TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

14 October 2005

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

Re: Cooperative Agreement GHS-A-00-4-00015-00

Dear Ms. Bacheller:

Please find, herewith, our annual report for year one of the four-year award to the Global Alliance for TB Drug Development (TB Alliance). The report covers the period of October 1, 2004 to October 1, 2005 and is in accordance with the budget we submitted to you on September 2, 2004.

We are grateful for the support from USAID and look forward to continued collaboration.

Sincerely yours,

Nina Schwalbe
Director of Policy

80 Broad Street, 31st Floor • New York, NY • 10004 • USA • +1 (212) 227-7540 • www.tballiance.org

Annual Report

Submitted to

The United States Agency for International Development

October 15, 2005

Organization:	The Global Alliance for TB Drug Development
Type of Organization:	Non-profit, tax-exempt organization recognized under section 501(c)3
Contact Person:	Nina Schwalbe Director of Policy Global Alliance for TB Drug Development 80 Broad Street, 31st Floor NY, NY 10004 Tel.: (212) 227 2750 x 234
Project:	New TB Drug Development
Grant Agreement Number:	GHS-A-00-04-00015-00
Grant Period:	October 1, 2004 – October 1, 2008
Reporting Period:	October 1, 2004 – October 1, 2005
Grant Amount:	U.S. $8 million

I. Background

The most significant shortcoming in current TB therapy is the long and complicated treatment regimen recommended for the 9 million new annual cases of active TB. In addition to imposing tremendous demands on local healthcare systems trying to deliver therapy under the WHO-recommended Directly Observed Treatment Short Course (DOTS) program, the need to take multiple drugs for a minimum of 6 months is also extremely difficult for the patient. Treatment noncompliance fuels the development of multi-drug resistant TB (MDR-TB) which is considerably more difficult to treat due to the lack of adequate second line therapy. Further, treatment of the TB/HIV co-infected population is even more problematic, complicated by the lengthy duration of TB treatment and the drug-drug interactions between current TB and HIV therapy as well as the potential need to take additional anti-retrovirals (ARVs) during the period of active TB treatment.

The TB Alliance, a not-for-profit global public-private partnership was created to develop new anti-tuberculosis drug regimens that shorten and/or simplify treatment, are effective against multi-drug resistant TB, can be administered together with ARVs and address both active and latent forms of the disease. The resulting medicines must be accessible, affordable to all in need, and promptly adopted for field use.

The TB Alliance employs three complementary strategies to achieve the mission. First, we identify, obtain and manage a portfolio of potential anti-TB compounds. Through competitive requests for proposals and active scouting, we solicit the most promising projects for drug development. After scientific, technical and legal due diligence, we select investments that fit our drug profile and strengthen the pipeline, thereby increasing the chances of success. Once in the portfolio, these compounds are driven through a comprehensive milestone-specific drug development process that includes partnerships with industry, agreements with contract research organizations (CROs) and support for collaborators in research institutions.

Second, we help coordinate and catalyze TB drug development worldwide. Specifically, we work to lower scientific and regulatory hurdles for companies and other organizations that are interested in developing affordable drugs to treat TB. Further, our investments in platform technologies, such as murine animal models that have been substantiated as predictors of activity for TB drugs in humans, databases and research to develop surrogate markers, serve to harmonize standards and provide research tools to buttress the TB drug development process.

Third, we recognize that if a successful drug candidate for TB is not affordable, not embraced by public health practitioners and not available to patients in need, our organization will not have achieved its ultimate mission – to ensure that new medicines reach the patient. Therefore, in addition to safety and efficacy, issues of affordability, adoption and access (the AAA strategy) are considered as part of the drug development process and influence priority setting, compound selection, and intellectual property management.

In October 2004, USAID awarded the TB Alliance a US $8 million grant for drug development. The grant funds were allocated for the following activities:

- **Compounds and platform technologies –** Costs involved in the creation and management of the portfolio of anti-TB drug candidates, including lead identification and optimization projects, as well as preclinical testing and clinical trials of promising molecules. These incorporate costs of contracting services for outsourced development and collaboration with appropriate public and private partners, and costs related to platform technologies that accelerate TB drug development.

- **Clinical trials and regulatory approval –** Costs associated with the improvement of, or development of Good Clinical Practice (GPC)-standard clinical trial capacity in key endemic countries to support clinical trials of drug candidates such as PA-824, moxifloxacin, and other late stage compounds.

- **Outreach and mobilization –** Costs involved in the development and management of critical alliances with public and private organizations, the enrollment of scientific expertise, and the mobilization of endemic countries and key international organizations.

II. Activities Supported by USAID

Over the last year, thanks to the support of USAID and others, the TB Alliance has introduced a completely new paradigm for TB drug development. The new paradigm rests on the basic premise that the unit of treatment in TB is the regimen, not the single drug and that assessments of safety and efficacy can only truly be made on the new combination regimen being contemplated, not on individual compounds.

From preclinical development through clinical trials, the TB Alliance is testing anti-TB drugs, first individually to assess a drug's inherent potential in a TB regimen, and then in combinations to determine that appropriate multi-drug regimens will have potential to shorten and simplify treatment, effectively treat MDR-TB, and are compatible with ARVs. While current compounds in the pipeline have the potential to shorten therapy to 2-3 months, new drugs yet to be discovered will be designed for their specific potential to shorten therapy down to days or weeks. An overview of the current pipeline can be found in Appendix 1. Since our inception, we have taken into consideration issues of affordability, adoption and access (AAA), because these requirements may affect the selection of compounds. For example, compounds that require intravenous administration or that are derived from expensive raw materials are not as attractive as those that can be easily synthesized, formulated and administered. Due diligence is carried out for each potential investment to ascertain these costs and characteristics.

All the investments made by the TB Alliance include provisions for AAA. The strategy is embodied in all implementing agreements. Language on AAA is part of the recitals, definitions, rights to the intellectual property (IP) and the royalty/pricing provisions. With respect to the latter, we have used several vehicles to reduce the final cost of the product, including but not limited to, the stipulation that neither party will receive royalties in the developing world or by establishing preferential pricing for specified countries or segments in a given country, particularly all TB endemic regions.

In addition, we negotiate non-blocking IP positions, thereby ensuring that the TB Alliance or a sub-licensee can continue to develop a given compound in the event that the collaborating party decides to discontinue development for non-technical reasons, such as profit or other business considerations. As a general practice, this is done by obtaining non-exclusive rights to pre-existing or background technology, in conjunction with rights (exclusive, co-exclusive or non-exclusive) to IP that arises from the agreement. The field of use for the agreements is the treatment of TB, although we negotiate a modest royalty should the resulting product have a profitable indication outside the TB field.

In 2004-2005, the TB Alliance used the funding from USAID for the following specific purposes.

1. Compounds and platform technologies

Funding from USAID in this reporting period was used to support lead identification and optimization for nitroimidazoles, macrolides, and quinolones. These promising classes of drugs have the ability to address all three goals of the TB Alliance drug development process – shortening treatment, addressing MDR-TB, and having the ability to be delivered concurrently with ARV therapy for HIV.

Nitroimidazoles: PA-824 and Analog Backup Program

Nitroimidazoles, a novel class of anti-tuberculosis agents, hold great potential to address the major unmet medical needs in tuberculosis therapy. Two compounds within the class, PA-824, a nitroimidazo-oxazine, and OPC-67683, a nitroimidazo-oxazole, have recently advanced into Phase I clinical development. These narrow-spectrum agents possess a novel mechanism of action and are active against all drug-resistant clinical isolates tested to date. More importantly, the compounds are potent against *M. tuberculosis* in both replicating and non-replicating states, and exhibit potent bactericidal and sterilizing activity in mice. Preclinical studies show no evidence of mutagenicity in a standard battery of genotoxicity studies and no significant cytochrome P450 interactions. Therefore, PA-824 and OPC-67683 hold great potential for shortening the duration of the current therapy and the treatment of multidrug-resistant tuberculosis (MDR-TB) and TB-HIV co-infections.

The Alliance believes that this new class of compounds is so promising for improving the treatment of TB that we have initiated studies to identify a back-up compound as well as second generation compounds in the same chemical series as PA-824 but with improved properties. Key objectives for this program are to:

- Understand the relationship between chemical structure and anaerobic activity (*i.e.,* SAR, or structure-activity relationship)
- Overcome mutagenicity
- Reduce QT prolongation potential
- Develop a better synthesis than PA-824

This program is underway with the Novartis Institute for Tropical Diseases (NITD) and Dr. Clifton Barry of the National Institute of Allergy and Infectious Disease (NIAID), who has a longstanding interest in this class of compounds, and an additional collaboration has begun with Dr. William Denny at the Auckland Cancer Society Research Center. Both initiatives are designed to identify and synthesize new chemical entities in this compound class. Research Triangle Institute (RTI), which has been a key collaborator in day-to-day management of the PA-824 development program, will continue to provide expertise for these projects. The TB Alliance has also secured the consulting services of Dr. William Baker of Corus Pharma, who was the head of chemistry at Pathogenesis during the discovery of PA-824, and the Alliance is currently in discussions with Corus Pharma to provide new chemical synthetic directions. The TB Alliance continues to develop the relationship with Otsuka Pharmaceuticals for possible future collaboration in the development of their nitroimidazole derivative for TB therapy.

