Annual Report to OLAW

Institution: **Southern Research**
Assurance Number: **D16-00025**
Reporting Period: **01 JAN 2019 – 31 DEC 2019**

This Institution's Institutional Animal Care and Use Committee (IACUC), through the Institutional Official, provides this annual report to the Office of Laboratory Animal Welfare (OLAW).

I. Program Changes [*Select A or B*]

[ ] A. There have been **no changes** in this institution's program for animal care and use as described in the Assurance. [*Skip to Item II.*]

[x] B. Change(s) in this institution's program for animal care and use as described in the Assurance have occurred during this reporting period. (FAQ 6)

Select all that apply:

[ ] This institution's AAALAC accreditation status has changed (PHS Policy IV.A.2.).

[ ] AAALAC Accredited – Category 1

[ ] Non-Accredited – Category 2

[x] This institution's program for animal care and use has changed (PHS Policy IV.A.1.a-i.). [*Attach a full description of the changes.*]

[x] The individual designated by this institution as the Institutional Official has changed. [*Provide name, title(s), address, e-mail, phone, and fax numbers in Item V.*]

[x] The membership of this institution's IACUC has changed. [*Provide current roster of members in Item VI.*]

II. Semiannual Evaluations

This IACUC has conducted semiannual evaluations of the institution's program and inspections of the institution's facilities (including satellite facilities) on the dates below. Reports of the evaluations and inspections have been submitted to the Institutional Official. The reports include any IACUC-approved departures from the *Guide* with a reason for each departure, any deficiencies (significant or minor) that were identified, and a plan and schedule for correction of each deficiency. [*Do not provide semiannual reports unless they include a minority view.*]

A. Program Evaluations

[*Two dates (month/day/year) must be provided to satisfy the PHS Policy requirement that evaluations be done at 6 month intervals. If the IACUC conducted more than 2 evaluations of the program during the reporting period, please attach a list showing the dates.*]

Date 1:April 23,24,26,29,30 2019	Date 2:October 21,22,23,24,29,30,31

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B. Facility Inspections

[Two dates (month/day/year) must be provided to satisfy the PHS Policy requirement that facility inspections be done at 6 month intervals. If the IACUC conducted more than 2 inspections of each site during the reporting period, please attach a list showing the dates.]

Date 1: April 9,11,12,19,23 2019 FINAL REPORT sent to IO 29 MAY 2019	Date 2: OCT 17,22,23,25 FINAL REPORT sent to IO 09 DEC 2019

III. Minority Views [*Select A or B*]

[ ] A. There were **no minority** views during this reporting cycle.

[x] B. Any minority views submitted by members of the IACUC regarding reports filed under PHS Policy IV.F. for this reporting cycle are attached.

IV. Signatures

IACUC Chairperson	**Institutional Official**
Name: Deborah S. Gohegan	Name: Dr. April Brys
(b) (6)	(b) (6)
Signature:	Signature:
Date: 08 JAN 2020	Date: 08 Jan 2020

V. Change in Institutional Official

Name: Dr. April Brys	
Title: VP Drug Development	Degree/Credential: PhD
Name of Institution: Southern Research	
Address: [*street, city, state, zip code*] 2000 9th Ave South Birmingham, AL 35205	
E-mail: abrys@southernresearch.org	
Phone: (b) (6)	Fax:

VI. Change in IACUC Membership [*Current roster*]

Institution: Southern Research			
IACUC Contact Information			
Address: [*street, city, state, zip code*] 431 Aviation Way Frederick, MD 21701			
E-mail: dgohegan@southernresearch.org			
Phone: (b) (6)		Fax: (b) (6)	
IACUC Chairperson			
Name: Deborah S. Gohegan (Member #13)			
Title: Dir Lab Operations DDV, DDV Tech Ops		Degree/Credentials: BS, LATG	
PHS Policy Membership Requirements***:			
IACUC Roster [*Provide below or attach*]			
Name of Member/ Code*	Degree/ Credential	Position Title/ Occupational Background**	PHS Policy Membership Requirements***
James Toomey/ #4[1]	DVM	Sr. Mgr. Vet Services/Attending Vet	Veterinarian***
(b) (6)			Practicing Scientist ***
			Member
			Member
			Member
			Member
			Member
			Vice-Chairperson
			Non-Affiliated/Non-Scientist***
			Member
			Member
			Member
			Member
			Member
			Non-Voting

[1] Primary Location-Birmingham, AL / [2] Primary Location-Frederick, MD

* Names of members, other than the chairperson and veterinarian, may be represented by a number or symbol in this report to OLAW. Sufficient information to determine that all appointees are appropriately qualified must be provided and the identity of each member must be readily ascertainable by the institution and available to authorized OLAW or other PHS representatives upon request.

