AD_____

AWARD NUMBER: W81XWH-14-1-0132

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

PRINCIPAL INVESTIGATOR: Charlie Strange, MD

RECIPIENT: Medical University of South Carolina
Charleston, SC 29425

REPORT DATE: October 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2015	Annual	30 Sep 2014 - 29 Sep 2015

4. TITLE AND SUBTITLE
LAM Pilot Study with Imatinib Mesylate (LAMP-1)

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-14-1-0132

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Charlie Strange, MD

Email: strangec@musc.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
.
Medical University of South Carolina
Charleston, SC 29425

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
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.

15. SUBJECT TERMS-

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU		19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

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.

Major goals of the project for year 1 include 1) Securing regulatory documents to begin study, 2) Coordinating clinical trial staff for clinical trial, several subtasks toward 3) Participant recruitment, therapy and participant evaluation, and one subtask toward 4) Data analysis.

Year 1 subtasks toward each major task as stated in the approved SOW are outlined below. Progress at the time of this annual report for each study site is noted.

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	Current	MUSC, Columbia	**Complete** (Quarter 1)	**Complete** (Quarter 1)
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 (Quarter 3)	N/A
Refine eligibility criteria, exclusion criteria, screening protocol	1-3	MUSC, Columbia	**Complete** (Quarter 1)	**Complete** (Quarter 1)
Finalize consent form & human subjects protocol	1-3	MUSC, Columbia	**Complete** (Quarter 1)	**Complete** (Quarter 1)
Coordinate with Sites for IRB protocol submission	1-3	MUSC, Columbia	**Complete approved July 21, 2015**	**Submitted and pending approval** (July 2015)
Coordinate with Sites for Military 2nd level IRB review (ORP/HRPO)	1-6	MUSC, Columbia	In progress Submitted (Quarter 4)	In progress Submitted (Quarter 4)
Submit amendments, adverse events and protocol deviations as needed	As Needed	MUSC, Columbia	N/A	N/A
Coordinate with Sites for annual IRB report for continuing review	Annually	MUSC, Columbia	Not yet needed	Not yet needed
Milestone Achieved: Local IRB approval at MUSC, and Columbia	3	MUSC, Columbia	**Complete; approved July 21, 2015**	**In progress Submitted** (Quarter 4)
Milestone Achieved: HRPO approval for all protocols	6	MUSC, Columbia	In progress, Submitted (Quarter 4)	In progress, Submitted (Quarter 4)

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** (Quarter 3)	N/A
Training of Study coordinators in protocol specific tasks	1-3	MUSC, Columbia	**Complete** (Quarter 2)	**Complete** (Quarter 4)
Milestone Achieved: Research staff trained	6	MUSC, Columbia	**Complete** (Quarter 2)	**Complete** (Quarter 4)

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	In progress; 60%	In progress; 60%
Purchase drug immediately prior to first patient	6	MUSC	Future	N/A
Finalize assessment measurements	1-4	MUSC, Columbia	**Complete** (Quarter 1)	**Complete** (Quarter 1)
Milestone Achieved: 1st participant consented, screened and enrolled	12	MUSC, Columbia	Future	Future
Begin subject recruitment	6-12	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

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 quarters 1-3 are detailed in quarterly reports and summarized below. Accomplishments of quarter 4 (months 10-12) are detailed below.

Major Task 1) Securing Regulatory Documents to Begin Study
MTAs and CTAs were finalized. IND submission occurred and IND-exempt status was determined. A letter of IND wavier was received from the FDA. Eligibility criteria, exclusion criteria and the screening protocol were finalized. The human subjects protocol and informed consent form were written and finalized. The IRB protocol submission occurred at MUSC. IRB approval was received on July 21, 2015. HRPO submission occurred in the 4th quarter and Ms. Nancy Englar has been assigned to review this project. IRB approval is pending at Columbia University; HRPO submission will follow.

