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 29425-6300

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TYPE OF REPORT: Annual

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

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LAM Pilot Study with Imatinib Mesylate (LAMP-1)

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5b. GRANT NUMBER

W81XWH-14-1-0132

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Medical University of South Carolina
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Charleston, SC 29425

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U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
FORT DETRICK, MARYLAND 21702-5012

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Approved for public release; distribution is unlimited.

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. VEGF-D level will define LAM disease activity in this small clinical trial design using 20 participants at two institutions. At the time of this report 13 participants have been enrolled, 12 completed the protocol and 1 withdrew due to inability to perform spirometry.

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
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	29	19b. TELEPHONE NUMBER *(Include area code)*

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INTRODUCTION:

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 (sirolimus) 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:

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.

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 4 (1OCT2017 – 30SEP2018). Our current NCE allows study continuation to 29MAR2019.

The major goals for year 4 were to obtain imatinib mesylate and complete SOW tasks in Major task 3: Participant Recruitment, Therapy, Participant Evaluation. There were also goals of maintaining good regulatory standing 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 making good progress toward these goals, which should be completed within the current NCE.

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,** Ongoing as needed	**Complete,** Ongoing as needed
Coordinate with Sites for annual IRB report for continuing review	Annually	MUSC, Columbia	**Complete** (Y4,Q3)	**Complete** (Y4, Q2)
Milestone Achieved: Local IRB approval at MUSC, and Columbia	3	MUSC, Columbia	**Complete** (Y1,Q3)	**Complete** (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	**Complete** (Y4,Q1)	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	**Complete** (Y4,Q2)	**Complete** (Y4,Q2)
Begin subject recruitment	6-12	MUSC, Columbia	**Complete** (Y4,Q1)	**Complete** (Y4,Q1)
Complete follow-up assessments 2 months after initiation for first patient	14	MUSC, Columbia	**Complete** (Y4,Q1)	**Complete** (Y4,Q2)
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.

Detailed quarterly reports have been submitted in January, April, July and October 2018. A summary of LAMP-1 year 4 activities and overall progress is below.

1. Obtain imatinib mesylate

In the first quarter of year 4 the CTA was finalized between Novartis and MUSC and study drug was received by the PI on 13DEC2017.

2. SOW tasks in Major task 3: Participant Recruitment, Therapy, Participant Evaluation.

Participant recruitment began in the first quarter of year 4. The study opened for enrollment on 11JAN2018 and the first participant visit occurred on 23JAN2018. At the conclusion of the 4th year, 13 participants were enrolled: 12 completed the protocol and 1 withdrew due to inability to perform spirometry.

Details of enrollment, participant demographics, adverse events and interim data are encompassed in the PI's 28SEP2018 report to the DSMB. This report is attached (Appendix A).

3. Maintaining Good Regulatory Status

MUSC and CUMC submitted and received IRB and HRPO Continuing Review (CR) Approval. MUSC CR IRB approval was received 15MAY2018 and HRPO CR approval was received 28AUG2018. CUMC IRB CR was received on 22NOV2017. A DoD no-cost extension was submitted and executed, allowing continuation of this study to 29MAR2019. The DSMB met three times this year: on 18DEC2017 before opening the study for enrollment (recommended opening and enrollment), on 12MAR2018 to review the first participants and the unexpected AE of hypoxemia (recommended enrollment hold to add safety procedures and amend risks in protocol and ICF), and on 28SEP2018 as a meeting was due to review study status and interim data (recommended continuation). Monthly enrollment reports were submitted to Novartis as required. Amendments and status changes have been submitted, as needed, to both IRBs and HRPO, including:

MUSC:

Amendment 4 (Approved 27DEC2017)

- Removed the inclusion criteria of "VEGF-D > 200 pg/ml within the last 6 months while on the same medications at time of enrollment."
- Removed Alison Garbarini – resigned from department
- Updates to advertisement and screening script to reflect previous IRB approved change in participant remuneration and change of coordinator at CUMC.