Work completed with these collaborators under the overall strategic guidance of the TB Alliance has markedly advanced the understanding of the biological activity in this series of compounds. The initial set of studies also helped identify the most promising new leads to pursue to improve the activity of PA-824.

Quinolones

Of all the antimicrobials that have progressed to the point of human testing for the treatment of TB, the quinolone class may hold the greatest potential for shortening treatment duration, overcoming MDR-TB and improving therapy of TB-HIV co-infections. As potent DNA gyrase inhibitors of *M. tuberculosis*, quinolones shut down DNA replication and transcription and have a direct impact on cell viability of both the replicating and the non-replicating states of bacterial growth.

Since initiating this project in the second quarter of 2003 with the Korean Research Institute of Chemical Technology (KRICT), more than 450 new quinolones, based on 20 structural scaffolds, have been synthesized and tested for their activity against *M. tuberculosis*. This has allowed us to identify compounds that are significantly more potent than moxifloxacin against *M. tuberculosis*, *in vitro,* under aerobic and anaerobic conditions and in macrophages and have demonstrated excellent oral efficacy in the murine animal model. We have also shown that members of the lead series are not cytotoxic and that they have a lower potential for QT prolongation.

As part of this program, we have also developed extensive structure-activity relationships (SAR), which led to the development of four potent scaffolds against *M. tuberculosis.* These studies revealed over 50 compounds with equal or better *in vitro* activity than moxifloxacin against *M. tuberculosis.* The *N-tert*-butyl naphthyridone scaffold showed the most selectivity for *M. tuberculosis* over other organisms, while the 2-pyridone scaffold was found to have the most potent activity against both replicating and non-replicating *M. tuberculosis.* Members of the 2-pyridone series exhibited excellent activity against *M. tuberculosis* in the non-replicating state, with 6-to-10-fold higher potencies than moxifloxacin. These compounds also demonstrated better intracellular activity than moxifloxacin in macrophages. Preliminary studies indicated that members of the 2-pyridone class are very efficacious in the mouse model when given orally. We have also demonstrated that compounds in this series are not cytotoxic, even at concentrations exceeding 1000 times their MIC (minimum inhibitory concentrations), and that they have no significant impact on the hERG channel at concentrations greater than 100 times the MICs.

Because of the success of our investment in KRICT, we are renewing our agreement and will synthesize additional 2-pyridones (quinolizinones), and related compounds. Yonsei University will carry out the preclinical evaluation of the most promising compounds.

We are pleased to report that we have secured a non-blocking IP commitment from Abbott Laboratories, who own extensive patent territories in the 2-pyridone area. This is a very important achievement because it allows the TB Alliance to make, use and distribute the new generation compounds worldwide.

Meanwhile, we continue our active scouting of quinolone initiatives. In 2004 we signed an agreement with Procter & Gamble for the evaluation of a non-fluorinated quinolone antibiotic that is presently in Phase I clinical trials. Should the compound prove to have anti-TB activity, we will move forward with a licensing arrangement.

Macrolides: Third Generation Program

With the help of USAID, we have made significant progress in the past six months in achieving our primary goal of optimizing the anti-TB activity of the macrolide antibiotics through the synthesis of additional derivatives of erythromycin. Preliminary results from Dr. Franzblau's laboratory at the University of Illinois in Chicago indicated that two such compounds, clarithromycin and RU-66252, were effective against *M. tuberculosis* under anaerobic

conditions, which represents the non-replicating of “latent” state of infection. We are optimizing the structure of the macrolides with the hope of improving potency against *M. tuberculosis* in the non-replicating state.

With support from USAID, a total of more than 160 erythromycin derivatives have been synthesized based on six scaffolds. Each scaffold allows modification to be performed at four different positions on the molecule [i.e., C-4” (or C-3 for ketolide), C-6, C-9 and C-11/12]. The permutation between the three scaffolds and the four positions creates a great structural diversity for helping to understand the relationship between the chemical structure and biological activity of compounds in this class.

So far, more than 100 structurally diverse compounds have been advanced to lead optimization and have been evaluated for *in vitro* activity and cytotoxicity. Several of the analogs exhibit promising activity and selectivity, especially a series of 9-oximes with potent activity against *M. tuberculosis* in the non-replicating state. Importantly, some of the new compounds have reduced propensity to inhibit hepatic drug metabolizing enzymes, which is important in treating TB because these drugs would likely be co-administered with other medications. Work recently completed has led to the selection of twenty compounds that will be further evaluated in animal models for tolerability and efficacy to determine whether or not these could be likely candidates for preclinical development.

2. Clinical trials and regulatory approval

The TB Alliance has two promising compounds in clinical trials – PA-824 and moxifloxacin. In 2004-2005, funding from USAID was used to support Phase I clinical studies for PA-824.

PA-824

The TB Alliance filed an Investigational New Drug Application (IND) with the FDA in April 2005 and initiated the first-in-man study with PA-824, one of a new class of compounds called nitroimidazoles, in June 2005. Thus far, single doses of up to 1000mg of PA-824 have been administered to healthy human volunteers with no untoward side effects, and drug levels in the blood have been higher than expected, a very favorable result. The single-dose study was completed in August, and based on data analyses of those results, a multiple ascending dose study will begin in November 2005. Planning is also underway for a study to evaluate PA-824 in an Early Bactericidal Activity test in patients with TB to assess the compound’s anti-TB activity in humans. Laboratory studies will continue during this period to further evaluate the drug’s properties and to synthesize additional quantities of the drug for the larger studies.

Prior to submitting the IND, additional studies were performed to determine whether or not PA-824 produced any effects on the cardiovascular, respiratory or central nervous systems that would have precluded testing the compound in human volunteers. Studies in rats showed mild central nervous system changes only at the highest dose (450 mg/kg), even shorter duration changes at the 150 mg/kg levels, but no changes at a dose of 50 mg/kg. The highest dose also produced significant decreases in respiration rate, but no such changes were observed in 50 or 150 mg//kg levels. In a cardiovascular safety pharmacology study in conscious cynomolgus monkeys, all three dosage levels were administered; no clinically relevant effect on systolic, diastolic and mean arterial pressure, heart rate, cardiac conductance, or body temperature. This work was performed with the support of the USAID grant.

3. Outreach and mobilization

In 2005, the TB Alliance negotiated partnerships with two major pharmaceutical companies – GlaxoSmithKline and Bayer. In support of the AAA mandate, funding from USAID has been used to support a business development consultant, responsible for incorporating language on adoption, affordability and access into each agreement of the TB Alliance.

The TB Alliance continues to develop and expand its Scientific Advisory Committee (SAC) The SAC and other *ad hoc* consultants, who include individuals from a wide range of relevant disciplines, provide technical expertise on all research and development issues and participate actively in the monitoring of progress in each portfolio project (Appendix 2). The SAC also meets (twice during this reporting period) to conduct such activities as designing requests for proposals, reviewing applications and recommending selected projects as portfolio investments. Each approved project has a designated Project Oversight Group, consisting of selected SAC members and external experts who regularly review each project (Appendix 3). As projects reach each development milestone, the R&D team, with advice from the SAC, conducts a scientific and technical assessment and then recommends advancing or terminating the project to the Alliance's Portfolio Committee, which prepares a comprehensive recommendation for action by the Board of Directors.

The TB Alliance continues its close collaboration with the Stop TB Partnership, a global collaboration of over 300 organizations dedicated to TB Control, by serving as the lead agency of the Working Group on New Drugs. The Working Group, with support from the Alliance, convened a symposium on New Drugs at the annual meeting of the International Union Against Tuberculosis and Lung Disease (IUATLD). The Union meeting is the largest conference dedicated to TB control. The Alliance also coordinated the development of the Working Group's contribution to the Global Plan to Stop TB II, the strategic plan developed by the Stop TB Partnership for achieving the Millennium Development Goals (MDGs) by 2015 (enclosed under separate cover).

In addition to the symposium organized with Stop TB, the Alliance also attended and organized presentations on drug development at a number of scientific and policy meetings, including the Keystone Conference, the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), and the International Aids Society (IAS) meeting in Brazil (Appendix 4).

The Alliance has an active and robust Stakeholders Association, currently 34 organizations that have made a commitment to support the Alliance in a variety of ways. An annual meeting of the Stakeholders Association is held each year, in recent years at the time of the IUATLD meeting in order to ensure maximum participation and reduce costs. Following last October's meeting, the Alliance initiated a survey among national TB program managers (NTPs) from the 22 high burden countries (HBCs) aimed at gauging demand and perceived impact of new drugs for TB. Initial results can be found in Appendix 5 and the work will be expanded upon in the coming year. With this information, the Alliance is planning a series of regional stakeholders meetings in select endemic countries to engage HBC stakeholders in the drug development process.

As part of the Millennium Development Project, the Alliance commissioned a study to examine the epidemiological impact of a new drug regimen. The study focused on South East Asia. The authors predicted that the introduction of a two month regimen in 2012 would save 1.2 million lives in this region alone in the years 2012-2030, while reducing annual TB incidence 24% by 2030. Because this project requires somewhat more time to complete than was originally anticipated, a follow-on study in partnership with researchers from endemic countries has been postponed until 2006.

III. Planned Activities for Period October 2005 to October 2006

Below please find a table describing our planned activities for October 10, 2005 to October 1, 2006, as submitted on 15 August 2005.

