Protocol

Title: IMPACT-TB*: A phase II clinical trial of the safety, pharmacokinetics and hematologic effects of imatinib on myelopoiesis in adults when given with and without isoniazid and rifabutin

*Imatinib mesylate per oral as a clinical therapeutic for TB

NCT Number: NCT03891901

Participants were enrolled under two different protocols:
Version 3.0 with addendums 1, 2, and 3, dated February 16, 2021
Version 5.0, dated June 22, 2022

IMPACT-TB*: A phase II clinical trial of the safety, pharmacokinetics and hematologic effects of imatinib on myelopoiesis in adults when given with and without isoniazid and rifabutin

*Imatinib mesylate per oral as a clinical therapeutic for TB

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SIGNATURE PAGE

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*Imatinib mesylate per oral as a clinical therapeutic for TB

DAIDS Protocol Number: Aim 1
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Protocol Aim 1, Version 3.0 with addendum changes for LoA #3, Feb 16, 2021
Protocol Aim 1, Version 3.0 with addendum changes for LoA #2, July 30, 2020
Protocol Aim 1, Version 3.0 with addendum changes for LoA #1, November 22, 2019
Protocol Aim 1, Version 3.0, July 12, 2019
Protocol Aim 1, Version 2.0, March11, 2019

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Investigator name	Signature	Date signed

NIH Grant Number	NIH4UH3AI122320 - 03
Investigational Product:	Imatinib
Protocol Number: **IRB Number:**	DAIDS-ES ID 38518 IRB00103001
IND/ IDE Number:	IND 143386
IND Sponsor	DAIDS
ClinicalTrials.gov Number	NCT03891901

Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, the site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Initial Registration

Site-specific informed consent forms (ICFs) will be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification will be retained in the site's regulatory files.

Amendment Registration Language

Upon receiving final IRB/EC and any other applicable RE approval(s) for a study amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. Site-specific ICF(s) will not be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification from the DAIDS PRO that approves the site specific ICFs and indicates successful completion of the amendment protocol registration process. A copy of the final amendment Registration Notification issued by the DAIDS PRO should be retained in the site's regulatory files.

Table of Contents

List of Abbreviations

AE.....adverse event
ART .....antiretroviral therapy
CI .....confidence interval
Cmax .....maximum concentration
CRF .....case report form
DAIDS.....Division of AIDS of NIAID
DDI .....drug-drug interactions
FBPU ……Fluorogenic BioParticles uptake
FDA .....US Food and Drug Administration
GCP.....good clinical practice
HDT .....host-directed therapy
INH……..isoniazid
IIV……interindividual variability
MDR .....multidrug-resistant
Mm …… *Mycobacterium marinum*
MN .....monocytes
Mtb……..*Mycobacterium tuberculosis*
OHRP……Office for Human Research Protections
PD.....pharmacodynamics
PK.....pharmacokinetics
PMN.....polymorphonuclear cells
qD……...once daily
RBT……rifabutin
SAE .....serious adverse event
SUSAR .....suspected unexpected serious adverse reaction
T½ .....elimination half life
TB .....tuberculosis
Tmax.....time to maximum concentration
XDR……...extensively drug-resistant

Study Summary

Title	IMPACT-TB*: A phase II clinical trial of the safety, pharmacokinetics and hematologic effects of imatinib on myelopoiesis in adults when given with and without isoniazid and rifabutin *Imatinib mesylate per oral as a clinical therapeutic for TB
Short Title	Imatinib Dosing Trial
IRB Number	IRB00103001
Protocol Number	DAIDS-ES ID 38518
Phase	Phase 2 evaluating safety, immunologic efficacy and pharmacokinetics (PK)
Methodology	Open label, sequential dose escalation design for Cohort 1, and randomized allocation to two imatinib doses for Cohort 2.
Study Duration	For Cohort 1 participants receiving imatinib followed by imatinib + rifabutin + isoniazid: Up to 50 days, including up to 8 days of screening, 14 days of imatinib alone, 14 days imatinib combined with isoniazid and rifabutin, and 14 days of post-drug follow-up. For Cohort 2 participants receiving rifabutin + isoniazid followed by imatinib + rifabutin + isoniazid: Up to 50 days, including 8 days of screening, 14 days of rifabutin + isoniazid, 14 days imatinib combined with isoniazid and rifabutin, and 14 days of post-drug follow-up.

Study Center	Winship Cancer Institute of Emory University And Georgia Clinical & Translational Science Alliance (Georgia CTSA) Georgia CTSA Clinical Research Center Emory University Hospital 1364 Clifton Rd. Atlanta, Georgia 30322 United States
Objectives	Primary: • Cohort 1: To determine the effects of different doses of imatinib on myelopoiesis in adults when given alone • Cohort 2: To determine the effects of different doses of imatinib on myelopoiesis in adults when given in combination with rifabutin and isoniazid • Primary Safety Objective: To determine the safety of different doses of imatinib in combination with isoniazid and rifabutin in adults Secondary: • To assess the impact of imatinib on isoniazid and rifabutin PK and the impact of isoniazid and rifabutin on the PK and PD of imatinib • To determine the effects of imatinib on cellular immune function and on circulating biomarkers of immune activation and on T cells and monocytes • To assess proteomic and transcriptomic changes associated with imatinib administration