Amendment 5 (Approved 1FEB2018)

- Remove Rana Kanaan - she is no longer at MUSC. Add Haitham Al Ashry, MD, who will now perform those roles.
- We added to the protocol that a study coordinator will call each participant 2 weeks +/- 4 days after the baseline visit and 2 weeks +/- 4 days after the 1 month visit to touch base and see how the participant is doing. This is added at the recommendation of the DSMB.

Status Change (Approved 27MAR2018)

- Temporarily closed for enrollment due to hypoxemia AE

Amendment 6 (Approved 24APR2018)

- Protocol
  1) Version and Date have been altered
  2) An inclusion age has been limited to 18-65 years
  3) An inclusion FEV1 % predicted has been added to be >30% predicted
  4) An inclusion DLCO >20% predicted has been added to the protocol
  5) Trough sirolimus levels have been specified6) A one week trough sirolimus level has been added
  7) A study coordinator telephone call or visit has been added at 1 week after drug initiation
  8) The specific side effect of hypoxemia has been added to known side effects
  9) The interaction between imatinib and sirolimus in which sirolimus levels rise has been added as a known study risk.
  10) An unblinded study coordinator and/or prescribing health care member(s) have been added to the study teams to monitor 1 week and one month sirolimus levels to prevent unblinding.
  11) Unblinding reporting has been added in the event sirolimus levels rise more than 50% because this would require sirolimus dose reduction (unblinding the patient).
- Consent
  1) Version number in the header has been changed
  2) Speaking to a coordinator at 1 week, 2 weeks, and 6 weeks into the study has been added
  3) Under risks, the sentence “One LAM patient developed low oxygen levels after exposure to study drug" was added.
  4) The drug interaction between sirolimus and imatinib has been added.
  5) One week trough sirolimus level has been added.
  6) Altered dose timing of sirolimus has been added.

Status Change (Approved 24APR2018)

- Re-opened for enrollment with approval of Amendment 6 and recommendation of the DSMB

Amendment 7 (Approved 1MAY2018)

- The recent ICF changes were not made to the most recent ICF document. Language regarding the drug supplier (Novartis), pregnancy prevention and reporting, and reimbursement ($200 per visit instead of $60 per visit) were lost. Previously approved verbiage has been re-integrated.

Amendment 8 (Approved 29MAY2018)

- This amendment removes the verbiage of "VEGF-D >200 pg/ml within the last 6 months" from the ICF and updates the version date.
  In amendment 4, we removed VEGF-D >200 pg/ml from the inclusion criteria and struck the corresponding verbiage from the ICF. In amendment 6 updates were made to an old ICF. Approved verbiage that had been added was lost, and this sentence came back in, but we did not notice it at the time of Amendment 7 which was to reincorporate previously approved changes. This amendment is to remove that line again to accurately reflect the eligibility criteria.

Amendment 9 (Approved 28AUG2018)

- Add Nick Fox, MD as unblinded study physician
- Add reimbursement for costs incurred for study-requested labs (1-week trough sirolimus level) as many patients are not close enough to MUSC to do it here

CUMC:
Amendment (Approved 3JAN2018)
- Remove VEGF-D as requirement prior to enrollment + added AE/SAE verbiage provided by Novartis

Amendment (Approved 4APR2018)
- Major modifications including change in eligibility criteria, addition of hypoxemia under risks, additional trough sirolimus level and coordinator phone call at 1 week, additional safety procedures as recommended by the DSMB

Amendment (Approved 17APR2018)
Change status from "on hold" to "open for enrollment

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.

Two third year fellows in Pulmonary and Critical Care Medicine training have completed participation in the study as supervised rare lung disease experts to learn trial design and study procedures (Rana Kanaan and Haitham Al Ashry).

