



**TB ALLIANCE**  
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

October 24, 2006

Ms. Susan Bacheller  
CTO (USAID/GH/HIDN/ID)  
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U.S. Agency for International Development  
1300 Pennsylvania Avenue, NW  
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Room 7.07-018-RRB  
Washington DC 20523

**Re: Cooperative Agreement No. GHS-A-00-4-00015-00**

Dear Ms. Bacheller:

Per section A.5.2. of the Cooperative Agreement No. GHS-A-00-4-00015-00, please find, herewith, our annual report for year two of the four-year award to the Global Alliance for TB Drug Development. This report covers the period between October 1, 2005 and September 30, 2006.

We are grateful for the continued support from USAID. Please let me know if you have questions.

Sincerely yours,

Maria C. Freire, Ph.D.  
CEO and President

Cc: Asmita Barve  
Christy Hanson  
Bradley Jensen  
Nina Schwalbe

**OFFICE OF HEALTH, INFECTIOUS DISEASES AND NUTRITION**

**PORTFOLIO REVIEW**

**Submitted by the Global Alliance for TB Drug Development**

**GHS-A-00-04-00015-00**

**24 October 2006**

I.

<b>Project Title/Activity:</b>	Phase I clinical trial (PA-824)
<b>Project Number:</b>	GHS-A-00-04-00015-00
<b>Reporting Period:</b>	October 1, 2005 – September 30, 2006
<b>CTO and Technical Advisor:</b>	Susan Bacheller and Christy Hanson

**Brief description of project:**

PA-824 is the Global Alliance for TB Drug Development's (TB Alliance's) lead nitroimidazo-oxazine, a new class of tuberculosis (TB) compounds with a novel mechanism of action. Studies in mice have shown that the compound has potent activity against metabolically active as well as non-replicating, persistent bacteria and therefore holds promise for shortening TB therapy. Further, PA-824 demonstrates activity against all drug-resistant clinical isolates tested to date and therefore may be efficacious against multidrug-resistant TB (MDR-TB) as well as extensive-drug resistant TB (XDR-TB). Also important, PA-824 does not demonstrate significant potential for drug-drug interactions and therefore can probably be co-administered safely with antiretroviral agents to treat TB-HIV co-infections.

At the start of year 2 of the USAID grant, PA-824 was in Phase I clinical trial. PA-824 activities planned during grant year 2 included completion of the Phase I, single-dose, dose escalating, pharmacokinetic and safety study in healthy volunteers; initiation and completion of the multi-dose phase I study, initiation of a Mass Balance Absorption, Metabolism and Excretion Study with radiolabeled PA-824 to determine disposition of drug in normal volunteers; and, completion (last patient out) of a renal study.

**Key Results and Accomplishments:** (provide bullet points to summarize quantitative and qualitative results categorized by the results areas below)

- The analysis and formal study report for the Phase I, single dose study was completed in February 2006. Safety and pharmacokinetic results indicate a good safety profile for the drug at high doses and substantial drug exposure.
  - Dose groups of 50, 250, 500, 750, 1000, 1250, 1500 mg PA-824 were used in the study

- Analyses of results through the 1500 mg dose indicate no clinically significant adverse events, QT changes within normal variation and not dose dependent, substantial bioavailability and exposure; and a half-life greater than 12 hours.
- Phase I, multi-dose study was initiated in November, 2006 and completed in February, 2006.
  - About two-thirds into the course of the study, blood tests in some volunteers showed an increase into the abnormal range in the level of serum creatinine, an indicator related to kidney function. However, levels of blood urea nitrogen (BUN), another indicator of kidney function, were not elevated in this study.
  - A renal study was initiated in June 2006 to investigate whether or not the rise in serum creatinine levels was linked to kidney damage.
- By September 30, 2006, three cohorts (46 subjects, total) had completed the study and analysis of still blinded data was being conducted to determine whether or not a fourth cohort would be required to adequately evaluate the primary endpoints.

**Implementation issues/contraints:** (encountered during the reporting period, and concerns for the coming reporting period)

- Blood tests of some patients in the multidose study showed increased serum creatinine levels. However, these levels returned to normal within a few days after the drug was stopped. There was no other indication of potential renal malfunction in study subjects. A consultants' meeting, including five leading experts in clinical pharmacology and nephrology, was held to review and help interpret the Phase I data. A renal study was planned and started to determine the cause and clinical significance, if any, of the rise in serum creatinine.
- Given the potential of the nitroimidazole class of drugs in improving TB therapy and the intrinsic uncertainty in the drug development process, the TB Alliance has an ongoing back-up program to produce a new generation of nitroimidazoles. Should the findings from the renal study not be satisfactory, then the PA-824 studies will be invaluable in informing and improving this PA-824 back-up program.

