(s) provided that the additional treatment is performed with Galil Medical technology. In this situation, for each index lesion retreated, follow-up visits will restart per the study protocol and continue through the 24 month visit after the date of the repeat cryoablation treatment. When possible, if multiple tumors are present, all efforts should be made to align all follow up visits. For any index lesion not subjected to retreatment, the data collection continues per protocol. If additional local treatment (e.g. radiofrequency ablation, microwave ablation, surgery, radiation) is required, then the patient must be withdrawn from the study.

Efficacy of cryoablation on local tumor control for each index tumor in patients with pulmonary metastatic disease undergoing additional cryoablation treatment(s) of a previously treated index tumor will be summarized using the proportion of tumor control at 12-months post re-treatment and a 95% CI.

Technically successful treatment

A technically successful treatment will be defined by an ablation volume, ground glass opacity, or frank consolidation encompassing the targeted index tumor(s) within 30 days of the cryoablation procedure. 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. Technical success rates and 95% CIs will be calculated using random effects logistic regression on a tumor level and logistic regression on a patient level.

Disease recurrence or progression

The reference date for disease progression evaluation will be associated with the initial (first) cryoablation procedure done per study protocol. In the event of multiple cryoablation procedure dates, such as with bilateral lesions or staged treatments, the date of reference for disease progression evaluation will be the initial (first of n) cryoablation procedure.

- **Local disease progression** will be determined locally by evidence of local tumor failure. Time to lung disease progression will be summarized by using Kaplan-Meier methodology.
- **Lung-disease-specific survival** rate is defined as the time in days from the first cryoablation procedure to death and **a)** the date of lung tumor progression (new lung tumors or incomplete response), **b)** the date of death without lung tumor progression, or **c)** the date of last follow up in patients who were still alive without lung tumor progression. 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. Lung disease-specific survival rates will be summarized by using Kaplan-Meier methodology.
- **Overall survival** rate is defined as the time in days from the first cryoablation procedure to death. Patients who are alive will be censored at the date of the last visit. Overall survival rates will be summarized by using Kaplan-Meier methodology.
- **Time to metastatic lung disease progression beyond the index tumor** is defined as the time in days from the first cryoablation procedure to metastatic disease beyond the index tumor site. Patients without metastatic lung disease progression will be censored at the date of their last visit or their date of death (due to any cause). Metastatic progression free survival rates will be summarized by using Kaplan-Meier methodology.
- **Time to overall cancer progression** is defined as the time in days from the first cryoablation procedure to cancer progression (i.e., any location of active cancer disease). Patients without cancer progression will be censored at the date of their last visit or their date of death (due to any cause). Overall cancer progression free survival rates will be summarized by using Kaplan-Meier methodology.
- **Time to untreatable metastatic lung disease control with cryoablation** is defined as the time in days from the first cryoablation procedure to the time when the metastatic lung disease cannot be treated with cryoablation. Overall time to untreatable metastatic lung disease progression rates will be summarized by using Kaplan-Meier methodology.
- **Time to untreatable metastatic lung disease control with focal therapy is** defined as the time in days from the first cryoablation procedure to the time when the metastatic lung disease cannot be treated by focal (e.g., ablation, surgery, SBRT) intervention for control of metastatic lung disease. Overall time to untreatable metastatic lung disease progression rates will be summarized by using Kaplan-Meier methodology.

Intra-procedural data

Initial cryoablation procedure information including the type of procedure, tumor size and number, cryoablation needle type and the number of each type of needle used, freeze and thaw times, procedure times, and anesthesia type will be summarized using descriptive statistics.

Physical performance and quality of life

Physical performance (KPS) and quality of life (SF-12) assessments will be made by examining the change in the baseline scores to those reported post-operatively and at follow-up visits. The 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 summarized using descriptive statistics. These measures include but may not be limited to:

Demographics

- Age at the date of consent
- Sex
- Race and ethnicity (Per French regulations, race and ethnicity will not be collected at any study site in France.)
- Height, weight, and BMI
- Comorbidities
- Smoking history
- Concomitant medications

Disease status

- Primary cancer diagnosis
- Prior treatment(s) for lung metastases
- Lung or other metastatic disease
- Baseline laboratory data

Index Tumor(s)

- Histology of primary tumor
- Proof of metastases
- Location of the index tumor(s) in the lung(s)
- Size of the index tumor(s)
- Number of index tumors
- Number of new tumors

Procedure/Discharge

- Number of tumors treated with cryoablation
- Index tumor size measurement:
- 3 axes of measurements (cm) and
- Number and type of cryoablation needles used
- Freeze and thaw times, per cycle
- Number and type of intra-operative complication(s)
- Severity of complication(s)
- Requirement for hospital admittance/stay
- Requirement for surgical intervention(s)

All protocol deviations
Study Completion/Withdrawals

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. Sensitivity analyses will be conducted to determine the effect of missing data on the primary efficacy endpoint.

