AWARD NUMBER: W81XWH-16-1-0719

TITLE: "Preclinical Development of a Novel Antimalarial Agent"

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CONTRACTING ORGANIZATION: Broad Institute
Cambridge, MA 02142

REPORT DATE: January 2019

TYPE OF REPORT: Final Report

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
January 2019	FINAL	30SEP2016 - 29SEP2018

4. TITLE AND SUBTITLE

"Preclinical Development of a Novel Antimalarial Agent"

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-16-1-0719

5c. PROGRAM ELEMENT NUMBER

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Broad Institute, Inc.
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Cambridge, MA 02142

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

We developed a series of compounds that show excellent *in vivo* antimalarial efficacy in mouse models against blood-, liver- and transmission-stage parasites. We demonstrated that these compounds act *via* a novel mechanism-of-action (inhibition of *P. falciparum* cytosolic phenylalanyl tRNA synthetase, *Pf*cPheRS) and as such this program represents an important development to combat antimalarial resistance. A lead compound, BRD5018, was identified that had potent *in vivo* efficacy and an improved safety profile relative to early lead compounds. In biochemical aminoacylation assays BRD5018 had weak inhibition of the enzymatic activity of human cPheRS while potent inhibition of *Pf*cPheRS. We defined the API manufacturing route and prepared sufficient API to enable non-GLP nonclinical studies such as in vivo efficacy and non-rodent DRF studies. We also performed physicochemical characterization, analytical development and salt selection studies on BRD5018. A synthetic route was developed that enabled the delivery of sufficient material to support non-rodent CV and dose range finding toxicity study studies. We also developed a completely new low-cost synthetic route to BRD5018. To support toxicological studies and human dose predictions, a series of pharmacokinetic studies were conducted in rodents and dogs. Overall, the toxicity profile was consistent across preclinical species, with primary findings related to gastrointestinal (GI) toxicity likely due to local irritation and no serious systemic toxicity identified. The GI toxicity is monitorable and reversible. These studies fulfill key steps on the path to first-in-man clinical studies for BRD5018 as an antimalarial agent.

15. SUBJECT TERMS

Malaria, phenylalanyl tRNA synthetase, novel mechanism-of-action, bicyclic azetidine, preclinical development.

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
Unclassified	Unclassified	Unclassified	Unclassified	21	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

U.S. service members deployed to endemic areas should be considered at high risk for malaria infection. The emergence of resistance to front-line antimalarial therapies has created an urgent need for drugs with new mechanisms-of-action (MoA). Additionally, while most antimalarials target the symptomatic asexual blood stage parasites, drugs targeting the liver and transmission stages are essential to protect populations such as military personnel operating in endemic regions. The Broad Institute, in collaboration with Eisai Inc., has developed a series of compounds that show excellent *in vivo* antimalarial efficacy including single-dose cures in *P. berghei* and *P. falciparum* mouse models against blood-, liver- and transmission-stage parasites. We have demonstrated that these compounds act *via* a novel mechanism-of-action (inhibition of *P. falciparum* cytosolic phenylalanyl tRNA synthetase, *Pf*cPheRS) and as such this program represents an important development to combat antimalarial resistance. Optimization studies produced a candidate, bicyclic azetidine BRD5018, that had good *in vitro* and *in vivo* efficacy and suitable ADME, PK and *in vitro* safety parameters for progression towards advanced studies. The purpose of this proposal was to optimize the synthetic route for this development candidate and perform the necessary Chemistry, Manufacturing and Control (CMC) studies. Additionally, our goal was to complete non-GLP dog cardiovascular safety and rodent and dog dose range finding toxicology studies to support follow-on IND enabling studies.

2. KEYWORDS:

3.

Malaria, novel mechanism-of-action, phenylalanyl tRNA synthetase, bicyclic azetidine, preclinical development, IND enabling studies, antimalarial resistance.

4. ACCOMPLISHMENTS:

The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official 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.