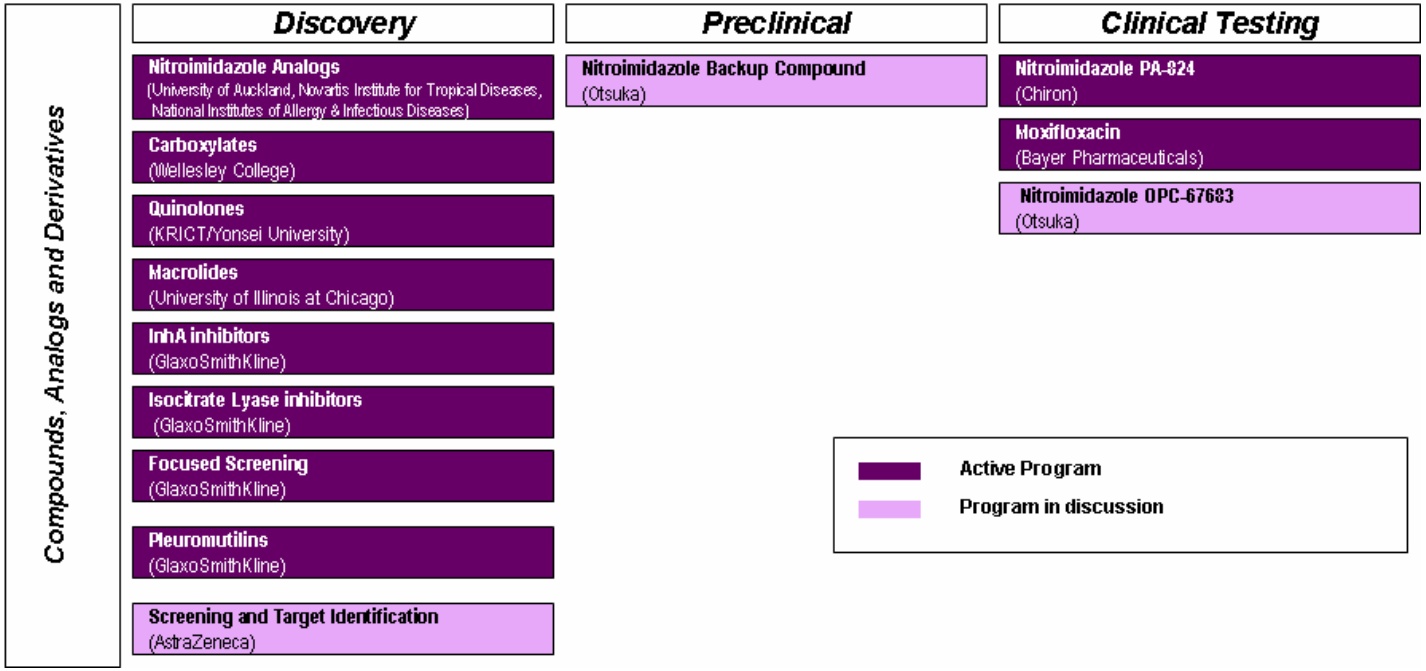
Activity	Performance Benchmarks	Time Line	Geographic Location
Phase I clinical trial (PA-824)			
Single dose (evaluate PK and safety of single dose in normal volunteers)	Complete study; analyze and report data; go/ no go decision to multiple dose study.	4Q05	U.S. (New Orleans, Louisiana)
Multiple dose (evaluate PK and safety of multiple dosing in normal volunteers)	Write protocol; initiate and complete study; analyze and report results. Go/ no decision and dose selection for EBA study.	4Q05-2Q06	U.S. (New Orleans, Louisiana)
Food effect (evaluate effect of food versus fasting on PK in normal volunteers)	Identify CRO; complete protocol; initiate study.	3Q06	TBD
Mass Balance/ADME (determine disposition of drug in normal volunteers)	Identify CRO; complete protocol; initiate study.	3Q06	TBD
EBA (proof-of-concept study in patients with TB at maximum tolerated dose)	Identify CRO; write protocol; initiate and complete study; analyze and report results; Go/no go decision to full Phase II program.	2Q06-4Q06	TBD
Phase II clinical trial (moxi)			
	Sign Bayer agreement. Ensure initiation of TBTC study #28 by hiring a CRO to monitor drug supplies. Hire a CRO to help coordinate TBTC study #27 and the Gillespie study. Ensure timely completion of Study #28 by hiring a CRO if necessary to help with recruitment.	4Q05 1Q06 1Q06 4Q06	Phase II sites are in: US, Canada, Brazil, Spain, Uganda, S. Africa, Tanzania and Zambia
Lead identification / optimization			
KRICT-Quinolone project	Go/no go to IND-enabling studies.	3Q06	Korea
University of Illinois-Macrolide project	Select compounds for *in vivo* optimization.	1Q06	U.S.

IV. Deliverables, Performance Indicators and Outcomes

Deliverables 2004-2005	Performance Indicators	Time Frame	Outcomes
Compounds and Platform Technologies			
Management of 10 portfolio projects	• Development Plan for each compound • Projects reaching key milestones	4Q04-3Q05	Detailed development plans and Gantt charts, with key go/no go decision points, milestones and time lines for all projects in our portfolio were implemented. Key milestones reached in the discovery projects included identification of new chemical series with potential to be developed as drugs. In the development projects, Phase I studies were initiated with PA-824 and a CRO was hired to manage the moxifloxacin project.
Portfolio expanded	• At least 3 projects in the portfolio	12/2/04	TB Alliance signed an agreement with GSK to collaborate on four new discovery projects (ICL inhibitors, InhA inhibitors, pleuromutilins and focused screening compounds active against known antimicrobial targets for anti-TB activity).
Support of AAA in contract negotiations	• All contracts include affordability clauses	4Q04-3Q05	Affordability clauses have been incorporated into all contracts
Further investment in platform technologies	• Additional platform project launched	4Q04-3Q05	TB Alliance has laid the ground work for implementation of regulatory guidelines and use of surrogate markers in TB clinical trials through meetings with regulatory agencies both in the US and Europe. Major follow up meetings have been scheduled with Key Opinion Leaders/FDA and EMEA for 4Q2005. Activities have been initiated and an RFP is being prepared to invest in facilities that will provide high capacity screening of clinical candidates administered in combination with each other.
Clinical Trials and Regulatory Approval			
Develop PA-824 investigators' brochure	• Investigators' brochure in place	4/27/05	The PA-824 Investigators' Brochure was submitted to the FDA with the IND.
Meet the FDA requirements for the PA-824 Investigational New Drug application process (IND)	• IND application document developed	4/27/05 (IND submission date)	Based upon the data in our IND, the FDA did not deny permission to evaluate PA-824 in humans.
Prepare trial sites	• Site explorations/evaluation reports	4Q04-3Q05	Study sites were evaluated for Phase I studies with PA-824, resulting in selection of MDS to perform the single and multiple dose studies, and ICON and PharmaNet to perform the site monitoring.
Plan trials	• Protocol for Phase I study established	1Q05	A protocol for the Phase I single ascending dose study with PA-824 was finalized.

Deliverables 2004-2005	Performance Indicators	Time Frame	Outcomes
Initiate and manage trials	• Contracts signed for PA-824 Phase I studies (single- and multiple-dose)	4/05 (single dose)	A contract was signed with MDS Pharma to perform single dose Phase I study. TB Alliance received proposals to perform Phase I multiple-ascending dose study from MDS Pharma, and from PharmaNet to perform the site monitoring. These contracts will be signed shortly.
Outreach and Mobilization			
Maximize expert input in portfolio management and trials	• Convene two SAC meetings and one meeting of each Expert Working Committee • Sponsor one Annual International Expert Meeting on selected Scientific Study (*e.g.,* latency or surrogate markers)	2/05 and 7/05 (SAC) 8/29/05 7/5/05	Held two SAC meetings. Of the five Expert Working Committees, a meeting was held with the Alternative Delivery Systems Group. A meeting of the Clinical Development Surrogate Markers Group is scheduled for 11/29/05. Meetings with the other Groups have not been required. TB Alliance sponsored an International Expert Working Group meeting on use of animal models in TB drug discovery
Mobilize expertise internationally	• Support two symposia on new drugs at international venues such as IUATLD, ICAAC, etc.	10/04(IUATLD) 7/05 (GRC)	TB Alliance sponsored a symposium on new drug development at the IUATLD meeting, and provided financial support to Gordon Research Conference on New Drug Development for scientists to travel from endemic countries
Mobilize endemic countries	• Execute six Memoranda of Understanding with endemic countries by end of 2005 • Sponsor a joint publication or study on new drugs with an endemic country • Convene Stakeholders' meeting in an endemic country		MOUs signed with Brazil, Peru, South Africa, and India with two additional planned for 2006 Join publication planned for 2006 Stakeholders meeting in endemic country planned for 2006
Stop TB collaborative projects	• Convene an annual meeting of the Stop TB working group	29/10	40 participants

Appendix 1. **TB Alliance Portfolio**



Appendix 2. Scientific Advisory Committee

Dr. Ken Duncan
Programme Director
Centre for Molecular Microbiology and Infection
Imperial College London

Dr. Bernard Fourie (Secretary)
Coordinator, South African TB Trials Consortium
South African Medical Research Council

Dr. Maria C. Freire
President & Chief Executive Officer
Global Alliance for TB Drug Development

Dr. Jacques Grosset
Visiting Professor
Johns Hopkins University School of Medicine

Dr. Barbara Laughon (Chair)
Chief, Complications and Co-infections Research Branch
Therapeutics Research Program
Division of AIDS
National Institute of Allergy and Infectious Diseases

Dr. Christopher A. Lipinski
Adjunct Senior Research Fellow
Pfizer Global Research and Development

Dr. Denis Mitchison
Professor Emeritus
Department of Medical Microbiology
St. George's Hospital Medical School

Dr. Rick O'Brien
Head of Scientific Evaluation
Foundation for Innovative New Diagnostics

Dr. Ramesh Panchagnula
Professor in Pharmacy
School of Biomedical Sciences
University of Ulster

Dr. Philippe Prokocimer
Vice-President, Clinical Drug Evaluation
Johnson & Johnson Pharmaceutical Research & Development LLC

Dr. Mel Spigelman
Director of Research and Development
Global Alliance for TB Drug Development

Dr. C. Kendall Stover
Senior Director, Antibacterial Research
Pfizer Global Research & Development

Appendix 3. Scientific Advisory Committee - Subcommittees

Expert Working Committees

Clinical Development and Surrogate Markers Ken Duncan, Ph.D.; Ann Ginsberg, M.D., Ph.D.; Bernard Fourie, Ph.D.; Denis Mitchison, M.D.; Rick O'Brien, M.D.; Philippe Prokocimer, Ph.D.