Number of Participants	72 participants total; 48 will receive 14 days of imatinib alone at one of 4 doses, followed by 14 days of imatinib together with rifabutin and isoniazid (Cohort 1); 24 will receive 14 days of rifabutin and isoniazid, followed by 14 days of rifabutin and isoniazid together with imatinib at one of 2 doses (Cohort 2)
Main Inclusion and Exclusion Criteria	The study will enroll healthy adult volunteers as defined in the protocol.
Investigational Product	Participants will receive imatinib mesylate. Volunteers in Cohort 1 will receive one of 4 doses orally - 50, 100, 200, or 400 mg per day. Volunteers in Cohort 2 will receive one of two doses, determined by analysis of results obtained from the first cohort.
Duration of administration	Volunteers in Cohort 1 will receive imatinib for a total of 28 days (14 days imatinib alone at one of 4 doses listed above, followed by 14 days of imatinib and isoniazid 300 mg per day and rifabutin 300 mg per day). Volunteers in Cohort 2 will first receive isoniazid 300 mg per day and rifabutin 300 mg per day for 14 days followed by 14 days of combination isoniazid 300 mg per day, rifabutin 300 mg per day, and imatinib at one of 2 selected doses based on results from Cohort 1.
Reference therapy	None

Statistical Methodology

Immunologic effects

There is a primary outcome for each cohort: For Cohort 1 the primary outcome is the change in the numbers of myelomonocytic cells in the blood between baseline and day 14 of the study; for Cohort 2 the primary outcome is the change in the numbers of myelomonocytic cells in the blood between day 14 and day 28 of the study. The change in these cells will be estimated with cohort-specific mixed models, combining all dose groups, with fixed effects for the two time points (Day 14, Day 28) and interactions between dose and each time point. Secondary efficacy analyses will also use mixed models to determine 1) the difference between the change in the numbers of myelomonocytic cells from baseline to day 14 in Cohort 1 and the change in the numbers of myelomonocytic cells from day 14 to day 28 in Cohort 2; 2) the change in the numbers of myelomonocytic cells from baseline to day 28 in Cohort 1; 3) the change in the numbers of myelomonocytic cells from baseline to day 28 in Cohort 2; 4) the pooled change in both cohorts in the numbers of myelomonocytic cells in the blood between baseline and day 28; 5) the relationship between imatinib exposures and change in the numbers of myelomonocytic cells during the imatinib-exposed periods in each cohort separately and in the pooled cohorts. The pooled comparisons will be estimated using the regression coefficients from the cohort-specific mixed models.

Safety

The incidence of all adverse events and in particular grade 3 or 4 adverse events and SAEs during all follow-up time and during imatinib-exposure time separately will be determined using point estimates and 95% CIs.

Pharmacokinetic analysis

Pharmacokinetic (PK) parameters, including absorption, distribution, and metabolism, will be determined using S-ADAPT software utilizing a compartmental PK analysis approach and summarized by treatment regimen. The rifabutin and isoniazid PK will be examined as covariates of imatinib PK parameters both in S-ADAPT and well as using machine learning method of multivariate adaptive regression splines (MARS), to identify the drug-drug interactions.

Study design

Dose-escalation trial with PK/DDI components

Power and Sample Size Analysis

48 participants with evaluable data in the first 14 days (imatinib only) of the first cohort will provide 90% power to detect a 0.48 SD in the change in the number of myelomonocytic cells on imatinib. Within each dose stratum, we will have 90% power to detect a 1.03 SD change.
24 participants with evaluable data in the 14 - 28 days (imatinib+TB drugs) in the second cohort will provide 90% power to detect a 0.69 SD in the change in the number of myelomonocytic cells from day 14 to day 28 (imatinib added to isoniazid and rifabutin).

Safety Evaluations

Clinical and laboratory adverse events including ECG changes and symptoms and signs of drug-drug interactions (e.g., high rifabutin levels) will be monitored prospectively while on study drugs and at 14 days after completion of imatinib and the TB drugs.

Study Progress and Safety Monitoring Plan	The Independent Safety Monitor, PI and study team, Data Safety Monitoring Board (DSMB), and Sponsor will be responsible for monitoring the data quality and the ongoing safety of participants. Twelve subjects will be enrolled into each dosage arm in an ascending manner, starting with the 50 mg imatinib dose. In Cohort 1, a formal safety analysis will be performed by the team and the DSMB after complete safety and PK data are available from 6 participants within a stratum. If safe, and after a total of 12 participants are enrolled for the first stratum, then the next higher dose will begin enrolling participants. Enrollment will proceed in this manner until the sample size for Cohort 1 has been reached. Formal safety analysis will then occur using the data from all dose groups in Cohort 1, and 2 doses will be chosen to evaluate in Cohort 2.

1. BACKGROUND AND STUDY RATIONALE

This document is a clinical research protocol and the described study will be conducted in compliance with the protocol, Good Clinical Practice standards, Good Clinical Laboratory Practice standards, associated federal regulations, NIAID/DAIDS funding agency requirements, and all applicable University research requirements. The study is being performed in the United States, at Emory University in Atlanta, and will therefore also comply with all US federal research requirements. All episodes of noncompliance will be documented.

Introduction

Therapeutic agents capable of improving treatment of all forms of TB are urgently needed. The cancer drug imatinib limits mycobacterial infections in culture and animal models by reducing both entry into macrophages and augmenting phagolysosomal fusion (autophagy), which may facilitate antigen presentation and pathogen killing (1). Additionally, imatinib induces increases in myeloid cells (myelopoiesis), and an innate immune response to infection that mimics so-called “emergency hematopoiesis,” a response that *Mycobacterium tuberculosis* (*Mtb*) appears to suppress (2). Importantly, these mechanisms can be induced in animal models by oral doses substantially lower than those used in people to combat cancer. The dose-dependence has important implications for TB clinical studies in humans, as it suggests that imatinib could improve TB treatment using doses that impart minimal if any toxicity.

This trial will evaluate the safety, immunologic effects and PK properties of several doses of imatinib when given alone and in combination with key anti-tubercular drugs in order to inform a subsequent phase 2 study evaluating the microbiologic effects of adjunctive imatinib at an optimized dose in patients with pulmonary TB. A full consideration of exposure-efficacy data and exposure-safety data from this study in healthy volunteers will be undertaken in collaboration with the DSMB and DAIDS prior to making recommentations for an appropriate treatment dose regimen of imatinib with isoniazid and rifabutin.