Specific Aim 1: Provide scaled-up material for preclinical studies

Define API manufacturing route

1. Optimize current synthetic route (**100% complete**)
2. Identify potential alternate synthetic route (**100% complete**)
3. Identification of manufacturing site or CMO **(100% complete)**
4. Technology transfer to pilot plant **(100 % complete)**

5. Manufacture API at 1 kg scale (non GMP) **(100 % complete)**

Specific Aim 2: Perform physicochemical characterization, analytical development and early formulation studies

5. Salt selection and physicochemical characterization (**100% complete**)

6. Analytical method development and qualification **(100% complete)**

7. Stability assessment (**100% complete**)

8. Initial formulation **(100% complete)**

Specific Aim 3: Perform non-GLP nonclinical studies

9. Perform *in vivo* efficacy studies (blood stage) (**100% complete**)

10. Perform *in vivo* efficacy studies (liver and transmission stages) (**0% complete**)

11. Single dose escalating non-rodent DRF studies MTD study (**100% complete**)

12. Dose range finding study (non-rodent model) **(100% complete)**

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.

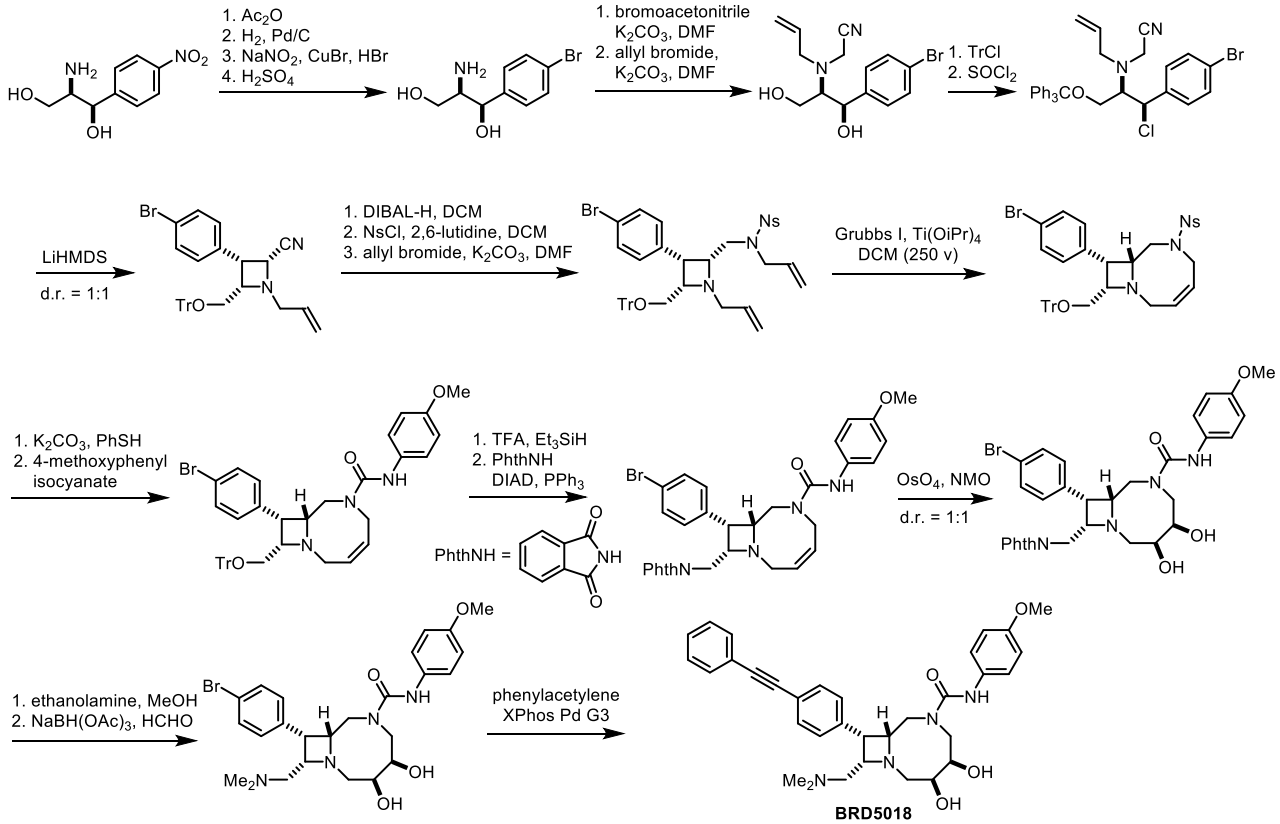
1) Major activities;
Major activities include optimizing the current synthetic route and developing a completely new low-cost synthetic route to BRD5018. We defined the API manufacturing route and prepared sufficient API to enable non-GLP nonclinical studies such as *in vivo* efficacy and non-rodent DRF studies. We also performed physicochemical characterization, analytical development and salt selection studies on BRD5018.

