DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:
Office of Laboratory Animal Welfare
Rockledge One, Suite 360
6705 Rockledge Drive - MSC 7982
Bethesda, Maryland 20892-7982
Home Page: http://grants.nih.gov/grants/olaw/olaw.htm

FOR EXPRESS MAIL:
Office of Laboratory Animal Welfare
Rockledge One, Suite 360
6705 Rockledge Drive
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 402-7065

November 17, 2017

Re: Animal Welfare Assurance
A3063-01 [OLAW Case W]

Dr. Lawrence E. Cornett
Vice Chancellor for Research
University of Arkansas for Medical Sciences
4301 W. Markham St., MS #718
Little Rock, AR 72205

Dear Dr. Cornett,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your November 14, 2017 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the University of Arkansas for Medical Sciences, following up on an initial November 2, 2017 telephone notification. According to the information provided, OLAW understands that thirty mice were intraperitoneally injected with an unapproved test article and vehicle resulting in the demise of fourteen mice and subsequent euthanasia of the remaining sixteen mice due to animal health and welfare concerns. It was also determined by the IACUC that non-pharmaceutical grade test article, copanlisib, was administered to mice without prior IACUC approval and that the 2% trifluoroacetic acid vehicle used in the formulation may have contributed to the observed toxicity. The associated animal activity was not supported by PHS funds.

The corrective actions consisted of the Principal Investigator (PI) submitting an amendment to include the use of non-pharmaceutical grade test article, copanlisib, and a more appropriate vehicle for drug administration and reviewing the noncompliance event with the PI and Research Associate.

Based on the information provided, OLAW is satisfied that appropriate actions have been taken to investigate, correct and prevent recurrence of the noncompliance. We appreciate having been informed about this matter and find no cause for further action by this Office.

Sincerely,

Signature

Neera V. Gopee, DVM, PhD, DACLAM, DABT
Animal Welfare Program Specialist
Division of Compliance Oversight
Office of Laboratory Animal Welfare

cc: IACUC Chair

Vice Chancellor for Research

4301 W. Markham St., #718
Little Rock, AR 72205-7199

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UAMS
UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES

Lawrence E. Cornett, Ph.D.
lcornett@uams.edu

November 14, 2017

Brent Morse, DVM
Acting Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
Rockledge 1, Suite 360
6705 Rockledge Drive
Bethesda, MD 20892-7982

Dear Dr. Morse:

The University of Arkansas for Medical Sciences (UAMS), in accordance with Assurance A3063-01 and PHS Policy IV.F.3., provides this final report of noncompliance related to an unapproved procedure performed on 30 mice.

On October 9, 2017, an investigator self-reported to the Attending Veterinarian and the IACUC Administrator that her research team had experienced an adverse event related to the use of the drug copanlisib. The study was initiated on October 5, 2017, and 30 animals were administered the drug formulated in 2% trifluoroacetic acid (TFA) water solution via intraperitoneal injection. Within 48 hours, the research team noticed that 14 of the animals had died. The Clinical Veterinarian checked the remaining animals and instructed the research team to euthanize them due to health and welfare concerns.

The Principal Investigator consulted with the IACUC Chairman and determined a more appropriate vehicle for administration of the drug. At that time, it was noted that neither copanlisib nor the vehicle used, TFA, were listed in the IACUC approved protocol. The Principal Investigator then submitted a Request for Veterinary Verification and Consultation (VVC) or Protocol Addendum to add both copanlisib and the vehicle/formulation recommended by the IAUC Chairman to the IACUC approved protocol. That request was approved by VVC on October 20, 2017.

The adverse event report and noncompliance issue were discussed in the convened IACUC meeting on October 20, 2017, where it was also noted that the compound used was non-pharmaceutical grade copanlisib formulated in TFA, which also was not included in the IACUC-approved protocol. It was further noted that the Principal Investigator had submitted a request to add the non-pharmaceutical grade compound and the new vehicle.

No PHS funds were used in this work.