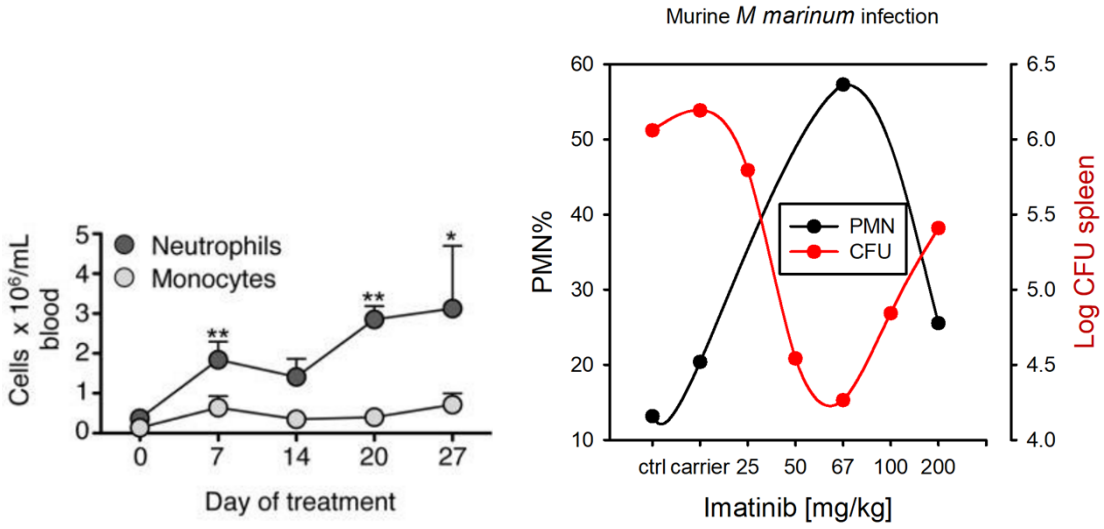
1.1 Background and Relevant Literature

With existing anti-tubercular drug therapies, treatment of drug-susceptible TB takes at least 6 months and success rates for multi-drug resistant tuberculosis (MDR-TB) and extensively drug resistant TB (XDR-TB) are a dismal 50 and 20%, respectively, highlighting the urgent need for new TB drugs (3). We have identified imatinib mesylate, a cancer drug used to treat humans with chronic myelogenous leukemia (CML) or gastrointestinal stromal tumors (GISTs), as a

potential “host- directed therapeutic (HDT)” for drug resistant TB infections and TB/HIV co-infections. Imatinib inhibits c-Abl tyrosine kinase (TK), which is dysregulated in CML, as well as related TKs (e.g. c-Kit). Data from tens of thousands of human patients indicate that imatinib is generally well tolerated, with few severe adverse events and little toxicity, especially at low doses (4-7). In animal models, imatinib facilitates clearance of *Mtb* by disrupting the cellular mechanisms that *Mtb* uses for entry and survival in host cells (1). Also, at doses substantially lower than those used for CML, imatinib stimulates “emergency hematopoiesis,” a host immune response to infection that mobilizes myeloid cell populations, but which is suppressed by *Mtb* (2). As an HDT, imatinib acts synergistically with antibiotics, is effective against antibiotic-resistant mycobacteria, and may be less likely to engender resistance compared to traditional anti-bacterial agents. Our proposal seeks to: determine the safety profile, immunologic effects, and PK properties of imatinib when given alone and with isoniazid and rifabutin. These studies will directly inform dosing for a subsequent phase 2 randomized clinical trial that will determine the safety and microbiologic efficacy of imatinib when used as an adjunctive therapy in pulmonary TB. **We will conduct this initial study in Atlanta at Emory University in order to facilitate timely completion of the study, which will aid in the rapid evaluation of imatinib in a subsequent phase 2 study that will explore efficacy in patients with TB.**

1.2 Imatinib mesylate

Imatinib mesylate is a tyrosine kinase inhibitor that is approved by multiple regulatory agencies for the treatment of several malignancies, including Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML), at adult doses of 400 - 800 mg/d (4, 5). The drug has a well-defined safety profile. It is well absorbed after oral administration, with a t½ of 15 hr, supporting once daily dosing (8). Doses of 400 mg/d produce mean plasma concentrations of approximately 1.1 mg/L (average male, 1.8 m^2) (9). Imatinib is both a substrate for and an inhibitor of CYP3A4. In CML its primary target is Bcr-Abl, a strongly expressed fusion protein with tyrosine kinase activity that results from the 9:22 chromosomal translocation. Inhibition of Bcr-Abl in CML by imatinib arrests myeloid cell proliferation and restores normal apoptosis.



Figures 1a and 1b. Effect of low dose imatinib on blood PMNs and MNs in mice and relationship between myelopoesis and mycobacterial growth. From (2).

Two distinct mechanisms of action of imatinib pertain to its potential role in TB. The first is a direct, pharmacologic effect on macrophage function. In normal individuals, therapeutic concentrations of imatinib inhibit c-Abl1, c-Kit and related tyrosine kinases. *Mtb* uses one or more of these enzymes to inhibit phagolysosome fusion, thereby evading innate host defenses. Treatment of *Mtb*-infected macrophages with imatinib blocks this pathogenic mechanism by altering intracellular trafficking, promoting vesicle acidification and restricting *Mtb* growth [1, 10]. In addition, low imatinib concentrations induce differentiation of hematopoietic stem cells and progenitors in the bone marrow, augmenting myelopoiesis but not lymphopoiesis, and increasing numbers of myeloid cells in blood and spleen of mice (Figure 1a) (2). Whereas progenitor differentiation relies on partial inhibition of c-Kit by imatinib, myeloid lineage commitment depends upon inhibition of other PTKs. Myelopoiesis in turn is associated with improved control of mycobacterial growth (Figure 1b). Thus, imatinib at low doses mimics “emergency myelopoiesis”, a physiological innate immune response to systemic infection. At higher doses, effects on myelopoiesis are still evident but exodus of mature myeloid cells from the bone marrow into the periphery does not occur.