For the formal primary endpoint hypothesis test, patients with missing 12-month tumor evaluations will be imputed using multiple imputation (SAS PROC MI using FCS logistic regression and including tumor status at prior visits), except in the following case where previous visit evidence can be used to impute 12-month status:

- Subjects with local tumor failure at 6-months will be considered a local tumor failure at 12-months post-index procedure.

Additional sensitivity analyses to be conducted:

- Worst case: all missing data are imputed to be failures
- Best case: all missing data are imputed to be successes
- Complete case: all missing data are treated as missing and not imputed

Subset Analyses

Analysis will be done on outcomes for subgroups including, but not limited to, gender and lesion size. Additional non-protocol defined subgroups include: number of needles used, number of lesions, primary cancer diagnosis, and lesion location.

Poolability Analyses

A poolability analysis among investigational centers and geographies (US/OUS) will be performed for the primary efficacy endpoint. This analysis will be performed on the ITT population.

Poolability of Sites

Combining of Small Sites

Sites contributing less than 5 subjects to the as treated analysis set will be considered "small sites" and ordered by the date of first enrollment in the as treated analysis set. Starting with the first "small site", a pseudo-site will be created by adding subjects from successive "small sites". If the number of subjects reaches or exceeds the size of the median enrollment of the "large sites", then a second pseudo-site will be created. Additional pseudo-sites, if needed, would be created in the same manner.

Primary Endpoint by Site

Among sites and pseudo-sites, the proportions of subjects who achieve local tumor control at 12 months will be compared using logistic regression. If the resulting p-value is ≤ 0.05, further exploratory analysis will attempt to identify covariates (baseline characteristics) that may explain differences among the sites. Otherwise, the data will be considered to be poolable across study sites.

Poolability of Geographies

Among geographies (US vs. OUS), the proportions of subjects who achieve local tumor control at 12 months will be compared using logistic regression. If the resulting p-value is ≤ 0.05, further exploratory analysis will attempt to identify covariates (baseline characteristics) that may explain differences among the geographies. Otherwise, the data will be considered to be poolable across study geographies.

Interim Reporting

Interim reports may be prepared until the initial manuscript reporting the treatment results has been submitted. The usual components of this report are:

a) patient accrual rate
b) distribution of pre-treatment characteristics
c) cryoablation procedure details
d) frequency and severity of the toxicities

Statistical Software

All statistical analyses will be produced using SAS software Version 9.3 or above (SAS Institute, Cary, NC.).

Version, Revision History, and Approvals

Current Version

Version 3.3 – Approval Date: Dec 8, 2016

Revision History

Version	Approval Date	Key Changes
1.0	Jan 21, 2014	Initial Release
2.0	Feb 12, 2014	Updated to reflect changed to study protocol v2.
3.0	May 14, 2014	Corrected endpoint text to correctly reflect the study endpoint of "12-month tumor local control".
4.0	Jan 4, 2017	• Study Design: Clarified enrollment targets - removed numbers not accounting for attrition. • Sample Size Justification: clarified rate being tested; defined C_{DEVICE}; removed 'exact' specification on CI as final endpoint test will be the random effects model. • Analysis Populations: clarified primary analysis will be on ITT using multiple imputation; expanded PP definition to include removal for major deviation; clarified missing data imputation and additional sensitivity analysis to be defined in another segment. • Efficacy Endpoint Analysis: removed "low number of multi-lesion subject" section as the study had >10 subjects with multiple lesions. • Supportive Endpoint Analyses: clarified wording on "weighted average response". • Handling of missing data: added specific imputations for primary hypothesis test; added specific imputation methods for sensitivity analyses. • Subset Analyses: Added additional subgroups of interest • Poolability Analyses: Corrected population to ITT as this is the primary endpoint population; Added a test of pooling by geography (US/OUS); changed pooling significance level to 0.05 (instead of .15 usually done to account for interactions) as this is a one group study and only main effects will be tested. • Added more specific methods of analysis throughout.

Approvals

Name	Study Role	Signature	Date
[redacted]	Galil – [redacted]	DocuSigned by: [redacted]	04-Jan-2017
[redacted]	Galil – [redacted]	DocuSigned by: [redacted]	05-Jan-2017
[redacted]	NAMSA – [redacted]	DocuSigned by: [redacted]	05-Jan-2017
[redacted]	BTG – [redacted]	DocuSigned by: [redacted]	05-Jan-2017