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 both study sites will continue to recruit and enroll participants. We will proceed with enrollment as rapidly as possible to complete enrollment and complete remaining SOW tasks in Data Analysis. We will maintain good regulatory standing with both IRBs 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.

The only current issue is that we have noticed a downward trend in enrollment as both study sites have already recruited, screened and enrolled eligible participants who live in close proximity. We are pursuing the possibility of increasing travel funds to allow interested LAM patients who live farther away to travel to the study sites to participate.

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 enrollment and procedures. He ensured reporting to the DSMB, HRPO, IRB and Novartis regarding all study issues or changes. He submitted the annual continuing reviews and amendments to maintain good regulatory standing at MUSC. Dr. Strange obtained study drug from Novartis. Dr. Strange facilitated submission of the request for no-cost extension. Dr. Strange engaged in participant recruitment, consent, direct participant care, management of study medications, assessment of AEs and participant follow-up. He participated in DSMB meetings. Dr. Strange 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 oversaw CUMC IRB and HRPO activity. She provided CUMC data to the DSMB and participated in DSMB meetings. Dr. D'Armiento engaged in participant recruitment, consent, direct participant care, management of study medications, assessment of AEs and participant follow-up. She collaborated with Dr. Strange and research staff to ensure that requirements for enrollment and data collection are met.
Funding Support: HL116346, HL086936, R21 A102239, Alpha-1 Foundation

Name: Kimberly Foil
Project Role: Study Coordinator
Researcher Identifier (ORCID ID):
Nearest person month worked: 3
Contribution to Project: Ms. Foil screened participants and scheduled study visits. She consented participants and guided participants through study procedures at each visit. She completed 1- and 2-week follow-up phone calls. She assisted with preparation of amendments, continuing reviews, and report including quarterly technical and annual reports to the DoD, monthly reports to Novartis and DSMB reports. She entered participant data, facilitated communication between the study sites and assisted with study reporting and correspondence.
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 screened participants, scheduled study visits and guided participants through study procedures at each visit. She completed 1- and 2-week follow-up phone calls. She assisted with CUMC IRB amendments and regulatory maintenance and reporting. Ms. Fonseca communicated with the MUSC site, entered participant data and assisted with study communications.
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.*

Novartis supplied imatinib mesylate for this study. The LAM Foundation has assisted in advertisement and recruitment.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

Appendix A.

LAMP-1 Data and Safety Monitoring Board (DSMB) Report

-Open Session-

Report Cover Page

Protocol Title/number:	LAM Pilot study with imatinib mesylate (LAMP-1)
Award Number:	W81XWH-14-1-0132
Principal Investigator (PI):	Charlie Strange, MD Medical University of South Carolina 96 Jonathan Lucas St MSC 630 Charleston, SC 29425
Meeting date:	28September2018
Date of Report:	25September2018
Data as of:	25September2018
Prepared by:	Kimberly Foil

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Enrollment Synopsis

Date Report Submitted: 9/25/2018	Person Submitting Report: Kimberly Foil	Phone Number: 843-792-6474
TOTAL STUDY ENROLLMENT NUMBERS		
Total # Patients *Screened* to Date: 37	**Study Enrollment Goal: 20 (10 at each site)**	
Total # Patients *Enrolled* to Date: 13	**Date Study Open For Enrollment: 1/11/2018**	
Total # Patients *Completed* to Date: 12	***Actual* First Patient First Visit Date: 1/23/2018**	
Total # Patients *Discontinued* to Date: 1	***Estimated* Study Completion Date (LPLV): 3/29/2019**	