**Strategic Activities and Results to be Achieved in FY 2007:** (by results areas, bullet points only)

- Analyse findings from renal study and complete final study report.
- If renal study results indicate that serum creatinine elevations are clinically insignificant, then complete proof-of-concept study evaluating early bactericidal activity (EBA) of PA-824 at multiple doses to confirm potential efficacy and identify the optimum dose.
- Complete a food effects study (last patient out).

## II.

<b>Project Title/Activity:</b>	Phase II clinical trial (moxifloxacin)
<b>Project Number:</b>	GHS-A-00-04-00015-00
<b>Reporting Period:</b>	October 1, 2005 – September 30, 2006
<b>CTO and Technical Advisor:</b>	Susan Bacheller and Christy Hanson

### **Brief description of project:**

Moxifloxacin is a member of the flouroquinolone class of antimicrobials, which is the only known drug class with a near-term potential to significantly impact TB treatment duration. By inhibiting DNA gyrase, an enzyme involved in DNA replication and transcription, quinolones directly impact bacterial cell multiplication, repair and survival. Moxifloxacin is currently marketed worldwide by Bayer Pharmaceuticals for treating acute respiratory tract infections. Based on its *in vitro* potency against *M. tuberculosis*, efficacy in mice infected with TB, and excellent human safety profile, moxifloxacin is one of the most promising candidates for improved treatment of TB. TB Alliance-supported studies, conducted at Johns Hopkins University and using an *in vivo* mouse model, indicate that the substitution of moxifloxacin for isoniazid may shorten the duration of therapy needed to eradicate infection from a total of six months to four months or less. Furthermore, because moxifloxacin acts on a new TB-drug target, it has excellent potential to improve treatment of MDR-TB.

In August 2005, Bayer and the TB Alliance signed a formal contract for a joint global clinical development program and registration of moxifloxacin for the treatment of TB. In this partnership, the TB Alliance will lead the definition, coordination and management of the program and Bayer will contribute clinical supplies, expertise, and regulatory support, along with a guarantee of commercial supply at an affordable cost in the developing world.

The two Phase II trials supported by USAID in year 2 of the grant period are TB Trials Consortium (TBTC) Study 28 and REMoxTB Study. TBTC Study 28 is a Phase II study evaluating the safety and efficacy of substituting moxifloxacin for isoniazid in standard TB therapy. REMoxTB is a Phase II/III study to test moxifloxacin substituted for either isoniazid (in a Phase II design) or ethambutol (in a Phase III design). The Phase II primary endpoint in these studies is the percentage of patients demonstrating conversion of sputum culture to negativity at two months.

**Key Results and Accomplishments:** (provide bullet points to summarize quantitative and qualitative results categorized by the results areas below)

- The TB Alliance hired the contract research organization (CRO), Quintiles-Scotland (recently renamed Aptuit), to provide GMP-compliant study drug, including packaging, labeling, stability testing, quality assurance (QA) release and distribution for TBTC Study 28.
- Weststat was contracted, following a competitive bidding process, to coordinate and monitor TBTC Study 28 and ensure Good Clinical Practice (GCP) compliance. Patient enrollment for the study began in February 2006.
- The TB Alliance contracted PharmaNet as the CRO to coordinate and monitor the REMoxTB study in August 2006.
- These clinical development programs serve as a “trail-blazer” for future clinical development programs of novel TB drugs by building needed clinical trial capacity.

**Implementation issues/contraints:** (encountered during the reporting period, and concerns for the coming reporting period)

