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TITLE: Adenosine A3 Receptor Agonists for the Treatment of Neuropathic Pain

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13. SUPPLEMENTARY NOTES

None

14. ABSTRACT

Our goal is to develop BIO-205, a highly-selective agonist for the A3 adenosine receptor subtype, as an orally-administered monotherapy analgesic for the treatment of neuropathic pain and as an adjunct for opioid analgesics that increases analgesic efficacy while blocking the opioid's unwanted effects (addiction potential, tolerance, and physical dependency). To reach this goal, the current grant supports drug manufacture, the development of analytic methods to measure the drug in biologic fluids, animal safety and toxicology studies, and the preparation of requisite documentation for an application to the FDA for an Investigational New Drug (IND) designation. In the past year we have successfully completed all tasks except for document preparatoin. Completion of documents (an Investigator Brochure and a plan for Phase 1 studies) are awaiting receipt of the toxicology Final Reports. These are expected prior to the end of 2020, which would put us on schedule for an FDA submission in Q1 of 2021.

15. SUBJECT TERMS

None Listed

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1. INTRODUCTION.

BioIntervene has discovered novel potential analgesic drugs that are not narcotics and are non-addictive. These drugs excite the A3 receptor subtype of adenosine receptor. Unlike currently available analgesic drugs, these compounds are effective against both the usual kinds of chronic inflammatory pain syndromes (for example, osteoarthritis) but also against the treatment-resistant neuropathic pain syndromes that occur when nerves are injured by disease, toxins or trauma. Our goal is to develop our lead drug candidate, BIO-205, as an orally-administered, monotherapy analgesic for the treatment of neuropathic pain. Moreover, we have found that BIO-205 greatly amplifies the analgesic efficacy of morphine-like drugs while simultaneously blocking the opioid's unwanted effects (the euphoria that promotes addiction, analgesic tolerance, and physical dependency). This suggests that adding BIO-205 to an opioid analgesic will yield superior analgesia while minimizing the potential for opioid abuse. The current grant supports drug manufacture, the development of analytic methods to measure the drug in biologic fluids, animal safety and toxicology studies, and the preparation of the requisite documentation for an application to the Food and Drug Administration (FDA) for an Investigational New Drug (IND) designation. The IND is required before we can test BIO-205's safety and efficacy in man. This Annual Report covers the second 12 months of progress. The original duration of this grant was for 18 months 9September 30, 2018 to March 30, 2020). We were granted a one-year's no-const extension on 22 January 2020, such that the grant's new termination date is March 29, 2021.

2. KEYWORDS.

Addiction, Analgesia, Analgesic tolerance, Drug manufacture, IND, FDA, Opioid, Opioid adjunct, Neuropathic pain, Chronic pain.

3. ACCOMPLISHMENTS.

What were the major goals of this project? As outlined in the Statement of Work, there are 5 Major Tasks supported by this grant. All of the manufacturing and safety/toxicology studies described below are conducted under FDA-mandated Good Laboratory Practices (GLP) guidelines. Safety/toxicology studies in two species are required by the FDA. We have chosen

rat and monkey; the dog was found to be unacceptable as it metabolizes the drug differently than mouse, rat, monkey, and man. The Major Tasks and Subtasks are:

Major Task 1: Drug manufacture and analytics.

1.1: Stage I – manufacture 100 g of BIO-205.

1.2: Analysis of Stage I compound.

1.3: Stage II – manufacture 650 g of BIO-205.

1.4: Analysis of Stage II compound.

Major Task 2: Toxicology studies.

2.1: Rat repeated dose, oral dose-range finding and toxicology study (118 rats).

2.2: Rat, 4-week oral dosing toxicology study with 4-week recovery (168 rats).

2.3: Monkey, single oral dose escalation and repeated dose range-finding and toxicology (14 rhesus monkeys).

2.4: Monkey, 4-week oral dosing toxicology study with 4-week recovery (16 rhesus monkeys).

Major Task 3: Safety pharmacology studies.

3.1: CNS safety pharmacology in rats (64 rats).

3.2: Pulmonary safety pharmacology in rats (64 rats).

3.3: Cardiovascular safety pharmacology in monkeys (8 rhesus monkeys).

3.4: *In vitro* hERG inhibition.

3.5: *In vitro* Genotoxicity studies: Ames assay, micronucleus assay, and chromosomal aberration assay.

Major Task 4: Bioanalysis/formulation analysis.

4.1: Rat bioanalytical method validation.

4.2: Monkey bioanalytical method validation.

4.3: Toxicology studies formulation validation.

4.4: hERG study formulation validation.

4.5: Genotoxicology study formulation validation.

Major Task 5: Approvals and prepare IND.

5.1: Submission to ACURO.

5.2: FDA planning meeting.

5.3: Design protocol for Phase I studies.

5.4: Prepare Investigator's Brochure.

5.5: Prepare and submit IND.

What was accomplished under these goals?