Latency and Persistence Clif Barry, Ph.D.; Ken Duncan, Ph.D.; Ann Ginsberg, M.D., Ph.D.; Jacques Grosset, M.D.; Mitchison, M.D.; C. Kendall Stover, Ph.D.

Screening/Targets Clif Barry, Ph.D.; Ken Duncan, Ph.D.; Barbara Laughon, Ph.D.; Christopher A. Lipinski, Ph.D.; Zhenkun Ma, Ph.D.; C. Kendall Stover, Ph.D.

Immunotherapeutics Ken Duncan, Ph.D.; Ann Ginsberg, M.D., Ph.D.

Alternative Delivery Systems Clif Barry, Ph.D.; Jacques Grosset, M.D.; Dean Haubrich, Ph.D.; Denis Mitchison, M.D.; Rick O'Brien, M.D.; Philippe Prokocimer, Ph.D.

TB Alliance Project Oversight Groups

PA-824 and Back-up Program Ann Ginsberg, M.D., Ph.D.; Barbara Laughon, Ph.D.; Christopher A. Lipinski, Ph.D.; Ramesh Panchagnula, Ph.D.

Wellesley Barbara Laughon, Ph.D.; Christopher A. Lipinski, Ph.D.; Zhenkun Ma, Ph.D.

KRICT Barbara Laughon, Ph.D.; Christopher A. Lipinski, Ph.D.; Zhenkun Ma, Ph.D.; Denis Mitchison, M.D.

JHU Bernard Fourie, Ph.D.; Dean Haubrich, Ph.D.; Barbara Laughon, Ph.D.; Denis Mitchison, M.D.; Rick O'Brien, M.D.

IUATLD Bernard Fourie, Ph.D.; Dean Haubrich, Ph.D.; Barbara Laughon, Ph.D.; Denis Mitchison, M.D.; Rick O'Brien, M.D.

Moxifloxacin Ann Ginsberg, M.D., Ph.D.; Rick O'Brien, M.D.; Philippe Prokocimer, Ph.D.

Macrolide Dr. William Baker; Zhenkun Ma, Ph.D.; Ken Duncan, Ph.D.; C. Kendall Stover, Ph.D.

GSK Dean Haubrich, Ph.D.; Ken Duncan, Ph.D.; C. Kendall Stover, Ph.D.; Christopher A. Lipinski, Ph.D.

Appendix 4. Selected Presentations by R&D Team at Key Scientific Conferences

Conference	Date / Location	Presenter
Tuberculosis Trials Consortium meeting	October 2004, Atlanta	Dr. Ann Ginsberg
International Union Against TB and Lung Disease meeting; New Drugs symposium	October 2004, Paris	Dr. Ann Ginsberg
Interscience Conference on Antimicrobial Agents and Chemotherapy: Novel Agents Against Mycobacterium Tuberculosis	November 2004, Washington, DC	Dr. Melvin Spigelman
Healing the Scar - Drugs for Neglected Disease Initiative seminar in association with Oxfam/MMV/TB Alliance/MSF	January 2005, London	Dr. Maria Freire
Tuberculosis Trials Consortium meeting	February 2005, Atlanta	Dr. Ann Ginsberg
Conference: A Time to Heal; Cracking Africa's Killer Diseases, Africa Genome Education Institute	March 2005, Nairobi	Dr. Gerald Siuta
Global Plan to Stop TB 2006-15, Working Group on New Vaccines	May 2005, Ethiopia	Dr. Maria Freire
Center for Strategic and International Studies meeting	May 2005, Washington, DC	Dr. Ann Ginsberg
Bill & Melinda Gates Foundation, Persistence meeting	May 2005, Tres Cantos, Spain	Dr. Ann Ginsberg
Tuberculosis Trials Consortium annual meeting	May 2005, San Diego	Dr. Ann Ginsberg
Gordon Research Conference	July 2005, Biddeford, ME	Dr. Doris Rouse
Gordon Research Conference: Lead Optimization and ADME	July 2005, Biddeford, ME	Dr. Melvin Spigelman
Workshop on Licensing and Social Responsibility, Association of University Technology Managers Eastern Region Meeting	July 2005, Annapolis, MD	Dr. Gerald Siuta
International AIDS Society: HIV/TB Co-infection: new Visions, New Directions HIV & TB: Addressing the Challenge Through New Treatment and New Strategies	July 2005, Rio de Janeiro	Dr. Melvin Spigelman

Appendix 5.

National TB Program Manager Survey

As a first step in predicting potential challenges and considerations surrounding the adoption of a new TB regimen, the TB Alliance conducted a brief, preliminary survey to gather anecdotal evidence about the external environment for new drugs. Distributed in late 2004, the survey gauged demand and perceived impact of new drugs for TB and polled respondents regarding likely obstacles to adoption of a new, shorter TB regimen. The survey also examined respondents' opinions on the need for new drugs to treat MDR-TB and TB/HIV co-infection.

The nine-question survey was made available by email attachment and through an interactive webpage to 39 potential respondents. It was sent to a target audience of NTP managers and TB control experts from the 22 high-burden countries (HBCs). In addition, the TB Alliance also selected a number of non-HBCs including NTPs from Japan, Malaysia, Mongolia, Peru, Singapore, and Sudan. The TB Alliance received responses from 15 NTPs, NGOs, and TB control experts from Indonesia, Malaysia, Netherlands, Peru, the Philippines, Singapore, Sudan, Tanzania, Thailand, Uganda, Vietnam, and Zimbabwe.

Responses indicate that nearly all survey participants feel that a shorter regimen for TB is important, including one that will treat MDR-TB and co-infected TB/HIV patients. Responders reported that a shortened therapy would have a significant impact for NTPs as well for patients. All respondents said that they would support the adoption of a hypothetical 4-month treatment regimen if one were available.

In the free response section, the respondents listed the following issues as key to adoption:

- Proof of efficacy in clinical trials (7)
- Endorsement by WHO (5)
- Fixed-dose combination (FDC)(5)
- ARV compatibility (3)
- Endorsement by national authorities or medical experts (3)
- Training of healthcare workers (2)
- Cost-effectiveness (1)

Identifying possible hurdles to adoption, survey respondents noted the following concerns:

- Availability in marketplace
- Cost of drug, cost of training and introduction
- Resistance to change among healthcare providers who may have recently invested time and energy into revising existing regimens (to FDCs, for example)

As compounds move from preclinical development into human trials, more extensive research into these questions and a better understanding of provider and patient perspectives will be critical. For this reason, in the coming years, the TB Alliance plans a series of roundtable discussions, interviews, and surveys to actively engage key stakeholders (service providers from endemic countries, patients and activists, and national TB programs) in drug design. Issues to be explored will include drug/drug interactions, side effects and dosing frequency.

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

October 24, 2006

Ms. Susan Bacheller
CTO (USAID/GH/HIDN/ID)
Agreement Officer
U.S. Agency for International Development
1300 Pennsylvania Avenue, NW
M/FM/CMP/MP
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.

Project Title/Activity:	Phase I clinical trial (PA-824)
Project Number:	GHS-A-00-04-00015-00
Reporting Period:	October 1, 2005 – September 30, 2006
CTO and Technical Advisor:	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 than12 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.

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

Project Title/Activity:	Lead Optimization and Preclinical
Project Number:	GHS-A-00-04-00015-00
Reporting Period:	October 1, 2005 – September 30, 2006
CTO and Technical Advisor:	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.

TB ALLIANCE
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October 11, 2007

Ms. Susan Bacheller
CTO (USAID/GH/HIDN/ID)
Agreement Officer
U.S. Agency for International Development
1300 Pennsylvania Avenue, NW
M/FM/CMP/MP
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 three of the four-year award to the Global Alliance for TB Drug Development (TB Alliance). This report covers the period between October 1, 2006 and September 30, 2007.