1.2.1 Preclinical Data on the effect of imatinib on Mtb infection

In one representative experiment, C57Bl/6 mice treated with low dose imatinib by continuous infusion were infected with a large inoculum of *Mtb*. Treatment continued for 28 days, after

which animals were sacrificed. *Mtb*-CFU counts were significantly lower in imatinib treated animals, of whom approximately one third had completely cleared the infection, a reduction of more than 7 logs (Figure 2a) (10). In a recent, ongoing experiment, macaques were infected with *Mtb* by the aerosol route. After 6 weeks, 2 cohorts began treatment with either 3 antimicrobial drugs used for MDR-TB treatment (moxifloxacin, ethambutol and pyrazinamide), or the 3 drugs plus imatinib 30 mg/kg/d. A 3rd cohort received no treatment. Animals underwent bronchoalveolar lavage (BAL) and immunologic evaluation after 3 additional weeks. Those treated with antimicrobials alone had a mean of $2x10^4$ CFU in BAL fluid, whereas those also treated with imatinib had no detectable bacilli (Figure 2b). In addition, serum concentrations of C-reactive protein, a marker of inflammation, had normalized in imatinib-treated animals, whereas they had remained markedly abnormal in the other cohorts (Figure 2c). This suggests that contrary to what one would expect in increasing autophagy and myelopoiesis, there was actually decreased inflammation. Indeed, lung pathology was also reduced with imatinib treatment when the drug was administered alone following reactivation with SIV, or when administered together with antibiotics (Figure 2d).

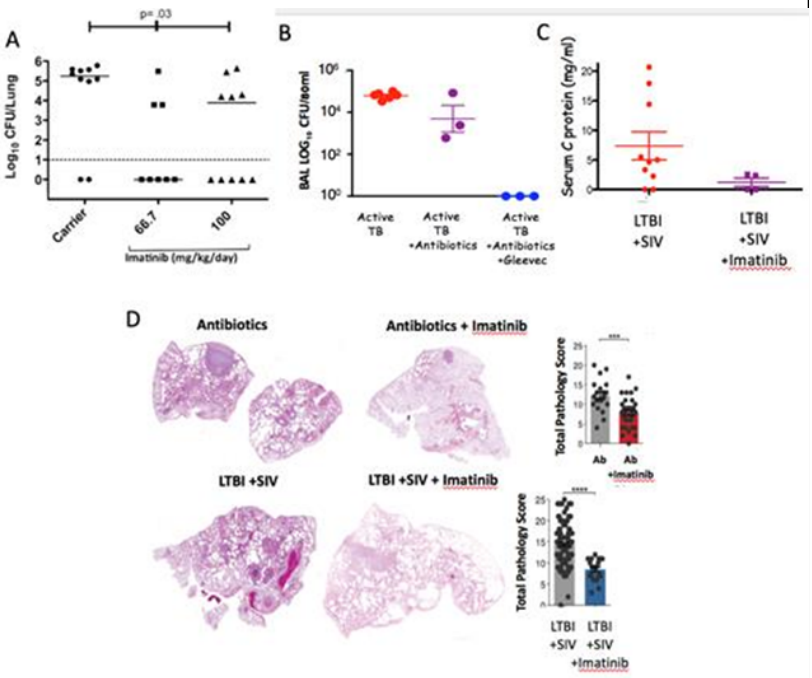


Figure 2. *Effects of imatinib of TB infection in mice and non human primates (NHPs).* ***A.*** *CFUs from lung following aerosol Mtb infection in mice. Control animals were administered placebo or imatinib at 66 or 100 mg/kg/d for 28d. Note that 80% of animals showed reductions of at least 2 orders of magnitude and in some animals Mtb was below detectable levels (from Napier et al., 2011).* ***B.*** *BAL CFUs in NHPs infected with high inoculum of Mtb (200CFU) for ~6 weeks, and then treated for three weeks with either antibiotic regimen (ethambutol (15mg/kg), pyrazinamide (20mg/kg) and moxifloxacin (40mg/kg)), or antibioitcs plus imatinib (30mg/kg/d).* ***C.*** *Serum CRP from animals infected with low inoculum of Mtb to induce a latent TB infction (LTBI), and then infected with SIV, which causes TB reactivation. Imatinib treatment commenced when animals showed signs of active disease; imatinib-treated animals were sacrificed pairwise when a control animal succumbed.* ***D.*** *Lung histology (H&E) and pathology scores from the antibiotic experiment (B) or the SIV reactivation experiment (C).*

1.2.2 Clinical Data on the effect of imatinib on Mtb infection to Date

There currently is limited clinical data on the effects of imatinib on TB treatment outcomes in humans. No trials have been performed, but individuals on imatinib for treatment of CML who developed TB anecdotally had successful treatment outcomes (11, 12).

1.2.2.1 Human Pharmacokinetics

Human population PK of imatinib have been identified by Scmidli et al in 371 patients and are also a one compartment model: clearance of 14 L/hr with an inter-individual variability (IIV) of 32% and a volume of 252 L (13). These data are also consistent with population PK data from Widmer et al using data from 59 patients with CML or GIST (8).

1.2.2.2 Clinical Studies in Adults and Children

There have been no clinical studies of adjunctive imatinib for TB treatment in adults or children.