2) Specific objectives;
Our goals were to 1) optimize the synthetic route to BRD5018 focusing on reducing the number of steps requiring chromatography to provide sufficient material to support safety studies, 2) perform physicochemical, pharmacokinetic and pharmacodynamic characterization, analytical development and salt selection studies on BRD5018 and 3) perform non-GLP nonclinical studies.

3) Significant results or key outcomes

1) Optimized the existing synthetic route and developed a novel lower-cost route to BRD5018.

We had three strategies to deliver sufficient material for *in vivo* safety studies and minimize the cost-of-goods of a therapeutic developed from this series. The initial synthetic route to the series was designed to enable medicinal chemistry optimization and required chromatography purification at every synthetic intermediate. Process chemistry optimization focused on reducing the number of intermediates that required chromatography, generally estimated to account for 80-90% of the cost of production. The optimized synthetic route allows for the preparation of BRD5018 with a fivefold relative cost reduction, compared to the original, achieved by eliminating 13 chromatographic purifications (Figure 1). This optimized route supplied sufficient drug substance (250g) for pre-clinical safety, salt selection, and formulation studies (Scheme 1).



Scheme 1. Initial optimized synthetic route to BRD5018 that supplied sufficient drug substance for pre-clinical safety, salt selection, and formulation studies.