** List specific position titles for all members, including nonaffiliated (e.g., banker, teacher, volunteer fireman; not "community member" or "retired").

*** PHS Policy Membership Requirements:

Veterinarian	veterinarian with training or experience in laboratory animal science and medicine or in the use of the species at the institution, who has direct or delegated program authority and responsibility for activities involving animals at the institution.
Scientist	practicing scientist experienced in research involving animals.
Nonscientist	member whose primary concerns are in a nonscientific area (for example, ethicist, lawyer, member of the clergy).
Nonaffiliated	individual who is not affiliated with the institution in any way other than as a member of the IACUC, and is not a member of the immediate family of a person who is affiliated with the institution. This member is expected to represent general community interests in the proper care and use of animals and should not be a laboratory animal user. A consulting veterinarian may not be considered nonaffiliated.

[Note: all members must be appointed by the CEO (or individual with specific written delegation to appoint members) and must be voting members. Non-voting members and alternate members must be so identified.]

SOUTHERN RESEARCH

Solving the world's hardest problems.

The following changes to the Institution's Program for Animal Care and Use, as described in our Assurance D16-00025, are as follows:

1. [redacted] (b) (6)
2. [redacted]
3. [redacted]
4. [redacted] (b) (6) Deborah Gohegan took the position of Chairperson 18 MAR 2019. The Org chart was updated in the CACUPG Issue #31, on 01 APR 2019 as approved at the 28 MAR 2019 IACUC meeting.
5. Policy #18 – Dog Walking Policy was added to the CACUPG Issue #31, on 01 APR 219 as approved at the 28 MAR 2019 IACUC meeting.
6. [redacted] (b) (6) Dr. Ray Watts became Interim CEO on 09 MAY 2019.
7. Dr. Watts appointed Dr. Brys-Vice President of DDV- the IO for Southern Research on 14 MAY 2019.
8. The Org chart was updated in the CACUPG Issue #32 on 28 MAY 2019 as approved at the 23 May 2019 IACUC meeting. Dr. Ray Watts was added as Interim CEO and [redacted] (b) (6) (b) (6)
9. [redacted] (b) (6)
10. Guidelines for Retro-Orbital Blood Collection in Rodents was added to Policy # 4- Policy of Blood Collection in Laboratory Animals. Policy #19- Policy on Social Acclimation was approved at 26 SEP 2019 IACUC. CACUPG #33 was updated with these additions.

Attached Minority Views as excerpted from the IACUC minutes of 27 JUN 2019.

SR SOUTHERN RESEARCH

Solving the World's Hardest Problems

The Chairperson asked the committee to review the Summary Report and asked if there were any questions.
Member 4 reviewed his responses to the contingencies for ACUP 19-01-003B Amendment #1, "IND-Supporting Studies (Pharmacokinetic and Toxicity) for a Biological Therapeutic (H2319) in Non-Human Primates (NHPs). Member 4 stated he did not object to the approval of the Amendment, rather he did not endorse some of the responses that the Sponsor made. The contingencies with Member 4's minority views in red are as follows:

Contingency 1: What is the justification for dosing with 5mg/kg? What specifically is to be learned from this study? How will these results help clinical treatment moving forward? Has a harm vs. benefit analysis been performed?