1.3 Dose Rationale

The optimal dose for adjunctive imatinib therapy in TB is unknown, necessitating a trial evaluating the safety, PK and PD relationships of multiple doses. We have used data from our NHP experiments to inform dosing for the proposed study. Specifically, we will aim to replicate drug concentrations associated with myeloid responses and *Mtb* killing in the NHP model. Based on the myeloid respone data, macaques treated with 10 mg/kg had no increase in myelomonocytic cell percentages by day 7, while in 2 animals treated with 30 mg/kg, one had an increase in the percentage of myelomonocytic cells and the other did not. In the macaque treated with 60 mg/kg there was a myelomonocytic cell response. The drug concentrations achieved by 30 mg/kg and 60 mg/kg in NHP were thus used to model the dosing target for human TB patients.

We utilized S-ADAPT for identifying PK parameters. The macaque concentrations with treatment of 30 mg/kg were best explained by a one-compartment model based on both Akaike Information criteria (score of 0.45 versus 6.51) and Bayesian Information criteria (score of 2.58 versus 9.54) when compared to a two-compartment model. The final clearance estimate was 23.95 L/hr, volume of 110.1 L, and absorption constant (K_a) of 0.22 per hour. This translates to a half-life of 3.19 hours in the macaques. The peak concentration was 1.35 mg/L at 4 hours and a trough of 0.05 mg/L at 24 hours (just prior to next dose). From this, we can calculate that the macaques treated with 30 mg/kg achieved a 0-24 hours area under the concentration-time curve (AUC_{0-24}) of 9.19 mg*hr/L. By scaling, doses of 60 mg/kg would achieve an AUC_{0-24} of

18.37 mg*hr/L, peak of 2.70 mg/L and trough of 0.1 mg/L. These sets of concentrations give us the target floor and ceiling concentrations to aim for in patients.

We performed Monte Carlo Experiments (MCE) of 5,000 patients each to identify the concentrations achieved by imatinib doses of 50 mg, 100, 150 mg, and 200 mg administered daily. The domain input were the PK parameter estimates and covariance matrix from Scmidli et al in 371 patients; these were entered into subroutine PRIOR of ADAPT. Results are shown in

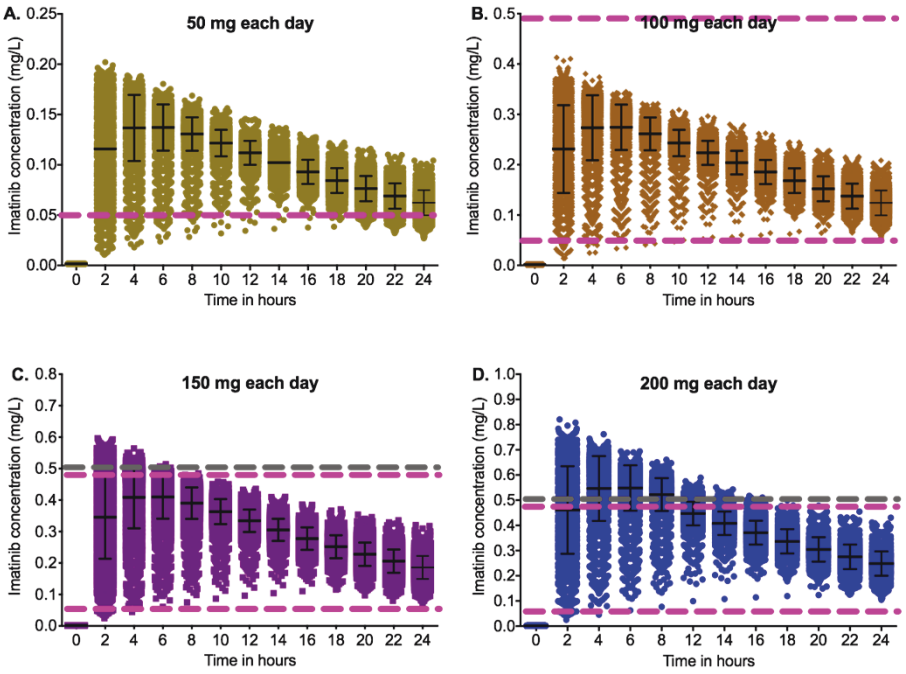


Figure 3. Model of PK/PD of imatinib in humans based on responses in non-human primates.

Figure 3, which also shows where concentrations for each would fall in relationship to the concentrations of 0.05-0.49 mg/L (pink lines) that have been associated with myelopoiesis, and 0.5-1.97 mg/L (grey lines) that have been associated with autophagy. In addition, the doses of 150 mg/day and 200 mg/day would also be able to fulfill the range on peak of 2.70 mg/L and a trough of 0.05 mg/L identified in the macaques that achieved both myelopoiesis and anti-TB effect. To begin our dose testing, we will use this range of 50 - 200 mg/day, as well as a higher dose of 400 mg/day to account for possible under-estimation of the effects in humans. Thus, we propose doses of 50 mg/day, 100 mg/day, 200 mg/day, and 400 mg/day to be tested in the first cohort (Cohort 1) of human volunteers. The trial design will allow for adjustment of the imatinib dosing for the second cohort (Cohort 2), based on the results of first cohort testing.