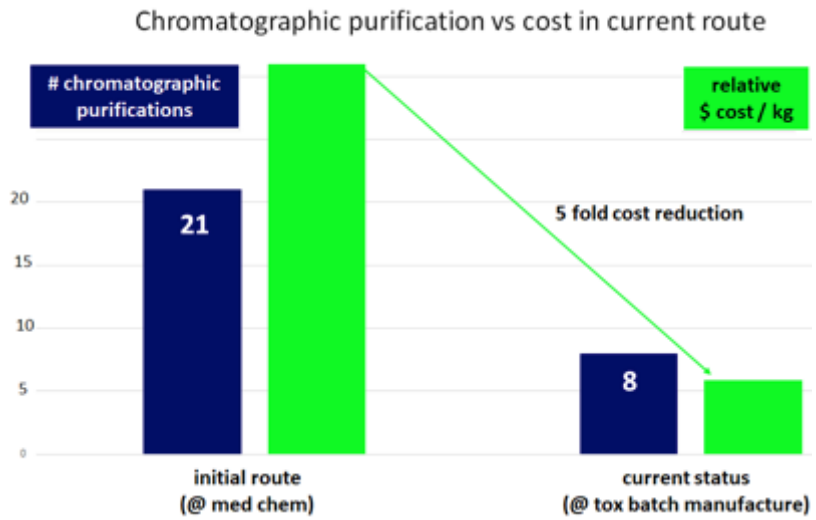
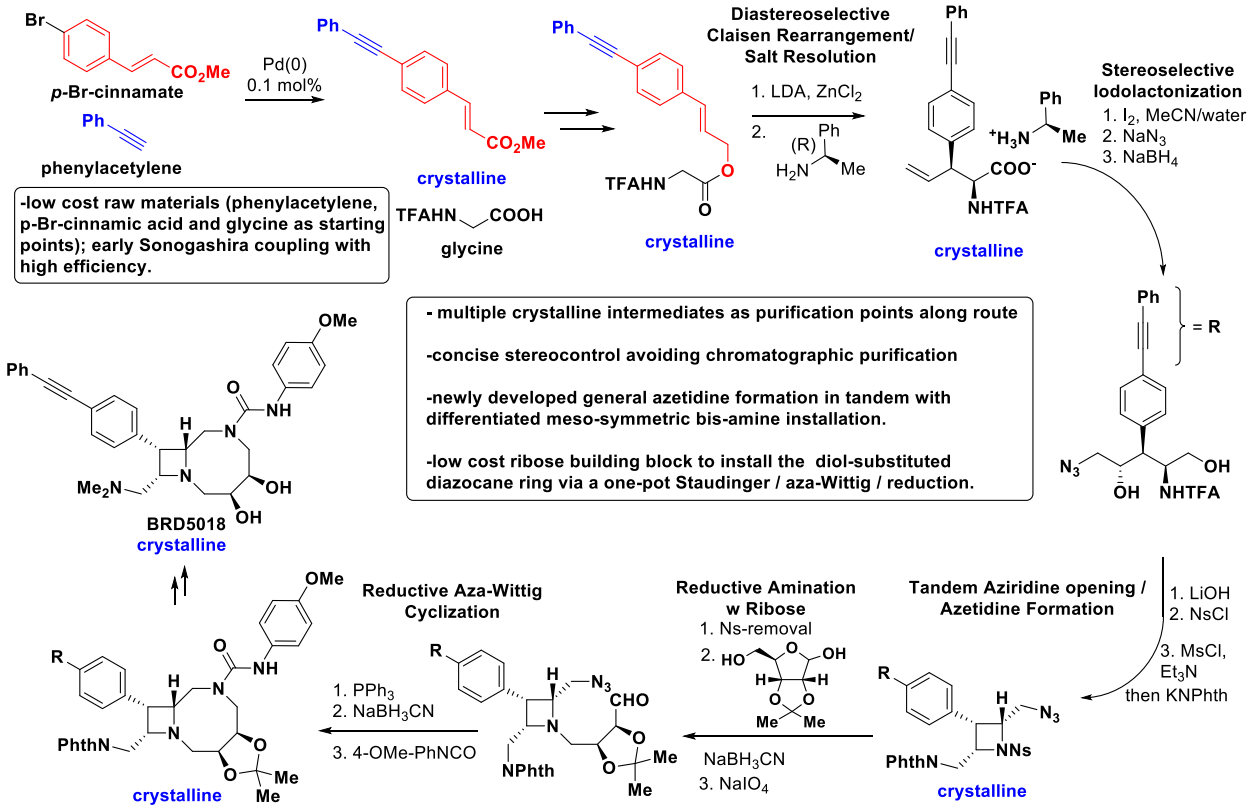


Figure 1. Cost and throughput improvement for the preparation of BRD5018 using the initial synthetic route.

Additionally, we initiated a study towards the identification of a completely new low-cost synthetic route to BRD5018 incorporating high yielding/stereoselective reactions coupled with crystallization-based purification methods. This strategy is based on chemistry that utilizes low-cost raw materials in efficient and stereoselective chemical transformations to build the core ring system and its appendages. One of the key features of the new route include an early construction of the diphenylacetylene group via a highly efficient Sonogashira reaction with low catalyst loading (e.g. 0.1 mol% Pd-catalyst). A novel tandem azetidine formation process from an amino-diol intermediate was developed leading to formation of a key crystalline azetdine intermediate with differentiated amine appendages. Furthermore, we used a diol building block derived from D-ribose (readily available sugar) to construct the 8-membered ring of analogues that incorporate a (8R,9S)-syn diol (such as BRD5018). We successfully demonstrated the preparation of BRD5018 using this route. The newly developed route (Scheme 2) will be implemented in future API manufacturing campaigns and is expected to provide substantial cost advantages over the existing synthesis.



Scheme 2. New low-cost synthetic route to BRD5018 incorporating high yielding/stereoselective reactions coupled with non-chromatographic purification methods.

2) Completed physicochemical, pharmacokinetic and pharmacodynamic characterization, analytical development and salt selection studies on BRD5018.