Response: I addressed these questions to the sponsor, and the sponsor's responses are as follows:

- The high dosage selection of 5mg/kg is based on previous finding that it would show drug-specific effects necessary to understand its use in 2 weeks repeated dose scenario without producing incidence of fatalities that would prevent a meaningful evaluation. To recap the single dose study result, we agree that morbundity/mortality was observed that are TA related in the groups 10 and 20mg/kg. However, in 5mg/kg group only 1 animal out of total 6 was found death, where the deceased animal was found only 3 days after injection (not sufficient enough time for death related to neutropenia). So it is scientifically justifiable to presume this is not TA-related event and therefore needs further investigation.
    - I do not believe this to be an accurate statement. Setting aside for a moment that the animal was clearly ill because of the immunosuppressive effects of the leukopenia, all of the animals dosed on the previous study, at all dose levels including 5mg/kg showed adverse effects from the test article; death is not the only relevant adverse effect and there should not be such a tunnel vision focus on it. All animals demonstrated significant post-dose leukopenia and anemia. Grossly many other animals on study had other indications of minor superficial infections. To state that because only 1 animal in the lowest dose group died means that "it is scientifically justifiable to presume this is not TA-related event" is indefensible. Stating that 3 days is "not sufficient enough time for death related to neutropenia" is factually inaccurate. – JT
- H2319 is being developed as an anti-cancer treatment for those patients with no other treatment option. The goal of this study is to study toxicology profile of H2319 and then evaluate its toxicity upon administration into animals. We have already established that H2319 could cause severe neutropenia when administered above certain dosage level via single dose toxicology study. Therefore, it is scientifically justified to test using animals the dosage level below the level in which TA-related morbundity/mortality was observed (10mg/kg).
    - Again, TA-related morbundity/mortality was observed was observed at 5mg/kg. Arguing otherwise cannot be justified. – JT
- In case of cancer patients who undergo chemotherapy, about 40~70% of them display neutropenia frequently as adverse event, where patients' health are closely monitored and treated (GM-CSF treatment), which is an already established and well-known method.
- In order to accurately evaluate H2319's toxicology and neutropenia induction it is absolutely necessary for us to test dosage level equivalent to causing grade 3 or 4 (hospitalized) to grade 5 (mortality). To do so is to use 5mg/kg as high dose. Therefore, it is absolutely necessary to test 5mg/kg in repeated dose setting.
    - The observed test article related anemia and thrombocytopenia deserve more attention. The anemia observed at 5mg/kg on the previous study approached life threatening levels after just 1 dose. Is it worth investigating a repeat dose? I see no reason to assume that the anemia would do anything but get worse with a repeat dose. – JT
- It is ideal to find a dose where test subject monkeys safely survive the treatment. However it is more important for us to test H2319's toxicity prior to human clinical trial for advanced cancer patients. It is therefore strategically advantageous and scientifically meaningful to administer wide dose range of H2319 to evaluate its toxicity rather than test doses where it will show little or no response to monkeys. This befits much more nicely to the goal of a toxicology study.
    - Again, there were significant adverse effects observed in all animals dosed at 5mg/kg. Death is not the only possible adverse effect. But setting that aside, death in 33% of the males in a dose group likely seems significant. – JT
- It is to our goal to properly assess toxicological dose range and efficacious dose range to evaluate H2319's therapeutic window. To this aim the use of 5mg/kg is necessary to satisfy our objective.

SOUTHERN RESEARCH
Solving the World's Hardest Problems

Contingency 2: Revise the Amendment to include escalated dosing starting with the lower doses. Please be sure to include the criteria for moving forward with dosing at the higher concentration (ie. If the blood test results show no sign in improvement at the lower doses, will the higher dose be administered?)

Response: The ACUP amendment has been revised to reflect that dosing will start with Groups 1 and 2 (1, 3 mg/kg), and then depending on the findings at these 2 dose levels, Group 3 dosing may or may not occur (highlighted text in Section 2.4). The criteria for moving forward with dosing Group 3 (5 mg/kg) is as follows:

- Clinical signs:
  - If no adverse clinical signs are observed at 1 and 3 mg/kg, then we will move forward with dosing Group 3
  - If adverse clinical signs/morbundity are observed, then we will not move forward with dosing Group 3
- Hematology data:
  - If blood parameters appear to be returning to normal after receiving 1 and 3 mg/kg, then we will move forward with dosing Group 3
  - If blood parameters do not appear to be returning to normal after receiving 1 and 3 mg/kg, then we will not move forward with dosing Group 3
  - In my opinion more clarity would be beneficial here. - JT

There was no further discussion.