1.4 Possible Drug-Drug Interactions with TB Therapy

Standard treatment of drug-susceptible TB involves two months of isoniazid, a rifamycin such as rifampin or rifabutin, pyrazinamide and ethambutol, followed by four months of isoniazid and a rifamycin. Isoniazid inhibits CYP3A4, which could increase the concentrations of imatinib when given together**(14)**. Both rifampin and rifabutin are inducers of cytochrome P450 enzymes, including CYP3A4. Although rifampin is the most commonly used rifamycin in TB treatment globally, in a single-dose PK study of 14 healthy human subjects rifampin reduced the mean imatinib C_{max}, AUC_{0-24} and $AUC_{0-\infty}$ by 54% (90% CI: 48–60%), 68% (64–70%) and 74% (71–76%), respectively. Rifabutin is substantially less potent in terms of inducing CYP3A and other drug-metabolizing enzymes compared to rifampin**(15)**. Thus, in this study and in the subsequent phase 2 efficacy trial we have planned that rifabutin will be evaluated as the rifamycin of choice. The combined effects on imatinib PK on use of both isoniazid and rifabutin are unknown and may be offsetting. Thus, before we can give imatinib to patients who are taking these standard anti-tubercular therapies, we must understand how imatinib PK is affected by the combination of isoniazid and rifabutin. To address this, we will include a PK evaluation of this drug combination in the study.

1.5 Conduct of Study: Emory University, Winship Cancer Institute, Clinical Trials Office

As Principal Investigator, Dr. Waller conducts clinical trials through his primary association with the Winship Cancer Institute. The Clinical Trials Office of the Winship Cancer Institute (Winship CTO) is staffed by highly-trained professional research personnel specializing in areas of clinical coordination, data management, specimen processing and regulatory management. Dr. Waller and co-investigators will work with the Winship CTO to ensure compliance with Winship clinical trials standard operating procedures, Good Clinical Practice (GCP), Emory University Institutional Review Board (IRB), US Food and Drug Administration (FDA), and other regulatory agencies (e.g., the OHRP) and NIAID/DAIDS (the Sponsor). Further information about the Winship CTO is found at: https://winshipcancer.emory.edu/research/clinical-trials-office/

1.6 Conduct of Study: Georgia Clinical & Translational Science Alliance (CTSA), Georgia CTSA Clinical Research Center (GCRC)

The study will be carried out using facilities of the Georgia CTSA GCRC located within the Emory University Hospital Clinical Research Site, with personnel based in the GCRC Nursing Staff and Core Laboratory.

http://georgiactsa.org/discovery/clinical-sites/emory-university.html

http://georgiactsa.org/discovery/nursing.html

Please see protocol Appendix Section 17.3 for further details.

1.7 Conduct of Study: Emory University Investigational Drug Service

The pharmacy that will serve the study is the Emory University Investigational Drug Service (IDS) - http://www.ocr.emory.edu/ids/index.html

The IDS is currently involved in a number of NIAID/DAIDS studies, demonstrating the capacity of IDS to initiate, conduct, participate in, and support NIAID/DAIDS funded research. Please see Protocol Section 17.4 for required IDS information.

1.8 Conduct of Study: Emory Medical Laboratory (EML)

Standard medical laboratory tests will be conducted by the Emory Medical Laboratory (EML). The EML is a fully accredited and licensed clinical laboratory. EML participates in the College of American Pathologists (CAP) Laboratory Accreditation Program and has CLIA (Clinical Laboratory Improvement Amendments) certification through CMS (Centers of Medicare and Medicaid Services). Emory Medical Laboratory also is licensed by the state of Georgia.

EML Lab Reference Ranges and CLIA certificate are found at the website.

http://www.emoryhealthcare.org/centers-programs/medical-laboratory/index.html

1.9 Protocol Review, Finalization, and Approval Processes

The protocol will undergo a review, approval and set-up phase with the Georgia CTSA GCRC during the first 2 months of funding, as well as the Protocol Registration process with NIAID/DAIDS. A protocol-specific Manual of Operational Procedures in accordance with NIAID/DAIDS requirements will also be prepared and approved during this timeframe, incorporating procedures needed for this study and existing SOPs from the Winship CTO, Georgia CTSA GCRC and Core Lab, IDS Pharmacy, and Emory University Medical Laboratory.

2 Study Objectives

The overall objective of the study is to determine safe and immunologically effective doses of imatinib that will subsequently be advanced to a phase 2 randomized clinical trial in adults with drug-susceptible pulmonary TB. Because of possible drug-drug interactions with isoniazid and rifabutin, we also aim to evaluate safety issues with eventual use in patients with TB taking TB drugs. These issues concern both effects of imatinib on TB drug levels as well as effects of TB drugs on imatinib levels. For example, imatinib's tendency to inhibit CYP3A4 could increase rifabutin levels and the risk of dose-dependent rifabutin toxicity. Rifabutin induction of CYP3A4

could in turn decrease imatinib exposure, as explained above. In addition, the time courses of CYP enzyme inhibition or induction in humans taking imatinib and in those taking rifabutin and isoniazid are uncertain.

Thus, the dosing schedules and rationale are as follows: in Cohort 1, we will give imatinib alone for 14 days – which is required to observe an effect of imatinib on myelopoiesis (the primary endpoint), followed by imatinib in combination with rifabutin and isoniazid for an additional 14 days. This should give imatinib sufficient time to inhibit CYP3A4, which could lead to high rifabutin levels, during the 28-day course of drug dosing in Cohort 1. However, in the clinical trial that will occur subsequent to this study, patients will be diagnosed with TB in the community, where they may be promptly started on TB drugs, and then if enrolled they will subsequently have imatinib added to these drugs. Thus, in Cohort 2 we will give TB drugs first for 14 days in order to reach steady state, followed by imatinib in combination with rifabutin and isoniazid for an additional 14 days. This should provide for sufficient time to examine how rifabutin's induction of CYP3A4 affects imatinib levels.

Although the imatinib doses we propose to study are at or below approved doses for CML and GIST, possible drug-drug interactions will be addressed by enrolling patients using a dose-escalation design as explained below.