As a result of USAID funding, the TB Alliance made great strides in its clinical trial program during this time; its nitroimidazole PA-824 initiated Phase II and the moxifloxacin-containing treatment-shortening regimen completed Phase II testing and is poised to start Phase III. USAID's continued support has been critical to TB Alliance's progress and we thank you. 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

80 Broad Street, 31st Floor • New York, NY • 10004 • USA • +1 (212) 227-7540 • www.tballiance.org

Office of Health, Infectious Diseases and Nutrition Portfolio Review

United States Agency for International Development (USAID)

October 09, 2007

Organization:	Global Alliance for TB Drug Development
Type of Organization:	Non-profit, tax-exempt organization recognized under section 501(c)3 of the U.S. Internal Revenue Service Code
Contact Person:	Maria C. Freire, Ph.D. President and Chief Executive Officer maria.freire@tballiance.org tel: +1 (212) 227 7540 x 202 or Asmita Barve Grants Analyst asmita.barve@tballiance.org tel: +1 (212) 227 7540 x 241 fax: +1 (212) 227 7541
Cooperative Agreement:	GHS-A-00-04-00015-00
Period Considered:	October 1, 2006 – September 30, 2007

New York: 80 Broad Street, 31st Floor, New York, New York, 10004
Brussels: Avenue Louise 179, 1050 Brussels, Belgium
Pretoria: Enterprise Building, 1st Floor, The Innovation Hub, Pretoria, South Africa

I.

Project Title/Activity: Phase I clinical trial (PA-824)

Project Number: GHS-A-00-04-00015-00

Reporting Period: October 1, 2006 – September 30, 2007

CTO and Technical Advisor: Susan Bacheller and Christy Hanson

Brief description of project:

PA-824 belongs to a highly promising class of anti-TB agents called nitroimidazoles, which possess a novel mechanism of action. In early tests, the compound has demonstrated several characteristics that make it a very desirable anti-TB drug candidate. For example, in mouse studies, PA-824 was active against replicating as well as persistent bacteria thereby demonstrating its potential role in shortening TB therapy. Further, the compound is effective against all drug-resistant clinical isolates tested to date and therefore may be useful in the treatment of drug-resistant TB, both multidrug resistant (MDR) and extensively drug resistant (XDR). Also noteworthy, PA-824 does not exhibit potential for drug-drug interactions and therefore can likely be co-administered safely with antiretroviral (ARV) agents to treat TB-HIV co-infections.

At the start of USAID grant year three, PA-824 was in Phase I clinical trials. A renal effects study had been initiated in response to an asymptomatic increase in serum creatinine levels in some volunteers during the Phase I, multi-dose study. Other planned activities for the grant year included a food effects study to evaluate the effect of food versus fasting on the pharmacokinetic (PK) profile of PA-824 in healthy volunteers; and a proof-of-concept study to assess extended Early Bactericidal Activity (EBA) at several doses of PA-824 in adult patients with newly diagnosed, drug-sensitive, uncomplicated pulmonary TB.

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

- The Phase I, double-blind, placebo-controlled, multi-dose, renal effects study initiated in June 2006 to determine the mechanism underlying the isolated serum creatinine elevations observed in some subjects receiving PA-824 during the Phase I multi-dose study was concluded as planned in Q4 2006. The formal study report was completed in Q3 2007.
    - The essential findings from the renal effects study are that although PA-824 transiently elevates serum creatinine, it does not cause an effect different from placebo on glomerular filtration rate, effective renal plasma flow, filtration fraction, blood urea nitrogen (BUN), or uric acid. PA-824, therefore, does not appear to cause kidney damage but rather causes an isolated and apparently clinically benign elevation of serum creatinine by inhibiting its tubular secretion. Other marketed drugs, for example, cimetidine, exert a similar effect.

- A Phase I food effects study was conducted end of Q1 – beginning of Q2 2007 in 16 healthy male and female volunteers to evaluate the PK profile of PA-824 under fed (high-fat, high-calorie) versus fasting conditions. Results show that exposure to PA-824 following a single 1000mg dose is increased 3.5- to 4.5- fold in the fed versus fasted state.

- Patient enrollment into a proof-of-concept study assessing extended Early Bactericidal Activity (EBA), safety, and PK of PA-824 in adult patients with newly diagnosed, drug-sensitive pulmonary TB was initiated in two Cape Town sites in Q3 2007 following approval of the study by the Medicines Control Council (MCC) and the relevant ethical review committees in South Africa. Over one third of the anticipated 68 patients have been enrolled as of September 24, 2007.

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

- The EBA study start date was postponed from Q2 2007 to Q3 2007 primarily because study and protocol approval by MCC and the appropriate ethical review committees in South Africa took longer than anticipated.

- Formulation work will be performed to try to increase bioavailability of PA-824 in the fasted state and at the same time mitigate the food effect. If the results of the extended EBA and fed-safety studies confirm the need to reformulate PA-824, then this work will likely delay start of Phase IIb.

- As PA-824 advances through clinical development and approvals are required from regulatory agencies and Ethical Review Committees in TB-high burden countries, estimating realistic timelines and planning for projects will be increasingly challenging.

- Centers capable of performing clinical studies under Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) registration standards are limited. Therefore, the timelines for clinical studies could be adversely affected as the necessary capacity is built or strengthened.

Strategic Activities and Results to be Achieved in FY 2008: (by results areas, bullet points only)

- Phase I Activities:
  - Conduct a mass balance ADME study with radiolabeled PA-824, this time with the radiolabel on the "warhead" part of the molecule instead of the "tail." The study is scheduled to begin and complete enrollment in Q1 2008, with draft analytical and metabolite results available in Q2 2008.

  - Perform a drug-drug interaction study. Patient enrollment is expected to be completed Q1 2008 and the report finalized in Q2 2008.

  - Conduct a fed-state safety study to evaluate PK and safety of multiple dosing in healthy volunteers under this condition. Patient enrollment is expected to begin in Q4 2007 and finish end of Q1 2008.

- Phase II Activities:
  - Complete the extended EBA study (last patient out) in Q1 2008.

  - Explore alternative formulations to minimize food effect while achieving higher exposures in humans than possible with current formulation in the absence of food (Q4 2007 – Q1 2008).

  - Plan a Phase IIb trial of two-month intensive phase treatment with a PA-824-based regimen in adult TB patients. Timing of study start may depend on duration and success of formulation work, if extended EBA and fed-safety states indicate that reformulation is required to achieve desirable efficacy.

II.

Project Title/Activity: Moxifloxacin Phase II clinical trial (TBTC Study 28)

Project Number: GHS-A-00-04-00015-00

Reporting Period: October 1, 2006 – September 30, 2007

CTO and Technical Advisor: Susan Bacheller and Christy Hanson

Brief description of project:

Moxifloxacin is a fluoroquinolone – a third generation subset of the quinolone class of antibiotics. Quinolones target DNA gyrase, an enzyme that unravels the tightly twisted DNA double-strand to allow DNA replication and facilitate transcription of some genes. By inhibiting DNA gyrase, quinolones directly impact bacterial cell multiplication, repair and survival. Of all the new TB regimens tested, moxifloxacin-containing regimens have yielded the most dramatic treatment-shortening results in animal models. In preclinical studies commissioned by the TB Alliance in 2002-03, investigators at Johns Hopkins University found that substituting moxifloxacin for isoniazid, a currently used first-line drug, in a mouse model system decreased the amount of time needed to eradicate TB infection by two months.

Moreover, since it has a novel target relative to first-line TB drugs, moxifloxacin is equally effective against many multidrug resistant strains as against drug-sensitive *M. tuberculosis*. Also, moxifloxacin does not interact with the cytochrome P450 enzyme system that is involved in the metabolism of some antiretrovirals used in the treatment of HIV/AIDS. Therefore, it can potentially be used safely to treat TB in individuals with HIV/AIDS concurrently taking antiretroviral agents.

The moxifloxacin clinical program funded by USAID helps to support two trials: TB Trials Consortium (TBTC) Study 28 and the REMoxTB Study. This section describes developments in the TBTC trial. A detailed description of the REMox TB study is provided later in the document in a separate section. TBTC Study 28 is a Phase II study evaluating the safety and efficacy of substituting moxifloxacin for isoniazid during the first two months of standard TB therapy. As reported in the work plan for year three, the TB Alliance had planned to complete the primary study endpoint (two-month sputum conversion) in this grant period.

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

- Enrollment into TBTC Study 28 (433 patients) was completed end of Q1 2007 – just over a year from enrollment of the first patient into the study. This was possible because the TB Alliance anticipated a potential future resource shortage and with help from USAID added funding, regulatory support, and staff to the main international

site (in Uganda) in time to ensure efficient enrollment. This site recruited approximately 50 percent of the total patients enrolled into the study. The last subject enrolled completed study treatment and the primary endpoint in Q2 2007, earlier than the Q3 2007 time frame estimated in the year three work plan.

- Because the primary study endpoint was achieved in Q2 2007, preliminary efficacy data became available in the same quarter. This information was useful in advancing a four-month, moxifloxacin substituted for isoniazid, treatment-shortening regimen into Phase III clinical development (please see description of revised REMoxTB trial, below).

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

- Due to the extensive involvement of third-parties in this project, the planning process is a challenging task. The TB Alliance creates project schedules and allocates resources such that it can respond efficiently to unexpected results and attempt to avoid or at least minimize delays.

Strategic Activities and Results to be Achieved in FY 2008: (by results areas, bullet points only)

- Complete the secondary endpoint (6-9 months after onset of treatment; Q4 2007) in the Phase II TBTC Study 28.

- Complete and finalize study report by Q2 2008.

III.