	JAN 2018	FEB 2018	MAR 2018	APR 2018	MAY 2018	JUN 2018	JUL 2018	AUG 2018	SEP 2018	OCT 2018	NOV 2018	DEC 2018
# Patients Screened in Current Month:	8	9	5	3	5	3	3	0	1			
# Patients Enrolled in Current Month:	2	2	1	2	2	2	1	0	1			
# Patients Currently Active:	2	4	3	3	4	2	2	0	0			
# Patients Completed Protocol in Current Month:	0	0	2	2	1	3	2	2	0			
# Patients Discontinued (Did not complete protocol) in Current Month:	0	0	0	0	0	0	0	0	1			
Date of Most Recent Patient Enrollment:	1/25/18	2/21/18	3/5/18	4/30/18	5/29/18	6/04/18	7/6/18	7/6/18	9/24/18			

Executive Summary

Study Overview Since the Last DSMB Meeting (12Mar18)	1. An enrollment hold was recommended by the DSMB due to the unexpected moderate AE of hypoxemia in one participant. On 04APR2018 the CUMC IRB approved the amendment with changes recommended by the DSMB. On 18APR2018 the MUSC amendment with the same changes received approval with minor contingencies. The DSMB reviewed the revised protocol, ICFs and both IRB letters and approved the study for re-opening on 20APR2018. Contingencies were met at MUSC and final amendment approval was received 24APR2018. The IRB status change to re-open was approved the same day. 2. DoD HRPO requested the same documents that were submitted to the IRB regarding the hypoxemia unexpected problem involving risks to subjects or others (UPIRTSO). These documents, along with DSMB letters and minutes of were submitted 7 May 18. 3. MUSC IRB Continuing Review was received on 16MAY2018. 4. On 24MAY2018 the former DSMB chair, Dr. Lisa Young, resigned from the DSMB due to a potential conflict of interest that arose outside the direct scope of this trial. Dr. Maryl Kreider, agreed to the role of DSMB chair and a new physician member, Dr. Rupal Shah, was added to the DSMB. HRPO was notified of this change. Upon review, a change in DSMB membership is non-substantive in nature and no HRPO action was required. 5. MUSC HRPO Continuing Review was received on 24AUG2018. 6. While enrollment was on-hold, 3 MUSC participants and 1 CUMC participant who were previously enrolled completed the protocol with no other AEs. 7. Following approval to re-open enrollment, both MUSC and CUMC continued screening and enrolling participants with additional safety procedures in place. Eight participants have since been enrolled (4 at MUSC, 4 at CUMC). 8. A total of 7 participants completed the protocol since the one-week sirolimus level was added at re-opening of enrollment. A table of sirolimus levels for participants on sirolimus enrolled since study re-opening is sent to the independent study monitor by an unblinded team member to share with the DSMB in closed session. 9. Quarterly reporting to the Department of Defense and monthly reporting to Novartis have continued.
Overall Study Status	Currently enrolling participants 37 participants screened 13 participants enrolled 12 participants completed protocol

	1 participant withdrew before drug (unable to perform spirometry)
Safety Summary	No serious adverse events have occurred. No unexpected adverse events have occurred since the event of hypoxemia in one participant that was previously reported, resulting in changes including increased safety precautions.
Summary of Protocol Changes since last DSMB Meeting (12Mar18)	1) Version and Date have been altered 2) Inclusion age has been limited to 18-65 years 3) An inclusion FEV1 % predicted has been added to be >30% predicted 4) An inclusion DLCO >20% predicted has been added to the protocol 5) Trough sirolimus levels have been specified 6) A one week trough sirolimus level has been added 7) A study coordinator telephone call or visit has been added at 1 week after drug initiation 8) The specific side effect of hypoxemia has been added to known side effects 9) The interaction between imatinib and sirolimus in which sirolimus levels rise has been added as a known study risk. 10) An unblinded study coordinator and/or prescribing health care member(s) have been added to the study teams to monitor 1 week and one month sirolimus levels to prevent unblinding. 11) Unblinding reporting has been added in the event sirolimus levels rise more than 50% because this would require sirolimus dose reduction (unblinding the patient).
Summary of Consent Changes	1) Version number in the header has been changed 2) Speaking to a coordinator at 1 week, 2 weeks, and 6 weeks into the study has been added 3) Under risks, the sentence “One LAM patient developed low oxygen levels after exposure to study drug" was added. 4) The drug interaction between sirolimus and imatinib has been added. 5) One week trough sirolimus level has been added. 6) Altered dose timing of sirolimus has been added.