2.1 Primary Objective

- Cohort 1: To determine the effects of different doses of imatinib on myelopoiesis in adults when given alone
- Cohort 2: To determine the effects of different doses of imatinib on myelopoiesis in adults when given in combination with rifabutin and isoniazid
- Primary Safety Objective: To determine the safety of different doses of imatinib in combination with isoniazid and rifabutin in adults

2.2 Secondary Objectives

- To assess the impact of imatinib on isoniazid and rifabutin PK and the impact of isoniazid and rifabutin on the PK and PD of imatinib
- To determine the effects of imatinib on cellular immune function and on circulating biomarkers of immune activation and on T cells and monocytes
- To assess proteomic and transcriptomic changes associated with imatinib administration

3 Investigational Plan

3.1 General Design

This is an open label trial evaluating the safety and immunologic effects of different doses of imatinib in healthy adult volunteers as well as the PK, PD, and DDIs of imatinib, isoniazid, and rifabutin when given in combination. In Cohort 1, 48 participants will be enrolled in a dose-escalting fashion to receive one of four imatinib doses alone for 14 days, followed by imatinib in combination with rifabutin 300 mg and isoniazid 300 mg orally per day for another 14 days (for a total of 48 participants). Twelve participants will be enrolled to dose 1 (50 mg/daily). After a successful safety evaluation to day 42 follow-up and PK/PD assessment from the first 6 participants, and enrollment of all 12 in the stratum, we will begin enrolling 12 participants in the 2nd dose stratum (100 mg/daily). Enrollment will proceed in this fashion, with a formal safety evaluation and PK/PD assessment after the first 6 participants at each dose. In this manner, 12 participants will be allocated to each imatinib dose.

Using the dataset from Cohort 1, the investigators, working with the Independent Safety Monitor, the DSMB, and the Sponsor, will then choose two imatinib doses that have the optimal safety, PK and PD profiles for advancement into Cohort 2. In Cohort 2, 12 participants will take rifabutin 300 mg per day and isoniazid 300 mg per day orally for 14 days, followed by 14 days of rifabutin and isoniazid in combination with one of the two selected doses of imatinib (i.e., 24 participants total will be enrolled into Cohort 2 to fulfill 12 participants for each of 2 doses).

It is anticipated that the two doses to be tested in Cohort 2 will be among those tested in Cohort 1 (50-400 mg/day). If we find that one of the optimal imatinib doses in the first cohort is 50 mg per day, we may choose to include a lower dose in Cohort 2 (e.g. 25 mg per day). The maximum dose we would test in Cohort 2 is 400 mg/day. The exact doses to be evaluated in Cohort 2 will be determined after analyzing data from Cohort 1.

3.1.1 Screening Phase

Advertisements will be developed to recruit healthy participants from the Emory community of staff and students, and from primary care clinics at Emory Healthcare locations. A preliminary informational and pre-screening phone call will take place before scheduling an in-person screening visit at the clinical site. In addition to general health questions, we will include review

of potential COVID-19 symptoms and any known or suspected exposures during the pre-screening phone call.

These questions are:

During the past 2 weeks, have you been in close contact with anyone known to have COVID-19 disease or who tested positive for the virus?

Do you have any of the following that started in the last 2 weeks, or have you had a COVID test within the last 14 days due to COVID-related symptoms?
- Fever greater than 100 F
- Shaking/chills
- Loss of taste/smell
- Cough
- Shortness of breath or difficulty breathing
- Sore throat
- Body/muscle aches
- Headache
- Diarrhea
- Rash

If the potential subject answers Yes to any of the questions, the individual will be encouraged to seek virus testing, and will not be invited to participate in the study.

The in-person screening evaluations will occur on days -7 to 0. Within 24 hours before the in-person screening visit, another phone call will take place and the same questions about potential COVID-19 disease and any known or suspected exposures will be asked again (exception - this additional call is not needed if the in-person screening visit is scheduled the day after the pre-screening phone call above). If the potential subject answers Yes to any of the questions, the individual will be encouraged to seek virus testing, and will not be invited to participate in the study. Upon arrival at the GCRC for the in-person screening visit, the participant’s temperature will be taken and participants will be asked to provide written informed consent. If consent is provided, demographic and medical history and medical record review will be conducted and an HIV test will be performed. Testing for HBV and HCV will also be performed. Inclusion and exclusion criteria will be examined. For women of reproductive

potential, a pregnancy test will be performed. Physical exam with vital signs, medication review, lab safety tests, urinalysis, and a 12-lead ECG will be performed. These activities may be spread over multiple visits within the indicated time window. Participants who consent and who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled.

3.1.2 Study Intervention Phase

Cohort 1: We will enroll Cohort 1 using a sequential dose-escalation design. Specifically, we will enroll 12 participants (e.g., 3 per week) in the imatinib 50 mg qD arm, with a formal review of safety data and PK/PD data from the first 6 participants enrolled in this arm. Enrollment of the second 6 participants in the dose group will continue while formal safety review of the first 6 participants is conducted by the DSMB. If after all 6 of these participants complete the 42-day study follow-up there are no treatment emergent grade 3 or 4 adverse events considered to be related to the study treatment, and there are no serious adverse events or other safety concerns in the opinion of the investigators, the Independent Safety Monitor, the DSMB, and the Sponsor that would prevent dose escalation, we will complete enrollment of the first dose group and then commence enrollment of the 12 participants in the next dose group (100 mg qD arm). After 6 participants complete day 42 followup in the 100 mg qD arm, we will review safety data and PK/PD data while enrollment in the 100 mg/day group continues. If the safety criteria above are met, we will complete enrollment of remaining participants in the 100 mg qD arm and then begin enrolling 12 participants in the 200 mg qD arm. This approach will proceed until there are 12 participants with evaluable myelopoiesis data in each dose arm and the sample size for Cohort 1 (48 participants) is fulfilled. All enrolled participants will be evaluable for safety and toxicity assessments if they have taken at least one dose of a study drug. Note that 42-day followup is required for a participant that “counts” toward the 6 needed for formal safety analysis. Therefore, if any of the first 6 participants in a dose group do not complete the study to day 42, we will need to include other participants who complete the day 42 visit to fulfill the requirement. Similarly, because study endpoints require data collection up to day 28, if a participant drops out prior to day 28, we will enroll another participant to complete the required complement of 12 participants with protocol-compliant evaluable data (has taken ≥85% of all doses of study drugs and completed visits to day 28, including the 2 PK studies) per dose group (see Section 8.1 and Section 8.2).