In order to correct this noncompliance and ensure that it does not recur, the following actions were taken:

1. The IACUC subcommittee for compliance, which consists of the IACUC Chairman, the Attending Veterinarian, a Clinical Veterinarian, two voting members of the IACUC, the Research Compliance Officer, and the Research Compliance IACUC Analyst, met to discuss the noncompliance issue on November 1, 2017.
2. Immediately following the IACUC compliance subcommittee meeting, the subcommittee met with the Principal Investigator and the Research Associate. During this meeting, discussions focused on how the noncompliance occurred, what the correct process would have been, and how to proceed in the future.
3. It was noted that the research team has an IACUC approved protocol for P13K inhibitors. They did not understand that each compound and vehicle administered to animals must be listed and approved in that protocol but rather thought that the drug was approved as it was in the same class of drugs approved in the protocol. They began using the P13K inhibitor copanlisib based on publications they had seen on the promising effects of the drug. They actually began administering the copanlisib in a 5% mannitol vehicle a few weeks prior to the adverse event. The formulation was well tolerated with no adverse events, but also was ineffective. Based on the datasheet from the chemical manufacturer, they decided to change the vehicle to 2% TFA water solution, and that formulation proved toxic. The datasheet from the chemical company was reviewed by the subcommittee and all agreed that it was very misleading as it recommended the formulation for "in vivo work."
4. The Principal Investigator and Research Associate were reminded that the purpose of the VVC and Addendum process is to help ensure that all animal work is appropriately reviewed and approved by people with expertise in the area. They were also reminded that any non-pharmaceutical grade compounds must have IACUC approval before use in animals. They now understand that any drug or vehicle administered to an animal must first be explicitly approved by the IACUC, and they agreed that they would ensure they had IACUC approval for any and every compound to be administered to an animal prior to the administration.
5. This event will be discussed again at the convened IACUC meeting to be held on November 15, 2017.

This incident was first reported to you on November 1, 2017, via a telephone call from me as the UAMS Institutional Official.

UAMS is committed to protecting the welfare of animals used in research and appreciates the guidance and assistance provided by OLAW in this regard. Should you have any questions regarding this report, please feel free to contact me.

Thank you for your consideration of this matter.

Sincerely,

Signature

Lawrence E. Cornett, Ph.D.
Vice Chancellor for Research and Institutional Official

Morse, Brent (NIH/OD) [E]

From: Morse, Brent (NIH/OD) [E]
Sent: Wednesday, November 15, 2017 8:20 AM
To: 'Cornett, Lawrence E'
Cc: [redacted]
Subject: RE: Letter from Dr. Larry Cornett - UAMS

Thank you for this report Dr. Cornett. We will send an official response soon.

Regards, Brent Morse

Brent C. Morse, DVM, DACLAM
Acting Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

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-----Original Message-----
From: [redacted] [mailto:[redacted]@uams.edu] On Behalf Of Cornett, Lawrence E
Sent: Tuesday, November 14, 2017 4:49 PM
To: Morse, Brent (NIH/OD) [E] <morseb@mail.nih.gov>
Cc: [redacted]@uams.edu>
Subject: Letter from Dr. Larry Cornett - UAMS

Dr. Morse,

Please see the attached letter from Dr. Larry Cornett. If you have any questions please let me know.

Thank you,

-----Original Message-----
From: PADM135 [mailto:toshiba@uams.edu]
Sent: Tuesday, November 14, 2017 4:53 PM
To: [redacted]
Subject: Send data from PADM135 11/14/2017 16:52

Scanned from PADM135
Date:11/14/2017 16:52
Pages:2
Resolution:600x600 DPI

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A3063-W

Office of Laboratory Animal Welfare

OLAW

Initial Report of Noncompliance

By: BM

Date: 11/2/17

Time: Voicemail

Name of Person reporting: Larry Cornette I.O.

Telephone #: [redacted]

Fax #:

Email:

Name of Institution: Univ of Arkansas for Med. Sci.

Assurance number: A3063

Did incident involve PHS funded activity? _____

Funding component: _____

Was funding component contacted (if necessary): _____

What happened? 30 mice injected w/ PI3K inhibitor not approved in protocol. Also used a diluent not meant for I.P. injection.

Species involved: Mouse

Personnel involved: Researcher

Dates and times:

Animal deaths: 30 mice had to be euthanized.

Projected plan and schedule for correction/prevention (if known): _____

Projected submission to OLAW of final report from Institutional Official:

OFFICE USE ONLY

Case #_____