Major Task 2) Coordinate Study Staff for Clinical Trials
Study staff were hired and trained on the scope of this project and coordinator responsibilities. All staff affiliated with this study have completed CITI research certifications and are trained in accordance with research standards of their respective institutions. Members of the DSMB were determined in Quarter 3.

Major Task 3) Participant Recruitment, Therapy, Participant Evaluation
Participant recruitment and enrollment will begin after HRPO approval, which is pending at MUSC at this time. Additionally, Columbia University IRB approval is pending, with subsequent HRPO submission. Purchase of drug is planned to occur just prior to the first patient, as stated in the SOW. Assessment measures are complete and ready for implementation as participants are enrolled in the coming year.

Major Task 4) Data Analysis
Coordinating with Sites & Data Core for monitoring data collection rates and data quality will begin when participants are enrolled and data is being collected.

Discussion:
Excellent progress has been made over the course of the first year toward the major goals with year 1 targets for completion as stated in the SOW. The areas in which the project is behind the projected timeline include HRPO approval, participant recruitment and enrollment, and portions of data monitoring and analysis. HRPO review is in progress and required before enrollment may commence.

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.

It is anticipated that during the next reporting period HRPO approval will be attained for the MUSC site. At that time, study drug will be acquired just prior to enrollment of the first participant, as stated in the SOW. MUSC will begin recruiting and enrolling participants in this study. IRB approval from the Columbia University IRB and subsequent HRPO approval are anticipated. Participant recruitment and enrollment will then begin at the Columbia site. Coordination for monitoring data collection rates and data quality will begin.

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.

Early in year 1 delays were incurred in the IND submission and designation process. This issue was previously resolved; however, all approvals needed to recruit and enroll participants are slightly behind schedule. Thus, at the conclusion of year 1 no participants are enrolled. Enrollment will begin at MUSC after HRPO approval is received. The MUSC study site is ready to begin enrolling participants at that time. Enrollment will begin at Columbia University following IRB approval and HRPO approval. Columbia University designated and trained a new coordinator in quarter 4 of year 1 to assist with conducting this research.

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.

Due to delays in enrolling participants this study did not spend the amount anticipated in Year 1; however the total expenditures of completing this research are expected to be the same, on a slightly delayed timetable. Specifically, consultant and materials costs have not yet been incurred, nor have research-related subject costs, patient travel reimbursement or shipping costs.

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 assembled and trained his MUSC research staff on the scope of this study. He oversaw all study activities and staff during this first year. He obtained IND wavier and supervised the IRB submission process. He collaborated with co-investigator and study coordinator on tasks necessary to obtain approvals and meet study goals. Dr. Strange maintained communications per the terms of the grant.

Funding Support: NIH/NHLBI U01 HL 112707, NIH/5 UL1TR000062-05, U01HL112694, Alpha-1 Foundation, CSL Behring, Grifols Therapeutics, PneumRx, Inc.

Name: Jeanine D'Armiento
Project Role: Co-Investigator
Researcher Identifier (ORCID ID): none
Nearest person month worked: 2
Contribution to Project: Dr. D'Armiento assembled and trained her research staff at Columbia University on the scope of this study. She prepared and submitted the Columbia University protocol to the institutional IRB. She collaborated with Dr. Strange and research staff regarding workflow and procedure at her study site.
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, submission to the institutional IRB, HRPO submission and preparation of reports. She collaborated with Dr. Strange to ensure that successful staffing and data infrastructure are in place for this study. 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: Caitlin Clancy
Project Role: Study Coordinator
Researcher Identifier (ORCID ID):
Nearest person month worked: 1
Contribution to Project: Ms. Clancy assisted with the revision and submission to the institutional IRB, HRPO submission and preparation of reports. She collaborated with Dr. D'Armiento to ensure that successful staffing and data infrastructure are in place for this study. She is familiar with the protocol and ready to implement recruitment and study steps once participants may be enrolled.
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: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.