- Careful review of initial enrollment, monitoring and drug supply plans for the REMox TB Phase III trial indicated that additional GCP/Good Laboratory Practice (GLP) compliant sites would need to be added to the trial to speed up enrollment; a qualified, central source would need to be identified to supply the study drug; and additional monitoring of the study data would be required. Therefore, Requests for Proposals (RFPs) were developed and issued, and CROs contracted to identify and build GCP/GLP capacity, to supply the study drug and placebos, and to provide additional data management support.
- Whether or not enrollment targets defined for the REMox TB trial in the coming reporting period are met will largely be determined by the time it takes to build adequate GCP/GLP capacity. Also, the study start date will depend on various factors including the timely provision of the study drug and placebos by the CRO (Aptuit US) responsible for the packaging, labeling, stability testing and distribution of the drugs, and the granting of final study approval and importation licenses by national authorities in the countries where study sites are located (currently Tanzania, Zambia and South Africa). The TB Alliance is working closely with Aptuit, the study sites, and Bayer’s Regulatory Affairs group to try and ensure that timelines are met.
- For TBTC Study 28, the TB Alliance has anticipated possible future resource constraints and is adding extra resources to assure that the study’s progress is according to schedule. To ensure that the study completes patient enrollment as planned by February 2007, that the trial is conducted under GCP/GLP standards, and that the data generated is of the quality to support a registration package, the TB Alliance is supporting additional study staff at the highest enrolling site (Kampala,

Uganda). In addition, it has contracted a CRO (Westat) to provide additional data management, monitoring and coordination support to the TBTC Study 28 team.

- A go/no-go decision to Phase III evaluation of a moxifloxacin-substituted for isoniazid-based regimen will be made based on results of Study 28, which are expected in the third quarter of 2007. If data are supportive, the TB Alliance expects to submit a New Drug Application (NDA) for the treatment shortening indication of this regimen by the end of 2010 or early 2011. Similarly, for the ethambutol-based regimen (REMoxTB), the TB Alliance anticipates filing for registration in 2009 if study results are promising. Despite very strong results thus far, due to the unpredictable nature of drug development, the TB Alliance has to be prepared for changes in current project plans and, at worst, even withdrawal of the project. To address this possibility and because of the great potential of the quinolone class of drugs in enhancing TB treatment, the TB Alliance had initiated a project to identify a moxifloxacin backup compound with optimized efficacy to treat TB.

**Strategic Activities and Results to be Achieved in FY 2007:** (by results areas, bullet points only)

- Complete primary end-point (2 month sputum conversion) in the Phase II TBTC Study 28.
- For the Phase III REMox study, the TB Alliance expects to conduct GCP/GLP and study-specific training as needed at study sites, conduct pre-study site assessments, and perform monitoring of the study sites and data for the duration of the trial. By September 30, 2007, approximately two-thirds of the patients (1000 of 1500) should be enrolled into this study.

### III.

<b>Project Title/Activity:</b>	Lead Optimization and Preclinical
<b>Project Number:</b>	GHS-A-00-04-00015-00
<b>Reporting Period:</b>	October 1, 2005 – September 30, 2006
<b>CTO and Technical Advisor:</b>	Susan Bacheller and Christy Hanson

#### **Brief description of project:**

USAID funds in 2005-2006 were used to support lead identification and optimization for three of the TB Alliance's discovery projects: quinolones, macrolides, and nitroimidazoles (PA-824 backup).

#### Quinolones

Of all the antimicrobials that have progressed to the point of human testing for the treatment of tuberculosis, quinolones probably hold the greatest potential for shortening treatment duration and improving treatment of MDR-TB and TB in HIV/AIDS infected individuals. The quinolone project initiated in the second quarter of 2003 has synthesized more than 600 new quinolone analogs based on 20 pharmacophores and identified several compounds that are significantly more potent against *M. tuberculosis* than moxifloxacin *in vitro*. *In vivo* efficacy for the lead series has been confirmed in mouse models.

#### Macrolides

Macrolides are potent protein synthesis inhibitors. As one of the most widely prescribed antibiotic classes, macrolides are safe, well tolerated, orally active and inexpensive to produce. Additional attributes specifically important to TB therapy include excellent intracellular activity, extensive lung distribution and synergistic effects with a variety of anti-TB agents. The objective of the macrolide project is to discover a new macrolide with significant advantages over the available anti-TB drugs. The project, initiated in July 2004, has synthesized more than 300 derivatives based on 6 structural series. Three of these were identified as having potent *in vitro* anti-TB potency superior to the benchmark macrolide, clarithromycin. At the beginning of grant year two, the project was in the lead optimization phase.