Project Title/Activity:	Moxifloxacin Phase III clinical trial (REMoxTB)
Project Number:	GHS-A-00-04-00015-00
Reporting Period:	October 1, 2006 – September 30, 2007
CTO and Technical Advisor:	Susan Bacheller and Christy Hanson

Brief description of project:
At the beginning of grant year three, the REMoxTB trial, then planned as a Phase II/III three-arm trial evaluating a regimen replacing isoniazid with moxifloxacin during the first two months of TB treatment in a Phase II design and a regimen substituting ethambutol with moxifloxacin to shorten treatment to four months in a Phase III design, was scheduled to begin patient enrollment in Q4 2006. However, study start was delayed primarily because of additional data requested by FDA on the study drugs and the need to re-source rifampin and its matching placebo. Enrollment for the REMoxTB study is now expected to commence in late Q4 2007 or early Q1 2008. In the meantime, because

results from TBTC Study 28 would now become available before enrollment for the REMoxTB study would begin, the TB Alliance and its partners in this project changed the REMoxTB trial design from Phase II/III to entirely Phase III with two treatment-shortening arms (one replacing ethambutol with moxifloxacin and the other, replacing isoniazid with moxifloxacin) compared to a control arm with standard treatment. This trial design change necessitated an increase in patient enrolment.

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

- As mentioned above, the start date for the REMox TB trial was delayed by approximately a year due to complications with the study drug supply and FDA requests for additional data (see section below on implementation hurdles for details). However, the TB Alliance took advantage of the delay to modify the study design such that the time required to evaluate the regimen substituting isoniazid with moxifloxacin would be several months shorter than originally planned. Assuming no further delays, filing for a TB treatment-shortening indication for moxifloxacin, whether moxifloxacin replacing ethambutol or moxifloxacin replacing isoniazid, or both, is now scheduled for Q3 2011.

- The TB Alliance added three additional trial sites to the original three selected for this trial, and provided Good Clinical Practice (GCP)-training and strengthened capacity to prepare all six sites for participation in the trial during grant year three.

- The TB Alliance assumed responsibility for ensuring the supply, stability testing, labeling and distribution of the study drug to the sites and also identified a Good Manufacturing Practice (GMP)-approved supplier of study drugs and matching placebos. In response to FDA recommendations (see below), the TB Alliance completed dissolution-equivalence studies for trial drugs sourced from a World Health Organization (WHO)/Global Drug Facility GMP-approved but non-US manufacturer in Q1 2007 and secured a US-approved replacement for its existing rifampicin supplier (please see following section for details).

- A modified REMoxTB trial protocol was submitted to appropriate regulatory authorities and ethical committees in four African countries for review and approval in Q1 2007.

- Packaging of initial drug supplies for the study was completed.

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

- The start of the REMoxTB study, originally planned for Q4 2006, was postponed for two main reasons: first, to take advantage of newly available Phase II results (from TBTC Study 28) and include <u>two</u> treatment-shortening regimens in Phase III

(discussed above), and second, because of issues with the study drugs. With regard to the study drugs,

- The TB Alliance needed to identify a GMP-certified source of study drugs (isoniazid, rifampin, pyrazinamide and ethambutol) that was able to supply matching placebos (isoniazid-, rifampin- and ethambutol- placebos) as opposed to over-encapsulated study drugs, which are less effective at maintaining the "blinded" study design. Eventually, a supplier was selected as the drug source for its WHO-GMP approved manufacturing sites and its record as a contracted supplier of anti-TB drugs to the Global TB Drug Facility (GDF)

- Further delay resulted because the FDA, at a pre-Phase III meeting in Q4 2006, requested dissolution-equivalence data with respective formulations approved for use in the US for ethambutol, isoniazid and pyrazinamide. The FDA also recommended that the TB Alliance obtain bioequivalence data for the rifampicin supply sourced from the same manufacturer with the rifampicin capsules formulation marketed in the US or replace it with a US-approved product. The TB Alliance chose to do the latter as it was the faster route to study start. The recommended dissolution-equivalence studies were successfully completed beginning of Q1 2007 and a donation of rifadin in capsule formulation was secured from Sanofi-Aventis, along with matching placebo.

Strategic Activities and Results to be Achieved in FY 2008: (by results areas, bullet points only)

- Begin patient enrollment into the REMoxTB trial in Q4 2007 or Q1 2008.

- The TB Alliance has planned an expansion in study size of the REMox TB trial from 1,500 to 2,400 patients. To accommodate this increase, additional sites in Africa, Asia, Europe and/or Latin America will be assessed, recruited to trial, and readied for study participation. This increase should provide increased statistical power (90%), helping to ensure a clear answer at study end. However, this increase in study size may extend the timeline as there are few, if any, sites currently available globally that are ready to participate without significant capacity-building and preparation in these registration-standard, pivotal trials for TB treatment evaluation.

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

December 22, 2008

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

Re: Cooperative Agreement No. GHS-A-00-04-00015-00

Dear Ms. Bacheller:

Per section A.5.3. of the Cooperative Agreement No. GHS-A-00-4-00015-00, please find, herewith, our final report for the award to the Global Alliance for TB Drug Development (TB Alliance). This report covers the entire award period, from September 14, 2004 to September 30, 2008.

With the support of United States Agency for International Development (USAID) funding, the TB Alliance has significantly advanced its clinical program over the past four years. Our nitroimidazole PA-824, which reached the first-in-man study milestone in June 2005, is now in Phase II development. The moxifloxacin program has begun patient enrolment for a pivotal Phase III trial, making it one of the most advanced clinical development programs for the treatment of active TB in over forty years.

The TB Alliance greatly appreciates USAID's support, which has been and continues to be critical to our progress in combating TB. Please contact us if you have any questions.

Sincerely,

Mel Spigelman, M.D.
Director of Research and Development

Cc: Christy Hanson
Erica Lessem

Office of Health, Infectious Diseases and Nutrition Portfolio Review

United States Agency for International Development (USAID)

December 22, 2008

Organization:	Global Alliance for TB Drug Development
Type of Organization:	Non-profit, tax-exempt organization recognized under section 501(c)3 of the U.S. Internal Revenue Service Code
Contact Person:	Mel Spigelman, M.D. Director of Research and Development melvin.spigelman@tballiance.org Tel: +1 (646) 616 8603 Fax: +1 (212) 227 7541 or Erica Lessem Grants Writer erica.lessem@tballiance.org Tel: +1 (646) 616 8638 Fax: +1 (212) 227 7541
Cooperative Agreement:	GHS-A-00-04-00015-00
Period Considered:	September 14, 2004 – September 30, 2008

New York: 40 Wall Street, 24th Floor, New York, New York, 10005
Brussels: Galeries de la Toison d'Or, 29 Chaussée d'Ixelles, #393/16, B-1050 Brussels, Belgium
Pretoria: Enterprise Building, 1st Floor, The Innovation Hub, Pretoria, South Africa

Final Narrative Report

I. Background and Rationale

Sixty years after the discovery of streptomycin, the first effective antibiotic against tuberculosis (TB), the disease remains a major infectious cause of death worldwide, second only to HIV/AIDS. In 2006, TB claimed 1.7 million lives and over 9.0 million new cases were recorded.[1] Existing therapy has serious shortcomings that limit its ability to adequately address the disease. The standard WHO-recommended treatment of drug-sensitive TB is six to eight months long, complex, hinders patient adherence, and thereby fuels drug resistance. Further, it places an enormous burden on already resource-strapped health systems. Findings of the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance clearly point to the link between incomplete or inadequate treatment and resistance development: previously treated cases are more likely not only to be drug-resistant but also to have resistance to more drugs than previously untreated cases.[2] Furthermore, data show that drug-resistance is rising. A recent WHO survey on anti-tuberculosis drug-resistance reported the highest rates of drug-resistant TB ever.[3] About half a million, or 5 percent of new TB cases reported in 2006, were multidrug-resistant TB (MDR-TB). Extensively drug-resistant TB or XDR-TB[4], a form of the disease which is even more difficult to treat, has been reported in 49 countries around the world.

One of the many challenges facing TB control is the deadly nexus between TB and HIV. It is estimated that one third of the 40 million people living with HIV/AIDS worldwide are co-infected with *Mycobacterium tuberculosis (M. tb)*, the pathogen that causes TB. The disease is a leading killer in this population, responsible for 200,000 deaths in 2006 alone. At the same time, HIV is fueling the TB epidemic. HIV-positive individuals are 50 times more likely to develop active TB in a given year than HIV-negative people. Treatment of TB in TB-HIV co-infected individuals is complicated by drug-drug interactions between rifampicin, a cornerstone TB drug, and commonly used antiretrovirals (ARVs). New drugs are urgently needed to tackle the many challenges that TB poses. As stated in the Stop TB Partnership's Global Plan, TB control cannot be achieved without new tools.[5]

Shortened and significantly improved anti-TB regimens would not only save countless lives of those afflicted with drug-sensitive and drug-resistant TB but also have a far-

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[1] WHO Report. 2008. *Global Tuberculosis Control—surveillance, planning and financing.*

[2] World Health Organization. 2004. *Anti-Tuberculosis Drug Resistance in the World: Third Global Report.* Geneva: WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance.

[3] World Health Organization. 2008. *Anti-Tuberculosis Drug Resistance in the World: Fourth Global Report.* Geneva: WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance.

[4] MDR-TB describes TB strains that are resistant to at least the two main first-line TB drugs - isoniazid and rifampicin. XDR-TB is MDR-TB that is also resistant to at least a fluoroquinolone and an injectable aminoglycoside.