The pKa values of BRD5018 were determined to be less than 3, 8.2 and 8.9 by capillary electrophoresis at the ionic strength of 0.05 and at 25 °C. The permeability coefficient for BRD5018 could not be determined by parallel artificial membrane permeability assay (PAMPA) due to its poor solubility at neutral pH. The measured log *D* value at pH7 was 3.2. The preliminary PK studies showed that the bioavailability of mouse, rat and dog were 46%, 19%, and 75%, respectively. Based on the PK results, gastrointestinal availability (Fa × Fg) was calculated to be approximately 58%, 25%, and 75%, respectively. In human projection, bioavailability (F) and gastrointestinal availability Fa are estimated to be 77%, and 85%, respectively. Based on these estimations, BRD5018 would be classified as a highly permeable compound.

BRD5018 showed excellent stability in liver microsomes and hepatocytes of five different (including preclinical) species. CYP reaction phenotyping using human recombinant CYP enzymes showed that CYP3A4 was the major metabolic pathway for the minimal metabolism of BRD5018 observed. Due to the excellent stability of BRD5018 in standard hepatocyte assays we performed cross species incubation (mouse, rat, dog, monkey and human) using the HμREL® cocultured plated hepatocytes assay, which enables longer incubation time, therefore leading to increased metabolism. Metabolite identification studies in mouse, rat, dog, monkey and human hepatocytes showed a similar metabolite

profile across all species and did not identify any metabolites unique to human. To support toxicological studies and human dose predictions, a series of pharmacokinetic studies were conducted in rodents and dogs. Low *in vivo* hepatic clearance was observed in mouse, dog and rat PK studies, which is consistent with the minimal degradation seen across species in hepatic microsomes and hepatocytes.

During this reporting period we developed a human cPheRS biochemical assay. Compounds from the series showed potent inhibition of the aminoacylation activity of *Pf* cPheRS with no significant inhibition of the enzymatic activity of human cPheRS. This trend was also observed in microscale thermophoresis binding assays where a large difference in Kd (SI 600-1574) was observed with two compounds tested against human and *Pf* cPheRS. In addition, we have established *P. vivax* and dog cPheRS biochemical assays. BRD5018, showed potent inhibition (IC_{50} = 0.09 μM) of the aminoacylation activity of *P. vivax* PheRS, which is similar to the IC_{50} observed with *Pf* cPheRS. BRD5018 showed no significant inhibition of the aminoacylation activity of dog cPheRS.

The pharmacokinetic profile of BRD5018 in mouse, rats and dogs after intravenous dosing was characterized by low plasma clearance, moderate to high volume of distribution, and a long half-life (11 to 75 hours). A bile duct cannulation study was performed with BRD5018 (IV, 1 mg/kg) in rats, with and without rifampicin (OATP inhibitor), to determine the significant routes of clearance. Metabolic cages and bile duct cannula facilitated the collection of plasma, urine, bile, and feces. Renal elimination was a minor route and accounted for less than 1% of the total dose administered, while biliary elimination contributed approximately 10-14% of total clearance, and fecal elimination accounting for 8-9% of total clearance. Collectively, the data supports the idea that clearance of BRD5018 is predominantly via slow metabolism. Additionally, slightly decreased biliary elimination was observed in the presence of rifampicin suggesting that BRD5018 is likely an OATP1B substrate *in vivo*. This finding is supported by in vitro hepatic uptake assay showing that rifampicin is capable of inhibiting uptake of BRD5018. Salt selection studies were carried out on BRD5018 using thirty acids and various organic solvents. From this study the crystalline free form, showing superior characteristics in terms of solubility, hygroscopicity and stability, was selected as API form for further development. Of the three forms shortlisted for further studies (crystalline free form, tosylate and amorphous free form) the crystalline free form was indeed the least hygroscopic (3.2 % weight gain at 25 °C / 95% RH). The crystalline free form also had greater solubility in FaSSIF than the tosylate and was chemically and physically stable at solid state (no change of impurity profile was observed even after 70º C, 75% RH after a week). The crystalline free form had acceptable exposure levels in a rat PK study.