Adverse Event Log

AE	#	Severity	Timing	Relationship to study	Treatment	Outcome
Hypoxemia	1 (1-2)	Moderate	Month 2 (B)	Possibly related	Study exit	Resolved
Nausea	7 (1-2, 1-3, 1-4, 2-1, 2-2, 2-4, 2-5)	Mild	Baseline (sirolimus & A (1), B (1)), Month 1 (sirolimus & B (2), B (1), sirolimus &	Possibly related	-Ginger ale -Dose reduction -Monitor -Monitor -Monitor	-Resolved -Resolved -Resolved -Resolved -Resolved

			A (1)), A (1)			-Resolved -Resolved
Vomiting (one occurrence)	1 (1-3, 2-4)	Mild	Month 1 (sirolimus & B (1)), B (1)	Possibly related	-Dose reduction -None	Resolved
Tiredness	1 (2-2)	Mild	Baseline (B)	Not related	None	Resolved
Muscle Pain & weakness	1 (1-3)	Mild	Month 1 (sirolimus & B)	Possibly related	Monitor	Resolved
Thrombocytopenia	1 (1-2)	Mild	Month 1 (sirolimus & B)	Possibly related	Monitor	Resolved
Dysgeusia (food tastes terrible)	1 (1-2)	Mild	Month 1 (sirolimus & B)	Possibly related	None	Resolved
WBC lower (does not meet definition of neutropenia)	1 (1-2)	Mild	Month 1 (sirolimus & B)	Possibly related	Monitor	Resolved
Rash (arms and face, red and bumpy, without pain or itching)	1 (1-6)	Mild	Month 1 (sirolimus & B)	Possibly related	OTC Lotion	Resolved
Finger infection with erythema and red streak headed toward hand 2 weeks after slamming finger in car door	1 (1-5)	Mild	Month 2 (A)	Possibly related	Kefflex 500 mg QID x 5 days	Resolved
Fatigue	2 (1-2, 1-7)	Mild	Month 1-2 (sirolimus & B, B only) Month 2 (B)	Possibly related	Monitor	-Resolved -Resolved
Headache	2 (2-1, 2-5)	Mild	Month 1 (sirolimus & A (1)), A (1)	Possibly related	-Ibuprofen -None	-Resolved -Resolved
Cough	1 (2-1)	Mild	Month 2 (A)	Not related	Z-pack and mucinex	Resolved
Swollen feet, hands, lip	1 (2-3)	Mild	Month 1 (sirolimus & B)	Not related	Benedryl	Resolved
Gastroenteritis	1 (2-3)	Mild	Month 1 (sirolimus & B)	Possibly related	Advil	Resolved after 3 days
Gas	1 (2-4)	Mild	Month 1 (B)	Possibly related	None	Resolved
Diarrhea	1 (2-4, 2-5)	Mild	Baseline, and Month 2 (B), Month 1 (B (1)), (A (1))	Possibly related	None	Resolved
Insomnia	1 (2-1)	Mild	Baseline (sirolimus & A (1)	Not related	Melatonin	Resolved
Dysuria	1 (2-5)	Moderate	Month 1 (A)	Not related	diuretic (D-Mannose - contains hibiscus and cranberry	Resolved
Epileptic Episode	1 (2-5)	Moderate	Month 1 (A)	Not related	Increase dose of Carbamazepine from 400mg to 600mg daily and 50mg of Benadryl – per neurologist	Resolved
Elevated 1 week trough sirolimus with co-adminstration	3 (1-5, 1-6, 1-7)	Mild	Month 1 (sirolimus & B (2)), (sirolimus & A (1))	Possibly related	Reduced sirolimus and/or study drug dose	Resolved

