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TITLE: LAM Pilot Study with Imatinib Mesylate (LAMP-1)

PRINCIPAL INVESTIGATOR: Charlie Strange, MD

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Charleston, SC 29425

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5f. WORK UNIT NUMBER

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Medical University of South Carolina
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Lymphangioleiomyomatosis (LAM) is a rare disease in which tumor cells (LAM cells) proliferate and destroy healthy lung tissue, leading to respiratory compromise or failure. Vascular endothelial growth factor-D (VEGF-D) is generated by LAM cells and is a robust biomarker for LAM disease activity and therapeutic response. Studies in the laboratory of Dr. D'Armiento suggest that imatinib mesylate (imatinib) could completely block the growth of LAM cells through initiation of targeted cell death. Currently, most LAM patients are treated with Sirolimus (rapamycin). Rapamycin growth inhibits but does not kill LAM cells. This pilot trial employs a dual agent design intended to generate safety and efficacy data sufficient to power and design a phase 3 study of imatinib vs placebo for LAM. The hypothesis is that imatinib will be equivalent to rapamycin in short term efficacy and safety. Importantly, VEGF-D level will be used as a marker for LAM disease activity in this small clinical trial design using 20 participants at two institutions. IRB and HRPO approvals are in place and enrollment of participants is anticipated in the upcoming quarter.

15. SUBJECT TERMS
Lymphangioleiomyomatosis (LAM), imatinib mesylate, VEGF-D

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The LAMP-1 study is designed to generate short-term safety and efficacy data regarding imatinib mesylate (imatinib) in the treatment of Lymphangioleiomyomatosis (LAM) sufficient to power and design a phase 3 imatinib vs. placebo clinical trial. The hypothesis is that imatinib will be equivalent to rapamycin in short term efficacy and safety. Currently, most LAM patients are treated with rapamycin, which growth-inhibits but does not kill LAM cells. In the laboratory of Dr. D'Armiento, imatinib was shown to completely block the growth of LAM cells through initiation of targeted cell death. This study employs a small clinical trial design using 20 participants at two institutions. 10 participants will be enrolled at Medical University of South Carolina and 10 at Columbia University. Importantly, VEGF-D level will be used to monitor LAM disease activity and therapeutic response.

1. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Lymphangioleiomyomatosis (LAM), imatinib mesylate, VEGF-D

2. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Two no-cost extensions (NCE) have allowed continuation of this study past the initial 2 years encompassed in the approved SOW. Delays are detailed in previous reports. The most significant delay pertained to obtaining imatinib mesylate. This annual technical report reviews year 3 (1 Oct 16 – 30 Sep 17). Our current and second NCE allows study continuation to 31 Mar 18.

The major goal for year 3 was to obtain imatinib mesylate so that we may resume SOW tasks and complete the study. There were also goals of coordinating study staff for clinical trials and maintaining good regulatory standing, and activities toward study preparations at both sites.

The approved SOW showing subtasks toward each major goal is below, with progress at the time of this annual report for both study sites noted. SOW tasks still remain in Major task 3: Participant Recruitment, Therapy, Participant Evaluation and Major task 4: Data Analysis. We are ready to proceed with all tasks as soon as we are in receipt of imatinib mesylate from Novartis.

Major Task 1: Secure Regulatory Documents to Begin Study	Months- per SOW	Site(s)- per SOW	MUSC Status	Columbia Status
Subtask 1: Prepare Regulatory Documents and Research Protocol for Study				
Coordinate with Sites for material transfer agreements (MTAs) and Clinical trial agreements (CTAs) submission	1-3	MUSC, Columbia	**Complete** (Y1,Q1)	**Complete** (Y1,Q1)
Submission of an Investigational New Drug (IND) application to the U.S. Food and Drug Administration	Within 60 days of grant notice	MUSC	**Complete** Submitted April 23, 2015, Exemption received (Y1,Q3)	N/A
Refine eligibility criteria, exclusion criteria, screening protocol	1-3	MUSC, Columbia	**Complete** (Y1,Q1)	**Complete** (Y1,Q1)
Finalize consent form & human subjects protocol	1-3	MUSC, Columbia	**Complete** (Y1,Q1)	**Complete** (Y1, Q1)
Coordinate with Sites for IRB protocol submission	1-3	MUSC, Columbia	**Complete, approved** (Y1,Q3)	**Complete, approved** (Y2,Q3)
Coordinate with Sites for Military 2nd level IRB review (ORP/HRPO)	1-6	MUSC, Columbia	**Complete** (Y3, Q3)	**Complete** (Y2,Q4)
Submit amendments, adverse events and protocol deviations as needed	As Needed	MUSC, Columbia	**Complete,** As needed (Y3,Q4)	**Complete,** As needed (Y3,Q4)
Coordinate with Sites for annual IRB report for continuing review	Annually	MUSC, Columbia	**Complete** (Y3,Q3)	**Complete** (Y3, Q2)
Milestone Achieved: Local IRB approval at MUSC, and Columbia	3	MUSC, Columbia	**Complete; approved** (Y1,Q3)	**Complete, approved** (Y2,Q3)
Milestone Achieved: HRPO approval for all protocols	6	MUSC, Columbia	**Complete** (Y3, Q3)	**Complete** (Y2,Q4)