[5] Stop TB Partnership and World Health Organization. 2006. *Global Plan to Stop TB 2006–2015.* Geneva: World Health Organization.

reaching socio-economic impact. TB primarily affects people in their most productive years, between the ages of 15 and 54.[6] Direct (e.g., cost of accessing treatment) and indirect (e.g., lost wages) costs associated with TB are substantial because of the long duration of treatment. The WHO calculates that the average patient loses three to four months of work-time due to this disease, with lost household earnings ranging from 30 to 100 percent. In some countries, loss of productivity attributable to TB is on the order of four to seven percent of GDP. The disease plays an important role in perpetuating the cycle of poverty by preventing families from investing in their future. For example, every year in India alone, more than 300,000 children leave school on account of their parents' TB.[7]

A shorter, more effective TB therapy would reduce the direct and indirect costs associated with TB treatment and thereby lower the prohibitive economic burden the disease places on poor families. On a macroeconomic level, shorter treatments can minimize productivity-related losses—which some estimates have put as high as $12.0 billion per year, decrease the burden on health systems and free up valuable resources for use in other critical development areas.

II. Program Goals, Objectives, and Activities

A. Program Goals and Objectives

The mission of the Global Alliance for TB Drug Development (TB Alliance or Alliance) is to markedly improve TB therapy by developing new and improved drugs and regimens that shorten and simplify TB treatment. This includes treatment of active disease, both drug-sensitive and drug-resistant, TB in patients co-infected with TB and HIV, and latent infection. Critical to this mission is the effort to ensure that these novel medicines, once developed, are *affordable*, *available* and can be *adopted* in poor countries, which disproportionately bear the heavy health and economic burden of the disease.

To accomplish its mission of universally available, affordable and significantly improved anti-TB treatments, the TB Alliance has adopted a multi-pronged approach.

- ***Expand and Strengthen its R&D Pipeline.*** In the eight years since its inception, the TB Alliance has built the largest single portfolio of potential TB compounds ever assembled, comprising compounds spanning early discovery through late clinical development. Through active monitoring and direct management, the TB Alliance maintains a robust and well-balanced product portfolio. After thorough scientific, technical and legal due diligence, those projects that fit a specific pre-defined drug profile and strengthen the overall pipeline are selected for inclusion in the portfolio. Once in the portfolio, drug candidates are driven through a milestone-based gated

[6] *HIV/AIDS, Tuberculosis, and Malaria: The Status and Impact of the Three Diseases.* A Global Fund publication with the Roll Back Malaria, Stop TB, and HIV departments of the World Health Organization and UNAIDS; 2005.
[7] Ibid.

drug development process to ensure that R&D investments are only used for advancing the most promising candidates.

The TB Alliance has made particular progress in the past four years with the initiation and advancement of its clinical development program. Currently two drug candidates, moxifloxacin and PA-824, are in late-stage clinical trials. Over the next few years, the TB Alliance expects to significantly expand its clinical development program through new collaborations and by advancing its own drug candidates into clinical trials.

- ***Catalyze TB Drug Development.*** Decades of inactivity in TB drug development have left the field in disarray with critical gaps related to clinical trial infrastructure, research tools, and a defined regulatory framework for the approval of new TB drugs and regimens. The TB Alliance has identified strategic initiatives to address these needs which, if successful, will drive considerable advances in the field of TB drug development. Examples of these initiatives include: development and testing of an innovative approach for developing new TB drug regimens that involves advancing optimized *combinations* (rather than single drugs) through the drug development pipeline; identification of biomarkers of treatment efficacy which could dramatically reduce the duration of clinical development timelines; the global mapping of registration-standard clinical trial capacity to aid planning and preparedness for TB trials; and the coordination of Open Fora to engage drug developers, regulatory authorities and other stakeholders worldwide in clarifying the registration process for new TB drugs.

- ***Ensure Affordability, Adoption and Availability (AAA).*** All activities of the TB Alliance, from early discovery through clinical development, registration and product introduction, are guided by the recognition that the ultimate success of its mission depends on the use of its drugs in the field. The TB Alliance, through its studies on TB-endemic markets, is building an evidence base to inform product development, including the clinical trial process, to identify key in-country and global stakeholders to facilitate drug availability and adoption, and to prepare for introduction of its products in different countries.

In September 2004, USAID awarded the TB Alliance a US $8 million grant to be disbursed over four years. The vast majority of this grant has been used to support clinical trials for drug candidates. Largely because of USAID's contribution, the Alliance's two clinical projects, PA-824 and moxifloxacin, have made significant strides over the past four years. In the case of PA-824, for example, the TB Alliance initiated a first-in-man study in June 2005. In 2007, the compound entered Phase II development. Moxifloxacin, the other clinical project, is one of the most advanced clinical development programs for the treatment of active TB in over forty years. As such, it is also blazing a trail for future TB drug development by identifying clinical trial capacity gaps, developing registration-standard trial and laboratory capacity in many high-burden countries, and defining and addressing regulatory issues specific to TB drug development with relevant authorities. Over the course of the grant period, the project has made significant progress and has now begun enrolling patients into a Phase III pivotal

registration trial evaluating the treatment shortening potential of two moxifloxacin-containing regimens.

While most of the USAID grant has been used to fund the TB Alliance's clinical development projects, a portion of the funds in the first two grant years was also allocated to discovery projects including lead identification and optimization for nitroimidazoles, macrolides and quinolones. A very small part of the grant was used during the first year to support AAA activities, such as a symposium on new TB drugs conducted in collaboration with the Stop TB Partnership's Working Group on New Drugs, a meeting of TB Alliance Stakeholders' Association and a study exploring the epidemiological impact of a new drug regimen.

The next section primarily focuses on the developments and accomplishments in the two clinical programs funded by USAID over the four-year grant period. For each clinical development program, a summary of progress made during the first three grant years is followed by a more detailed overview of activities and results achieved in grant year four, since the last grant year has not been covered in previous annual reports. The section also includes a brief description and update on discovery projects funded by USAID during the first two grant years

B. Update on Program Activities

1. PA-824

Project Title/Activity:	Phase I clinical trial (PA-824)
	Phase II clinical trial (PA-824)
Project Number:	GHS-A-00-04-00015-00
CTO and Technical Advisor:	Christy Hanson and Susan Bacheller

Brief description of project:
PA-824 belongs to a highly promising class of anti-TB agents called nitroimidazoles, which possess a novel mechanism of action. In early tests, the compound has demonstrated several characteristics that make it a very desirable anti-TB drug candidate. For example, in mouse studies, PA-824 was active against replicating as well as persistent bacteria, thereby demonstrating its potential role in shortening TB therapy. Further, the compound is effective against all drug-resistant clinical isolates tested to date and therefore should be effective in the treatment of drug-resistant TB, both multidrug resistant (MDR) and extensively drug resistant (XDR). Also noteworthy, PA-824 does not exhibit potential for drug-drug interactions and therefore can likely be co-administered safely with antiretroviral (ARV) agents to treat TB-HIV co-infections. Currently, PA-824 is in Phase II clinical trials; a detailed description of the project's status is provided below.

Key Results and Accomplishments:

Grant Years One, Two and Three:
The TB Alliance filed an Investigational New Drug Application (IND) with the FDA in April 2005 and initiated the first-in-man study with PA-824 in June 2005. USAID funding in grant year one was used to support the PA-824 Phase I single dose study. Safety and pharmacokinetic results indicated a good safety profile for the drug at high doses and substantial drug exposure. The subsequent Phase I, multi-dose study to examine safety, tolerability and PK of PA-824 in healthy male and female volunteers was initiated and completed in grant year two. Two-thirds into the course of the study, some volunteers showed an abnormal increase in serum creatinine levels, one indicator related to kidney function. A renal effects study was subsequently initiated in June 2006 to determine the cause and clinical significance, if any, of the serum creatinine elevations. The study was completed in grant year three and revealed that, like other drugs such as cimetidine, PA-824 does not appear to cause kidney damage but rather causes an isolated and apparently clinically benign elevation of serum creatinine by inhibiting its tubular secretion.

A Phase I food effects study was also conducted in grant year three to evaluate the PK profile of PA-824 under fed (high-fat, high-calorie) versus fasting conditions. Results show that exposure to PA-824 following a single 1000mg dose is increased 3.5- to 4.5-fold in the fed versus fasted state. An important milestone in grant year three was the initiation of the Phase II dose-ranging study assessing the extended Early Bactericidal Activity (EBA), safety and PK of PA-824 in adult patients with newly diagnosed, drug-sensitive pulmonary TB. The study was initiated in two Cape Town sites, following approval of the study by the Medicines Control Council (MCC) and the relevant ethical review committees in South Africa. Over one-third of the anticipated 68 patients had been enrolled by the end of grant year three. Additionally, a regulatory milestone was achieved in the PA-824 program when it was awarded orphan drug status by the FDA in July 2007.

Grant Year Four:
The in-life portion of the Phase II study was completed ahead of schedule in December 2007. The study demonstrated that PA-824 is effective in decreasing the number of *M. tuberculosis* bacteria in the sputum (and therefore, it is presumed, in lung cavities) of adult patients with newly diagnosed, pulmonary TB. Additionally, in the study PA-824 appeared safe and well-tolerated in this patient population, with a PK profile similar to that seen in healthy volunteers. Furthermore, the study showed excellent and equivalent activity at all four of the doses tested (200, 600, 1000 and 1200 mg/day for 14 days), including the lowest dose of 200 mg/day. Based on these somewhat unexpected but very exciting findings, the next clinical study planned is another dose-ranging, extended EBA trial, evaluating once daily doses from 50 - 200 mg/day.