Demographics

Gender	Male: 0 Female: 13 (100%)
Age	Mean: 44 Range: 31- 71
Race	White: 11 (84.6%) American Indian or Alaska Native: 1 (7.7%) Black or African American: 1 (7.7%)
Ethnicity	Not Hispanic or Latino: 12 (92.3%) Hispanic or Latino: 1 (7.7%)

Sirolimus at Baseline: 10 of 13 (76.9%) were on sirolimus at baseline. 3 of 13 (23.1% were sirolimus naive).

Interim Data

Figure 1. 6MWT distance (feet) Drug A

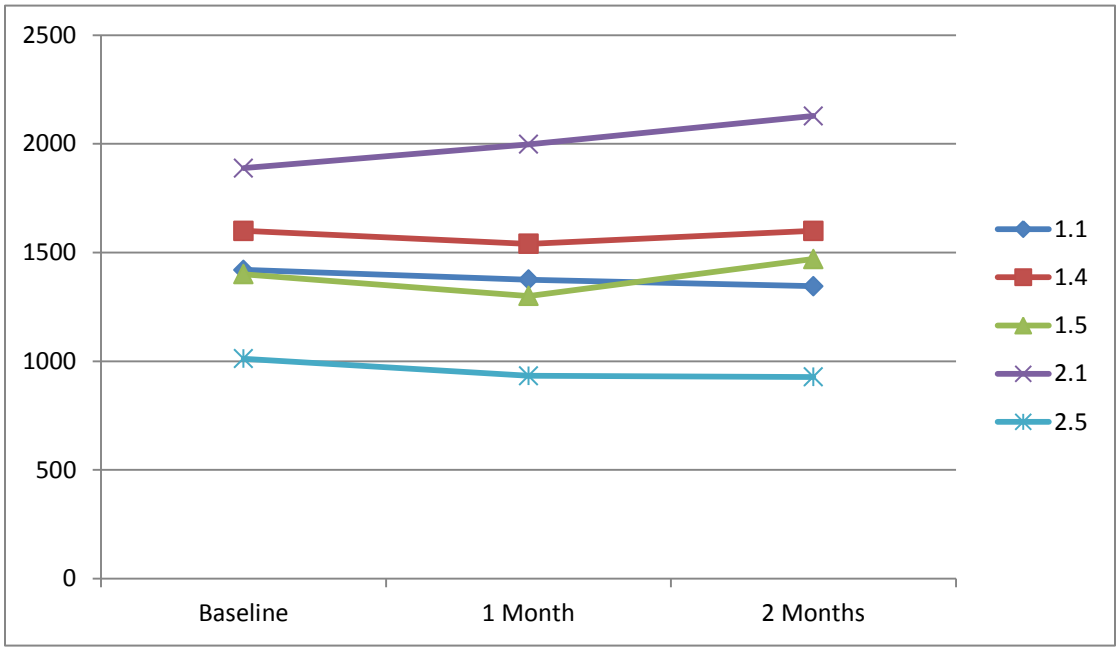


Figure 2. 6MWT distance (feet) Drug B

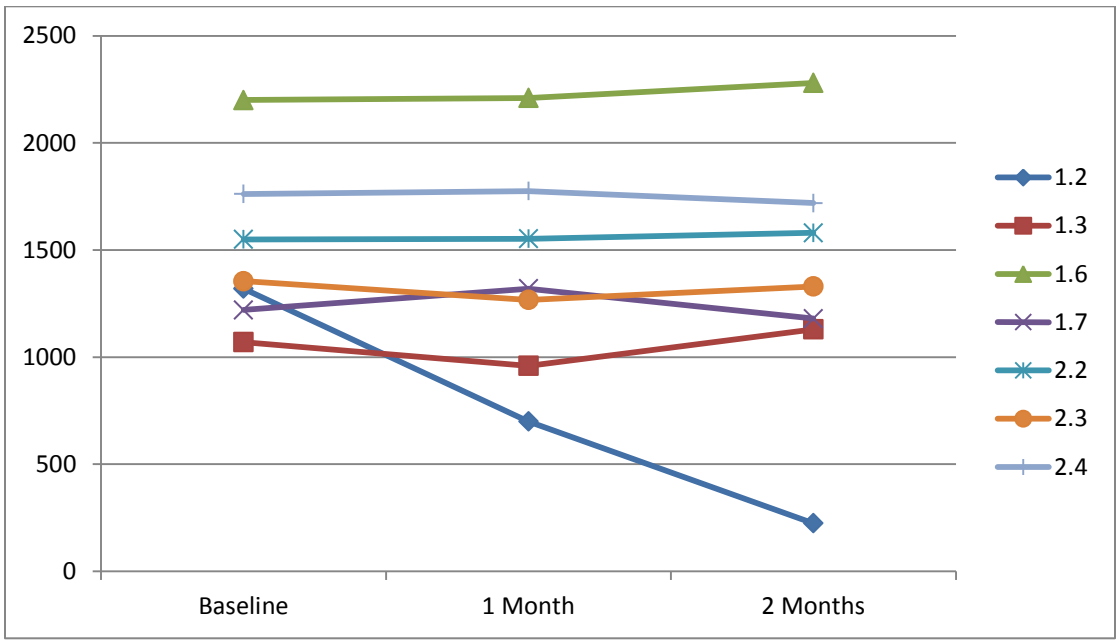


Figure 3. Drug A FEV1 (post %pred)