Major Task 2: Coordinate Study Staff for Clinical Trials				
Subtask1: Hiring and Training of Study Staff				
Select and Establish DSMB members	1-3	MUSC	**Complete** (Y1,Q3)	N/A
Training of Study coordinators in protocol specific tasks	1-3	MUSC, Columbia	**Complete** (Y1,Q2)	**Complete** (Y3,Q1);
Milestone Achieved: Research staff trained	6	MUSC, Columbia	**Complete** (Y1,Q2)	**Complete** (Y3, Q1)

Major Task 3: Participant Recruitment, Therapy, Participant Evaluation				
Coordinate with Sites for flow chart for all study steps, web data collection and database requirements	4-8	MUSC, Columbia	**Complete** (Y2,Q3)	**Complete** (Y2,Q3)
Purchase drug immediately prior to first patient	6	MUSC	**Pending**	N/A
Finalize assessment measurements	1-4	MUSC, Columbia	**Complete** (Y1,Q1)	**Complete** (Y1,Q1)
Milestone Achieved: 1st participant consented, screened and enrolled	12	MUSC, Columbia	**Future**	**Future**
Begin subject recruitment	6-12	MUSC, Columbia	**Future**	**Future**
Complete follow-up assessments 2 months after initiation for first patient	14	MUSC, Columbia	**Future**	**Future**
Last patient enrolled	18	MUSC, Columbia	**Future**	**Future**
Last patient, last data entered	21	MUSC, Columbia	**Future**	**Future**

Major Task 4: Data Analysis				
Coordinate with Sites & Data Core for monitoring data collection rates and data quality	6-18	MUSC, Columbia	**Future**	**Future**
Perform all analyses according to specifications, share output and finding with all investigators	23	MUSC, Columbia	**Future**	**Future**
Work with data core and dissemination of findings (abstracts, presentation, publications, DOD)	24	MUSC, Columbia	**Future**	**Future**
Milestone Achieved: Report findings from 2 month follow-up assessments	24	MUSC, Columbia	**Future**	**Future**

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant

results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Accomplishments for year 3 quarters 1-3 are detailed in quarterly reports. A summary of LAMP-1 year 3 quarters 1-3 is below, with details of 4th quarter activities and overall progress.

1. Obtain imatinib mesylate

In the first quarter of year 3 Novartis agreed to re-review our request for imatinib mesylate. Commitment to provide the requested drug was received on 31 Mar 17 following medical science committee review, multiple meetings with the investigators and clarifications regarding the study design. Since 31 Mar 17 the PI and study staff have continually engaged with Novartis to accomplish Novartis requirements that must be fulfilled before they will ship study drug. Additional verbiage was required in the ICF and protocol regarding SAE reporting and pregnancy reporting. The requirements were incorporated and underwent a review process by Novartis that resulted in approval in the 4th quarter of this year. Subsequently, the MUSC IRB reviewed and approved an amendment with these changes and the CUMC IRB review is in process. MUSC has collected and provided documents to Novartis such as the IND exemption for this study and PI medical license so that a drug-only clinical trials agreement (CTA) between MUSC and Novartis can be fully executed. MUSC grants administration and Novartis Contracts Management are in the process of finalizing the CTA. Once executed, Novartis should rapidly ship imatinib mesylate to the PI at MUSC so that enrollment of participants may begin.

2. Training of Study coordinators in protocol specific tasks

There was a staffing change at CUMC in quarter 4 of year 2. During the first quarter of this year, the new study coordinator, Laura Fonseca, was trained on the LAMP-1 study and protocol specific tasks. She completed all required human subjects protections trainings and the staffing change amendment was submitted to the CUMC IRB and approved on 24 Oct 2016.