3) Performed non-GLP nonclinical studies

Study Type	Dose (mg/kg)	Findings
Rat oral 3-day DRF with 14-day recovery	0, 60, 180 3/sex/group	≥60 mg/kg • Dose dependent weight loss/ ↓food consumption • Reversible GI toxicity (regenerative hyperplasia) 180 mg/kg: MTD (21% BW loss D7, reversible)
Dog oral 3-day MTD	10, 30, 100 1/sex/group	• Well tolerated up to 100 mg/kg • Vomiting without accompanying weight loss • No change in clinical pathology (D4/14) • Exposure increased less than dose proportional
Dog oral 3-day DRF with 10-day recovery	100, 300 1/sex/group	≥100 mg/kg • Vomiting / diarrhea • Transient tremors D2 /D3 • Dose dependent weight loss • No change: serum chemistry (D4/10), hematology (D4), gross necropsy or histopathology 300 mg/kg: MTD (20% BW loss D8)
Dog exploratory CV (oral)	0, 30, 100, 450 Dose escalation 4 dogs	• No findings of concern • Plasma concentrations up to 2.7µg/ml

Figure 2. Overview of non-GLP nonclinical studies and significant findings.

In a SCID mouse efficacy study using a single oral dose of BRD5018 (P.O., 3, 10, 30, 60, 120 mg/kg) potent *in vivo* antimalarial activity was observed with >99.8% reduction of parasitemia at day 7 at all doses tested at and above 30 mg/kg. The exposure based on C_{max} and $AUC_{0\text{-}24h}$ increased in an approximately dose-proportional manner. The ED_{90} is estimated to be between 3-10 mg/kg (single dose), which compares favorably with chloroquine and mefloquine (ED_{90} 4.3 and 7.7 mg/kg/day respectively, 4-day dosing). *In vivo* efficacy studies against *P. falciparum* liver and transmission stages were not completed for BRD5018 due to unavailability of mosquitos required for these experiments at the time of execution. Additionally, we were in contact with Walter Reed Army Institute of Research, LTC Mara Kreishman-Deitrick, Ph.D. as well as MAJ Pybus and his Deputy Ms. Patty Lee to determine if AFRIMS may be able to execute the studies. In the end, the discussion took longer than expected and our grant period ended without a resolution. Although the studies were not completed, we previously established that a related initial lead compound (BRD7929) had potent *in vivo* efficacy against *P. falciparum* liver and transmission stages and given this we decided to focus on establishing sufficient safety prior to testing BRD5018 for activity against these additional stages of the parasite life cycle.

BRD5018 was tested in the Glu/Gal assay (cyprotex) for its potential to impair mitochondrial function. BRD5018 did not cause cell loss at any concentration tested for either the glucose condition or the galactose condition and tested negative as mitochondrial toxins in this assay.

In addition, in a screening Ames assay, BRD5018 was not mutagenic in bacteria and did not cause increased numbers of revertant colonies in *Salmonella typhimurium* strains TA-100, TA-1535, TA98, TA1537 and *Escherichia coli* WP2 *urvA* with or without S9 activation.