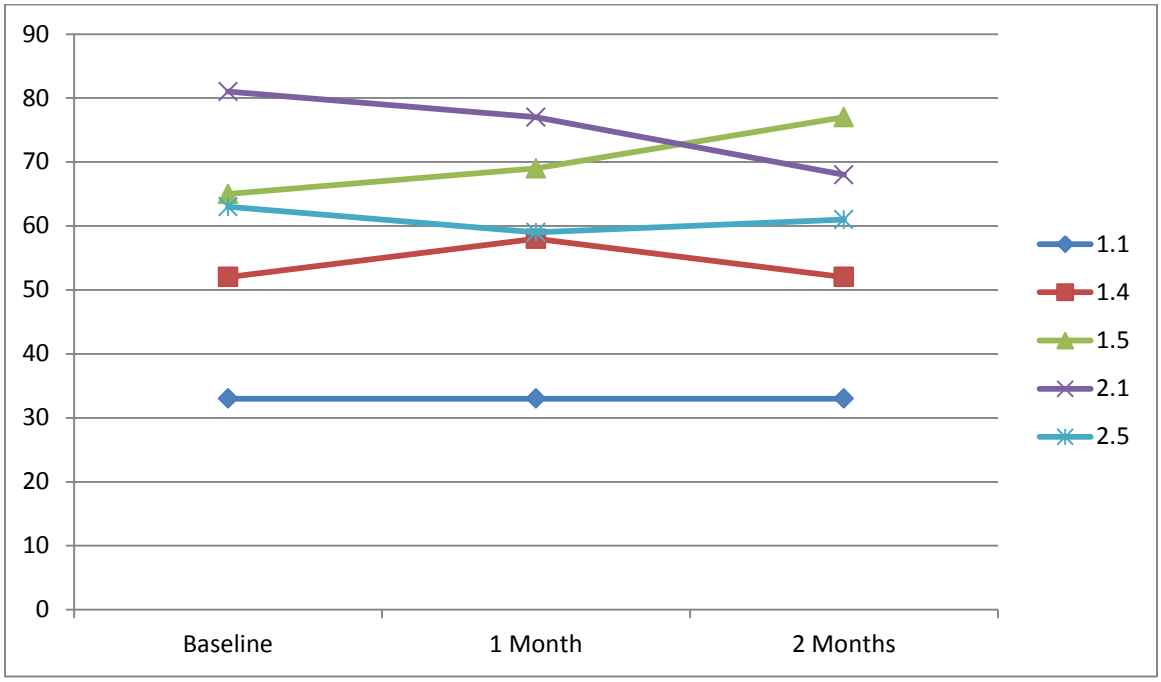
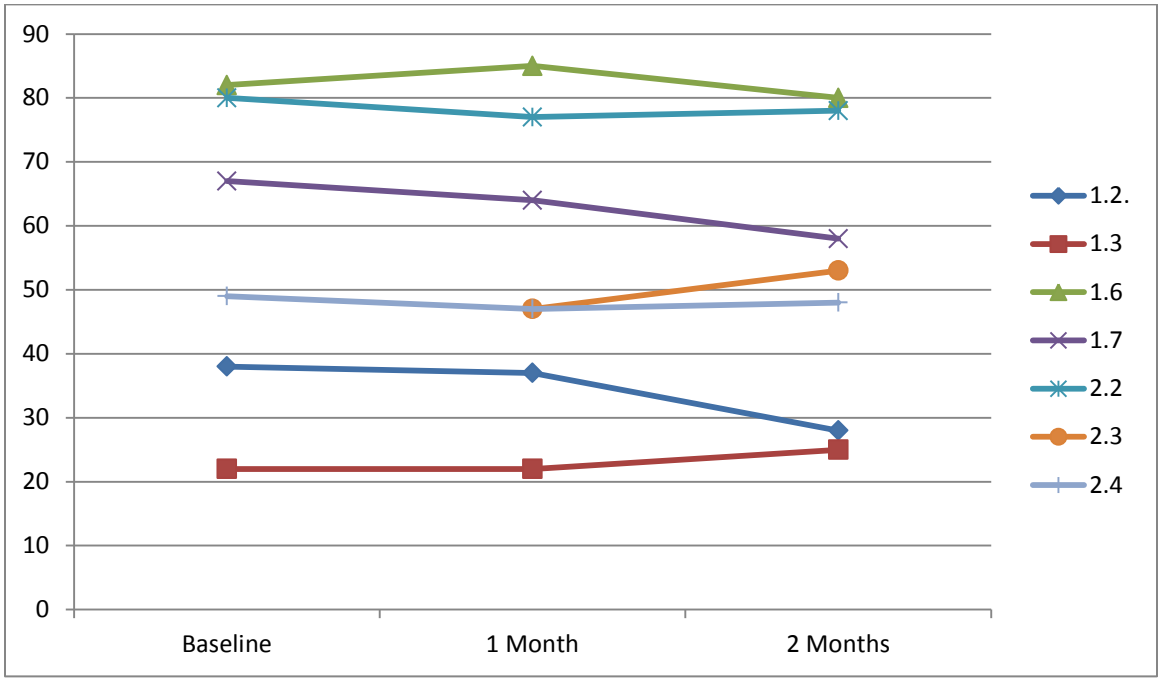


Figure 4. Drug B FEV1 (post %pred)



Changes/Problems:

a. Actual Problems or delays and actions to resolve them

The only problem encountered in this reporting period was resignation of the DSMB chair. Another DSMB member assumed the position of DSMB chair and a new DSMB physician member was added, leading to rapid resolution of this issue. There are no problems or delays at the time of this report.

b. Anticipated Problems/Issues

Provide a description of anticipated problems or issues that have a potential to impede performance or progress. Also provide course of actions planned to mitigate problems or to take should the problem materialize.

Nothing to report.

Next Steps:

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

Both study sites will continue to enroll participants and maintain regulatory requirements. Upon completion of enrollment and follow-up VEGF-D levels will be run as a batch.