3. Maintaining Good Regulatory Status

This year in quarter 3 MUSC HRPO documents were submitted for final review. HRPO approval was received on 17 Apr 17. The CUMC IRB continuing review was submitted in quarter 1 and approved on 29 Dec 16. The MUSC IRB continuing review was submitted in quarter 3 and approved on 12 Jun 17. The second no-cost extension was submitted and executed, allowing continuation of this study to 31 Mar 18. IRB amendments have been submitted, as needed, to both IRBs. The study was listed on clinicaltrials.gov for initial recruitment and to prepare for enrollment: https://clinicaltrials.gov/ct2/show/NCT03131999?term=imatinib&cond=Lymphangioleiomyomatosis&rank=1

4. Other Study Preparations

In quarter 4 the study coordinators met to discuss flow during participant visits and ensure consistency of case report forms between the sites. Internal scheduling procedures and LAM patient rosters have been examined so that contact and scheduling will happen smoothly as soon as we are able to enroll.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to Report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

In the upcoming period we expect the final drug-only CTA with Novaris to be fully executed and to receive the shipment of imatinib mesylate. As soon as drug is received, MUSC will rapidly proceed with enrollment and study procedures. We anticipate CUMC IRB approval of the latest amendment with Novartis-requested verbiage. Following approval and receipt of drug, CUMC will also enroll participants and complete remaining SOW tasks as quickly as possible. We will maintain good regulatory standing with both IRB and HRPO. The next CUMC continuing review will be submitted to the IRB and HRPO in the upcoming quarter.

4. IMPACT: Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to Report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report.

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

We are pleased that this year we obtained commitment from Novartis to provide the requested imatinib mesylate to conduct this study. This resolved the previous major problem of whether we would be able to obtain study drug. However, the process has been prolonged with multiple steps and reviews. Much of this year has been spent engaging in this process. At the time of this report only finalization of the CTA remains and we expect this to be executed in the upcoming quarter.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to Report.

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time*

conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to Report.

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to Report.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to Report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report.

- **Other Products**

  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

  - *data or databases;*
  - *biospecimen collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award).*

Name: Charlie Strange
Project Role: Principal Investigator
Researcher Identifier (ORCID ID): 0000-0002-8109-8067
Nearest person month worked: 3
Contribution to Project: Dr. Strange supervised all study activities. He collaborated with co-investigator and study coordinators on addressing HRPO, IRB and Novartis requests for changes and additional documentation. He submitted the annual IRB continuing review to maintain good regulatory standing at MUSC. Dr. Strange was integral to securing Novartis commitment to provide study drug and engaged in many meetings and written document preparation. Dr. Strange facilitated submission of the request for no-cost extension. Dr. Strange listed the study on clinicaltrials.gov. He communicated with our program officers and maintained communications per the terms of the grant.
Funding Support: HL116346, HL086936, R21 A102239, Alpha-1 Foundation

Name: Jeanine D'Armiento
Project Role: Co-Investigator
Researcher Identifier (ORCID ID):
Nearest person month worked: 2
Contribution to Project: Dr. D'Armiento supervised study activities at CUMC. She collaborated with the principal investigator and study coordinators on addressing Novartis requests and oversaw submission of CUMC IRB and HRPO continuing reviews.
Funding Support: HL116346, HL086936, R21 A102239, Alpha-1 Foundation

Name: Kimberly Brown
Project Role: Study Coordinator
Researcher Identifier (ORCID ID):
Nearest person month worked: 3
Contribution to Project: Ms. Brown assisted with preparation of study documents for MUSC HRPO submission, IRB continuing review and amendments, Novartis requested documentation and revisions, and study reports. She collaborated with Dr. Strange to ensure that successful scheduling plans and data infrastructure are in place for this study. She worked with the CUMC coordinator on visit flow and case report forms. She is familiar with the protocol and ready to implement recruitment and study steps once participants may be enrolled.
Funding Support: Alpha-1 Foundation, Cystic Fibrosis Foundation, Alpha-1 Coded Testing Study

Name: Laura Fonseca
Project Role: Study Coordinator
Researcher Identifier (ORCID ID):
Nearest person month worked: 2
Contribution to Project: Ms. Fonseca became fully trained on the protocol and procedures this year and assisted with IRB and HRPO continuing reviews and IRB amendments. She collaborated with Dr. D'Armiento to ensure that successful staffing and data infrastructure are in place for this study at CUMC and collaborated with the MUSC coordinator on visit flow and case report forms.
Funding Support: Departmental (LAM Center)

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS: N/A

9. APPENDICES: N/A