Major Task 1: Drug manufacture and analytics. This Task was completed in early Y2. Liquid chromatography and mass spectrometry analytics confirmed that the drug product has the correct molecular structure and showed that the product contains no significant impurities.

Major Task 2: Toxicology studies. Repeated dose, oral dose-range finding and toxicology studies for both rat (Subtask 2.1) and monkey (Subtask 2.3) were successfully completed this year. The FDA regulations for an Investigational New Drug submission require studies with 4-weeks of oral dosing followed by 4-weeks of recovery in two species. The in-life portion of these key toxicology studies recovery, rat (Subtask 2.2) and monkey (Subtask 2.4), have been completed. Tissues have been sent for histological study (i.e., microscopic exam). These studies were successful. We established a NOAEL dose (no adverse effect level, i.e., a high dose that demonstrates toxicity) that is far greater than our anticipated therapeutic dose. This indicates that our compound will have a large safety window. Draft study reports are in hand and Final, certified reports are expected before the end of 2020.

Major Task 3: Safety pharmacology studies. FDA approval of an Investigational New Drug requires various tests for safety. All of these studies were successfully completed this year. Our compound had no adverse effect in a behavioral assay of Central Nervous System pharmacology (Subtask 3.1), in studies of pulmonary function (Subtask 3.2), and in heart safety studies in monkeys (Subtask 3.3.). Our compound has no significant effect on a cardiac muscle ion channel called hERG (Subtask 3.4). Effects on hERG are often predictive of cardiotoxicity.

Our compound was also negative in the Ames assay for drug-induced genetic mutations (Subtask 3.5).

Major Task 4: Bioanalysis/formulation analysis. Bioanalysis studies showing that we can measure the levels of our compounds in biological fluids (urine and plasma) from rats or monkeys were completed successfully. Formulation studies for the compound solutions used in the toxicology, hERG, and Ames studies (Subtasks 4.3, 4.4, and 4.5 respectively) were completed successfully.

Major Task 5: Approvals and prepare IND. As required for an Investigational New Drug (IND) submission to the FDA, we are preparing the Investigator Brochure (IB) and the study protocols for the Phase I first-in-man safety trials.

We have prepared a draft IB that is current up to the results of the key 4-week toxicology studies in rat and monkey. The IB will be completed when we have the certified Final Report of these studies (which will include the results of the ongoing histological examination).

The IND submission must include a description of the plans for Phase 1 first-in-man safety studies. The Phase 1 studies are primarily aimed at safety issues but they also determine which doses of BIO-205 can be given without producing unacceptable side-effects. As is usual for such trials, we will test healthy human volunteers. The Phase 1 protocol is under development.

An FDA planning meeting is anticipated early in 2020. Its primary purpose is for an informal review of our Phase 1 study protocol.

What opportunities for training provided? Nothing to report – not applicable.

How were the results disseminated to communities of interest? Nothing to report – not applicable.

What do you plan to do during the next reporting period? We will finish the Investigator Brochure was soon as the Final Reports of the toxicology studies are received. We will finish the protocols for the Phase 1 studies. When these two documents are complete, we will submit

an application for an Investigational New Drug to the FDA. We anticipate doing this submission in Q1 of 2021.

4. IMPACT.

Nothing to report – not applicable.

5. CHANGES/PROBLEMS.

Changes in approach. None.

Actual or anticipated problems or delays. None.

Changes with impact on expenditures. The grant's duration was September 30, 2018 to March 30 2020 (18 months). No new expenditures have been made since the grant's termination date. A request for reimbursement of approximately $130,000 in expenditures made prior to grant termination is pending receipt of an invoice We are now operating under a one-year no-cost extension (granted 22 January 2020; duration: 30 March 2020 to 29 March 2021).

Significant changes in use or care of animals, biohazards, etc. No changes. The in-life portion of all studies has been completed and all animals have been deposed of according to protocol. No further animal work will be done. ACURO has been informed that all animal use protocols have been terminated.

Significant changes in use or care of human subjects. Not applicable.

Significant changes in use or care of animal subjects. None.

6. PRODUCTS.

Publications, conference papers, presentations. None, not applicable.

Website or other internet. None.

Technologies or techniques. None.

Inventions, patent applications, licenses. None.

Other products. None.

7. PARTICIPANTS & OTHER ORGANIZATIONS

What individuals have worked on this project?

Name	Gary J. Bennett, PhD	Daniela Salvemini, PhD
Project role	PI	Consultant
Nearest person month worked	24 months	18 months
Contribution to project	Initiation and supervision of all CRO contract work; review and approval of all work and work reports; all financial and reporting tasks.	Review of contracts, CRO progress reports, safety and toxicology protocols, analytics development and draft Investigators Brochure and Phase I study protocols.
Funding support	None other than this grant	Not applicable.

Has there been any change in the active other support during this reporting period of the PI or senior/key personnel? Nothing to report.

What other organizations were involved as partners? None.

8. SPECIAL REPORTING REQUIREMENTS.

Collborative awards. None.

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9. APPENDICES. None.