In vivo toxicity of BRD5018 was explored in mouse, rat and dog (Figure 2). Overall the safety profile was consistent across species, with the main safety events related to gastrointestinal toxicity being monitorable and reversible. No serious systemic toxicity was identified. In the initial toxicity study in male ICR mice, BRD5018 was well tolerated as a single oral dose of 100 mg/kg. At doses of 300 and 600 mg/kg, mortality (1/3 and 3/3 of animals respectively) was associated with gastric ulceration and hepatocellular fatty degeneration. In Sprague Dawley rats, BBD5018 was dosed orally at 200 mg/kg/day for 3 consecutive days resulting in a reversible loss in body weight of approximately 25%. Based on the body weight-loss, this dose was considered to be above the maximum tolerated dose. A 3-day repeated dose exploratory DRF study was conducted in Sprague Dawley rats. In this study, BRD5018 was administered orally to male and female rats once daily for 3 consecutive days at doses of 0, 60 and 180 mg/kg. In the DRF study clinical signs, body weights, food consumption, hematology, clinical chemistry, toxicokinetics (D1 and D3 up to 264 hours post dose), gross necropsy, liver weight, and histopathology were evaluated. Doses of up to 180 mg/kg were tolerated. The primary test-article related changes were dose dependent decreases in body weight (up to 21% on day 4, post dosing) and reductions in food consumption associated with mucosal hyperplasia in the small intestine (on histopathology). Clear evidence of recovery was observed two weeks after the last dose of BRD5018. BRD5018 was administered by oral gavage once daily for 3 days to beagle dogs (1/sex/group) at doses of 100 and 300 mg/kg/day followed by a 7-day observation period and necropsy. No mortality occurred at any dose. There were no changes in clinical pathology or histopathology. The dose of 300 mg/kg/day was associated with emesis, abnormal feces, decreased food consumption and significant body weight loss (up to 20%). In the exploratory cardiovascular study, BRD5018 was administered once a day in a daily dose escalation regimen to telemetered male beagle dogs at doses of 0, 30, 100, or 450 mg/kg to assess the effects on the cardiovascular system. Emesis occurred at 100 and 450 mg/kg. There were no significant CV findings at plasma concentrations up to 2.7 μg/ml. Overall, the toxicity profile was consistent across preclinical species, with primary findings related to gastrointestinal (GI) toxicity likely due to local irritation and no serious systemic toxicity identified. GI toxicity is monitorable and reversible.

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.

Nothing to Report

4. **IMPACT:** D*escribe 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).

This project has established that inhibition of P. falciparum cytosolic phenylalanyl tRNA synthetase is an important new antimalarial mechanism of action with promising therapeutic potential. We have identified a P. falciparum cytosolic phenylalanyl tRNA synthetase inhibitor (BRD5018) with good selectivity over the human ortholog and good PK profile. We have determined the non-GLP, non-clinical safety profile of BRD5018 and found no serious systemic toxicity identified. GI toxicity is monitorable and reversible. This has increased interest in the malaria field for this target as well as for the discovery of other aminoacyl tRNA synthetase inhibitors for the treatment of malaria.

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.

We have discovered that inhibition of parasite cytosolic phenylalanyl tRNA synthetase is applicable to other disease areas. We discovered that compounds from this program have in vitro potency against C. parvum, L. donovani, T. cruzi and T. gondii in vivo efficacy in C. parvum and L. donovani mouse models. We are following-up on these results. For instance, a program has been initiated to develop analogues from this series with CNS penetration for the treatment of T. gondii.

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 PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official 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:*

There are no significant changes in the project or its direction. There was a deemphasis on the liver and transmission stage in vivo efficacy studies for reasons below.

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.

In vivo efficacy studies against *P. falciparum* liver and transmission stages were not completed for BRD5018 due to unavailability of mosquitos required for these experiments at the time of execution. Additionally, we were in contact with Walter Reed Army Institute of Research, LTC Mara Kreishman-Deitrick, Ph.D. as well as MAJ Pybus and his Deputy Ms. Patty Lee to determine if AFRIMS may be able to execute the studies. In the end, the discussion took longer than expected and our grant period ended without a resolution. Although the studies were not completed, we previously established that a related initial lead compound (BRD7929) had potent *in vivo* efficacy against *P. falciparum* liver and transmission stages and given this we decided to focus on establishing sufficient safety prior to testing BRD5018 for activity against these additional stages of the parasite life cycle.

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 or care of vertebrate animals

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.*

• Project was positively reviewed at the MMV Annual Review of Discovery Projects Geneva, July 2017, July 2018. "Development of an antimalarial targeting phenylalanyl–tRNA synthetase" was presented.

Discovery and development of a multistage antimalarial with new mechanism of action using next generation synthesis, Eamon Comer, 2nd Symposium on Medicinal Chemistry for Global Health, 19 June 2017 (poster presentation).

• Discovery and Development of a Multistage Antimalarial with New Mechanism of Action

- **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. Describe the technologies or techniques were 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. 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.