Two regulatory milestones were also achieved in the PA-824 development program in grant year four. Specifically, orphan medicinal product status was awarded by the European Medicines Agency (EMEA) and a fast-track designation by the FDA was also awarded in October 2007.

However, an important development in the PA-824 program occurred during grant year four, which affected the planned program timeline. Specifically, preliminary findings from the non-clinical toxicology studies in rat and monkey indicated that PA-824 at high doses may potentially have an effect on male fertility in rats and may cause cataracts in rats and monkeys. Clinical studies for PA-824 have been put on hold while the TB Alliance conducts additional studies to explore these initial findings in detail. These studies include a 3-month chronic toxicity study in sexually mature male monkeys, a 6-month chronic toxicity study in mature rats and ocular monitoring of patients from the Phase II study and the subjects from the Phase I renal effects study (who received the highest exposure to PA-824 of all the Phase I subjects).

The ocular monitoring has not provided any evidence of PA-824 causing cataracts in these studies, according to an independent Ophthalmology Review Board established by the TB Alliance to review these data. Results from the ongoing rat and monkey toxicity studies suggest that both the cataract and male reproductive effects of high-dose PA-824 are limited to rats.

Next Steps:

The results of all these additional studies will be submitted to the FDA in late December 2008 with a request to remove the clinical hold and enable initiation of the Phase II, low-dose (50 - 200 mg/day) EBA study. Assuming approval, this study is slated to initiate in South Africa in the second quarter of 2009.

Additional critical path activities planned for 2009 include preparations for 2-month treatment, Phase II trials at the clinical dose to evaluate safety and efficacy of PA-824 in both newly diagnosed, drug-sensitive patients and MDR-TB patients. These preparations will include the appropriate, supporting drug-drug interaction studies, and explorations, if needed, of novel formulations to mitigate any food effect.

2. MOXIFLOXACIN

Project Title/Activity:	Moxifloxacin Phase II clinical trial (TBTC Study 28)
	Moxifloxacin Phase III clinical trial (REMoxTB)
Project Number:	GHS-A-00-04-00015-00
CTO and Technical Advisor:	Christy Hanson and Susan Bacheller

Brief description of project:
Moxifloxacin is a third generation fluoroquinolone antibiotic. Quinolones target DNA gyrase, an enzyme that unravels the tightly twisted DNA double-strand to allow DNA replication and facilitate the transcription of genes. By inhibiting DNA gyrase, quinolones directly impact bacterial cell multiplication, repair and survival. Several newly tested TB treatment regimens including moxifloxacin have dramatically shortened treatment in animal models. In preclinical studies commissioned by the TB Alliance in 2002-03, investigators at Johns Hopkins University found that substituting moxifloxacin for isoniazid, a currently used first-line drug, in a mouse model system decreased the amount of time needed to eradicate TB infection by two months.

Moreover, since it has a novel target relative to current first-line TB drugs, moxifloxacin is equally as effective against many multidrug-resistant strains as against drug-sensitive *M. tuberculosis*. Also, moxifloxacin does not interact with the cytochrome P450 enzyme system that is involved in the metabolism of some antiretrovirals used in the treatment of HIV/AIDS. Therefore, it can potentially be used to safely treat TB in individuals with HIV/AIDS concurrently taking antiretroviral agents.

The moxifloxacin clinical program funded by USAID helped to support two trials: the TB Trials Consortium (TBTC) Study 28 and the REMoxTB Study. The TBTC Study 28 was a Phase II study evaluating the safety and efficacy of substituting moxifloxacin for isoniazid during the first two months of standard TB therapy. REMoxTB was conceived of as a Phase II/III study to test moxifloxacin substituted for either isoniazid during the first two months of treatment (in a Phase II design) or ethambutol during four months (in a Phase III design). The Phase II primary endpoint in these studies was to be the percentage of patients demonstrating conversion of sputum culture to negativity at two months. However, as described below, due to a delay in the REMoxTB study start, the results from the TBTC study were available before its initiation. Thus, the REMoxTB trial design changed to entirely Phase III with two treatment-shortening arms and a third standard treatment control arm, thereby reducing the overall timeline for the development of a moxifloxacin regimen.

Key Results and Accomplishments:

Grant Years One, Two and Three
Patient enrollment for the TBTC Study 28 began in grant year two. Enrollment (433 patients) was completed early in grant year three – just over a year from enrollment of the first patient into the study. The last subject completed study treatment and the primary endpoint in time to make preliminary efficacy data available to support the initiation of the Phase III REMoxTB trial.

The availability of preliminary results from the TBTC study in grant year three coincided with a delayed start date for the REMoxTB trial, due to complications with the study drug supply and FDA requests. However, the TB Alliance took advantage of the delay and the

TBTC results to modify the study design into an entirely Phase III design. In the revised scheme, two treatment-shortening arms, (one replacing ethambutol with moxifloxacin and the other replacing isoniazid with moxifloxacin) are compared to a control arm with standard treatment, reducing the overall time for the development of a moxifloxacin regimen. This change in trial design also necessitated an increase in patient enrolment from 1,500 to 2,400 patients. Accordingly, in grant year three the TB Alliance added three additional REMoxTB trial sites in Africa to the original three, and strengthened capacity to prepare all six sites for participation. A modified REMoxTB trial protocol was submitted to regulatory authorities and ethical committees in four African countries for review and approval. Additionally, the TB Alliance undertook ensuring the logistics for the supply, distribution, packaging and Good Manufacturing Practice of the study drugs.

Grant Year Four

TBTC project activities primarily focused on TBTC Study 28 data analysis and report writing. TBTC Study 28 results indicate that substitution of moxifloxacin for isoniazid in the first two months of standard therapy causes a statistically non-significant increase in the percent of patients who have converted to sputum negativity at two months. Further, the experimental treatment appeared safe and well-tolerated relative to the standard regimen. Taken together with other Phase II moxifloxacin studies — including TBTC Study 27, a JHU/FDA study and a study by the OFLOTub Consortium, all of which substituted moxifloxacin for ethambutol in the first two months of treatment — these results supported initiating the Phase III, REMoxTB Trial, to evaluate the safety and efficacy of two, four-month, moxifloxacin-based regimens relative to the 6-month standard regimen for the treatment of drug-sensitive, pulmonary, adult TB.

The REMoxTB Phase III trial reached the First Patient In milestone, enrolling its first patient in January 2008 at the Lusaka, Zambia site. The TB Alliance also assessed additional trial sites in Africa, Asia, South America and Eastern Europe in order to involve a necessary minimum of twenty to thirty sites to meet REMoxTB's challenging goal of enrolling 2,400 patients as expeditiously as possible. This greater geographic spread of sites will also better help achieve global registration should one or both regimens be successful in demonstrating treatment-shortening to four months. As of September 30, 2008, some 235 patients were enrolled in REMoxTB, and 16 additional sites had been approved and were being readied for participation in the trial.

Next Steps:

By the end of 2009, all REMoxTB sites are expected to be actively enrolling. It is projected that by September 30, 2009, approximately 2,000 of the planned 2,400 patients will have been enrolled in the trial.

3. DISCOVERY

Project Title/Activity: Discovery

Project Number: GHS-A-00-04-00015-00

CTO and Technical Advisor: Christy Hanson and Susan Bacheller

Brief description of project:
USAID funds in grant years one and two were used to support lead identification and optimization for three of the TB Alliance's discovery projects: quinolones, macrolides, and nitroimidazoles (PA-824 backup). These projects were not supported by the grant during years three and four.

Key Results and Accomplishments:

Quinolones
Quinolones are mycobacterial DNA gyrase inhibitors that hold great potential for shortening treatment duration, thereby improving treatment of MDR-TB and TB in HIV/AIDS infected individuals. During the first two years of the grant, part of the USAID contribution was used to support quinolone lead identification and optimization activities. At the end of the second grant year, a select group of compounds was prioritized for *in vivo* efficacy, pharmacokinetic and safety studies. Since then, the program has successfully completed lead optimization, and a novel DNA gyrase inhibitor, TBK-613, has been identified and advanced into preclinical development.

Macrolides
The macrolides project was initiated in 2004, and reached the lead optimization phase, with support from USAID during the first two grant years. However, the project was discontinued as part of the TB Alliance's active portfolio management after the most promising lead compounds failed to demonstrate acceptable *in vivo* activity in the TB mouse model.

Nitroimidazoles (PA-824 Backup)
Nitroimidazoles are a novel class of anti-TB agents. Described above, PA-824 is the TB Alliance's lead nitroimidazole drug candidate. Recognizing that this new class of compounds could have a major impact on improving TB treatment, the TB Alliance has initiated a program to identify a back-up compound as well as second generation compounds in the same chemical series as PA-824, but with an even better pharmacological profile. USAID support in the first two grant years helped establish the PA-824 backup program and advance it into the lead optimization stage. Since then, the program has made significant progress, and has identified compounds more potent *in vitro* and *in vivo* than PA-824 and OPC-67683 (Otsuka Pharmaceuticals' nitroimidazole currently in clinical development). The project is now successfully in the final stage of the lead optimization phase, and is slated to identify a drug candidate and begin preclinical development at the beginning of 2009.