#### Nitroimidazoles (PA-824 Backup)

Nitroimidazoles are a novel class of anti-TB agents. PA-824, the TB Alliance's lead nitroimidazo-oxazine, and OPC-67683, a nitroimidazo-oxazole, are currently in Phase I clinical trials. The TB Alliance believes that this new class of compounds is so promising for improving TB treatment that it has initiated studies to identify a back-up compound as well as second generation compounds in the same chemical series as PA-824 but with an improved pharmacological profile. This program is underway with Auckland Cancer Society Research Center (ASRC) and the University of Illinois at Chicago (UIC). Currently, about 600 new nitroimidazoles have been synthesized based on ten structurally distinct pharmacophores. About 30 structurally diverse nitroimidazoles

are being evaluated for QT prolongation and mutagenicity. These studies have resulted in information that can be used for the design of next-generation compounds. New synthetic routes that are shorter and free of explosive intermediates are also being developed.

**Key Results and Accomplishments:** (provide bullet points to summarize quantitative and qualitative results categorized by the results areas below)

#### Quinolones

- Extensive structure-activity relationships (SAR) were developed, which led to the development of 4 potent scaffolds against *M. tuberculosis*.
- 2-pyridone (quinolizinone) and 8-methoxy quinolone were identified as the lead scaffolds. A large number of C-8 derivatives of the 2-pyridone and 8-methoxy quinolone core were designed and synthesized.
- Compounds with good selectivity in DNA gyrase and whole-cell assays, low potential for QT prolongation, negative mutagenicity and excellent liver microsome stability were advanced into *in vivo* studies.
- Preliminary *in vitro* testing for human topoisomerase II activity, potential mutagenicity, QT prolongation and human liver microsome stability was performed.
- 18 compounds were scaled up to the gram scale and advanced into efficacy, pharmacokinetic and safety studies.

#### Macrolides

- Optimization of *in vitro* activity of the three most promising series was completed, a total of 300 analogs were prepared, and 9-oxime and 6-O-alkyl series were identified as the most promising leads.
- The 9-oxime series was optimized and 20 compounds in the series were scaled up to gram quantity. *In vivo* tolerability and efficacy studies indicated that the series exhibited acute toxicity in mice and therefore the series was discontinued.
- As optimization of the remaining 6-alkyl lead series continues, several compound in the series have been scaled up to gram scale and *in vivo* tolerability and efficacy evaluations are currently ongoing.

#### PA-824 Backup

- SAR and structure-toxicity relationship (STR) studies for mutagenicity and QT prolongation potential with 30 structurally diverse compounds were completed.
- Ten structurally distinct pharmacophores and more than 600 analogs were designed and synthesized. SAR for improving *in vitro* potency was accomplished and a number of new series that have superior potency to PA-824 against rapidly replicating and non-replicating organisms were identified.
- Selected compounds were evaluated for cytotoxicity and P450 inhibition, which indicates interaction with antiretroviral (ARV) drugs used to treat HIV/AIDS.
- More than 20 compounds were prioritized and scaled up for *in vivo* studies including pharmacokinetics (PK), acute toxicity, and acute efficacy in mice.

**Implementation issues/contraints:** (encountered during the reporting period, and concerns for the coming reporting period)

### Quinolones

- A laboratory identified by the project collaborators to perform *in vivo* studies was unable to properly formulate the compounds. As a result, the *in vivo* studies could not be completed on schedule and the project milestone identified in the work plan for year two - a go/no go decision to Investigational New Drug (IND)-enabling studies - was delayed. The TB Alliance brought in consultants to help resolve the formulation issues and train the laboratory in toxicity and efficacy studies. The project is now back on track and *in vivo* studies are in progress. Upon completion of the current *in vivo* studies, a key go-no go decision to IND-enabling activities will be made early in 2007.

### Macrolides

- So far, extensive lead optimization studies for various structural series of macrolides have been performed. Compounds with significantly improved *in vitro* potency relative to clarithromycin were identified. However, none of the compounds that were tested has demonstrated acceptable *in vivo* efficacy in mice. The final series, 6-O-alkyl, is currently under *in vivo* evaluation. Upon completion of these *in vivo* studies, a key go/no go decision to IND-enabling activities will be made in the fourth quarter of 2006.

### PA-824 Backup

- This project did not encounter any implementation issue in year 2 of the grant. Project objectives were accomplished ahead of schedule.
- A renal study is currently underway to determine if the elevated serum creatinine levels detected in the Phase I multi-dose study for PA-824 are indicative of any effect of clinical significance on kidney function. If metabolism of PA-824 is revealed to be an issue, then the PA-824 backup series may not be able to bypass it since it likely has the same metabolic pathway.

**Strategic Activities and Results to be Achieved in FY 2007:** (by results areas, bullet points only)

All activities supported by USAID in FY 2007 will be related to clinical development. No preclinical development project is included in the FY 2007 work plan.