COMPOUNDS AND METHODS FOR THE TREATMENT OF PARASITIC DISEASE, International application PCT/US2018/023270, filed March 20, 2018.

- **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;*
  - *physical 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".

Name:	Stuart Schreiber
Project Role:	PD/PI
Nearest person month worked:	1
Contribution to Project:	Scientific and administrative oversight
Funding Support:	HHMI

Name:	Eamon Comer
Project Role:	Medicinal Chemist
Nearest person month worked:	4
Contribution to Project:	Project management
Funding Support:	DoD

Name:	Nobutaka Kato
Project Role:	Biologist
Nearest person month worked:	3
Contribution to Project:	*in vivo* efficacy studies
Funding Support:	DoD

Name:	YVONNE A. VAN GESSEL
Project Role:	Eisai
Nearest person month worked:	2
Contribution to Project:	Oversight of *in vivo* safety studies
Funding Support:	Eisai

Name:	Renee Hukkanen
Project Role:	Eisai
Nearest person month worked:	3
Contribution to Project:	Oversight of *in vivo* safety studies
Funding Support:	Eisai

Name:	Vaishali Dixit
Project Role:	Eisai
Nearest person month worked:	3
Contribution to Project:	DMPK studies
Funding Support:	Eisai

Name:	Sean Eckley
Project Role:	Eisai
Nearest person month worked:	3
Contribution to Project:	DMPK studies
Funding Support:	Eisai

Name:	Branko Mitasev
Project Role:	Eisai
Nearest person month worked:	6
Contribution to Project:	Route optimization and CMC studies
Funding Support:	Eisai

Name:	Jiong Yang
Project Role:	Eisai
Nearest person month worked:	6
Contribution to Project:	Synthetic route development
Funding Support:	DoD

Name:	Vijay Gupte
Project Role:	Eisai
Nearest person month worked:	6
Contribution to Project:	Alliance Management
Funding Support:	Eisai

Name:	B Venkata Sasidhar
Project Role:	Eisai
Nearest person month worked:	6
Contribution to Project:	Route optimization, scale up studies, Identification & evaluation of CMO (Contract manufacturing organization), and technology transfer to CMO. Manufacturing and supply of BRD5018 for pre-clinical safety studies, physicochemical studies and salt studies etc.
Funding Support:	Eisai

Name:	Anil Khile
Project Role:	Eisai
Nearest person month worked:	3
Contribution to Project:	Synthetic process optimization
Funding Support:	Eisai

Name:	Masaharu Gotoda
Project Role:	Eisai
Nearest person month worked:	2
Contribution to Project:	Structural analysis/salt form selection
Funding Support:	Eisai

Name:	Mie Kamoto
Project Role:	Eisai
Nearest person month worked:	2
Contribution to Project:	Physico-chemical analysis/salt form selection

Funding Support:	Eisai
Name:	Dev Kant Shandilya
Project Role:	Eisai
Nearest person month worked:	6
Contribution to Project:	Drug substance analytical development
Funding Support:	Eisai
Name:	Hiroharu Kojima
Project Role:	Eisai
Nearest person month worked:	2
Contribution to Project:	Drug Product dosage form development
Funding Support:	Eisai
Name:	Jonathan French
Project Role:	Eisai
Nearest person month worked:	2
Contribution to Project:	CMC-Coordination
Funding Support:	Eisai

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.*

The Broad institute (non-profit) and Eisai (industrial) are the principle organizations in this project. CiToxLAB (commercial) in Canada performed rat DRF safety studies, dog DRF and CV studies.

Organization Name: Eisai
Location of Organization: Andover, MA; Tsukuba, Japan; Parawada, India; Kakamigahara, Japan
Partner's contribution to the project: In-kind support; Facilities; Collaboration; Personnel exchanges.

Organization Name: CiToxLAB
Location of Organization: Quebec, Canada
Partner's contribution to the project: Facilities

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: ***N/A***

QUAD CHARTS: ***N/A***

9. APPENDICES: *N/A*