After assignment to a group, each participant will be assessed for baseline data according to Table 1 prior to their first imatinib dose. They will then take their first imatinib dose. Participants will then come back at various times during the 14-day period of imatinib-only dosing (see Section 6 on Study Procedures). During this time, safety assessments will be performed and blood will be collected for lab assays. Participants will be given imatinib in pre-filled pill containers at study visits indicated in the schedule of events. There will also be an intensive PK study performed on day 14. On this day, participants will have an IV placed to minimize discomfort related to phlebotomy at repeated time-points after dosing. Participants will return to complete the last PK blood draw on day 15 and will then continue taking imatinib at the same dose with addition of isoniazid 300 mg and rifabutin 300 mg orally per day for the subsequent 14 days. Study visits will include safety and efficacy assessments. In addition, we will conduct a PK study on day 28, with the final PK blood draw on day 29. Volunteers will then discontinue all study drugs and will complete one additional follow-up visit at day 42, 14 days after receiving their last dose, for safety. This will conclude data collection for Cohort 1.

Cohort 2: Enrollment in Cohort 2 will occur after the PK, PD, and safety data from Cohort 1 has been reviewed and two imatinib doses have been selected for further evaluation. The screening and intervention phase for Cohort 1 is the same as for Cohort 2 in terms of data collection. However, participants in Cohort 2 will begin taking rifabutin 300 mg per day and isoniazid 300 mg per day for 14 days followed by these drugs in combination with one of two selected doses of imatinib for an additional 14 days. Volunteers will be randomized to one of the two different imatinib dose levels. PK studies and the final study visit at day 42 will be completed as for Cohort 1. The primary and secondary objectives for Cohort 2 requires evaluable myelopoiesis and PK study data through day 28 from 12 participants in both of the imatinib dose groups (total 24 participants in Cohort 2, see Section 8.1 and Section 8.2).

Meal Timing for all participants in Cohorts 1 and 2: We will instruct participants to take drugs on an empty stomach in order to avoid the attenuation of INH absorption and potential for masking toxicity associated with higher drug levels when INH is taken with food. While taking imatinib without food may reduce drug levels, we want to describe a drug administration program that can be transferred to TB-infected patients in Africa, who are commonly instructed to take their anti-TB drugs after fasting. Our hypothesis is that low levels of imatinib will be associated with the optimal myelopoietic effect. If fasting reduces imatinib absorption and

imatinib drug levels, the recommended imatinib dose (from participants instructed to take all drugs while fasting) that is associated with the optimal myelopoietic effect may be higher than if imatinib were taken with a meal (i.e., 200 mg in fasting participants rather than 100 mg in participants who take the drug with a meal). In contrast, taking INH with a meal during this dose-finding study may reduce INH levels and could lead to an erroneous conclusion that the recommended dose of 600 mg INH in combination with imatinib is safe, when "real-world" consumption of the same INH dose in combination with imatinib while fasting could lead to INH toxicity. Thus we prefer to design a drug administration schedule in which participant safety is paramount. For the purposes of this study, all 3 drugs should be taken upon waking, within a 5-minute timeframe. Imatinib, then INH, then rifabutin. Breakfast may be eaten 1 hour after taking the study drugs. On study visit days, participants may eat a small breakfast at home at least 2 hours before the scheduled time of study drug administration (e.g. 7am), anticipating that the study drugs will be administered at the GCRC at 9am. On the PK study days (visits 4 and 8), a meal or snack will be provided 1 hour after study drug administration at the GCRC.

3.1.3 *Follow Up Phase*

Participants will be followed for an additional 14 days after study drug administration. All participation in the study should be complete by day 50 after enrollment.

3.1.4 Allocation to Interventional Group

Imatinib dose allocation in Cohort 1 will occur in an ascending manner, with safety evaluations before proceeding to the next higher dose as described in Section 3.1.2. Dose allocation for Cohort 2 will be randomized. The study statistician will generate the randomization allocation list. The list will be used for assignment of pill containers, prepared by the Emory IDS, corresponding to drug dose. The master list of pill container assignments will be kept by the data coordinating center in a password protected and encrypted computer.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

- The primary endpoint for Cohort 1 is the change in the number of myelomonocytic cells in the blood between baseline and day 14 of imatinib (imatinib alone).

- The primary endpoint for Cohort 2 is the change in the number of myelomonocytic cells in the blood between day 14 and day 28 of imatinib (imatinib given to participants already taking isoniazid and rifabutin).
- The primary safety endpoint will be grade 3 or 4 events and SAEs. All AEs regardeless of grade will be recorded and monitored. Safety will be primarily determined by the percent of participants on study who experience a grade 3 or 4 AE or a serious adverse event (SAE) that are considered related to the study drug. An SAE is defined as any untoward medical occurrence that meets any of the following criteria:
  - Results in death, or is life-threatening
  - Results in participant hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability/incapacity
  - Is a congenital anomaly/birth defect

  Other medically important conditions will also be assessed. These conditions include important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the definition above.

3.2.2 Secondary Study Endpoints

- Evaluation of the PK parameters and drug-drug interactions of imatinib, rifabutin and isoniazid.
- Additional research endpoints related to immunologic effects will include measures of cellular immune function and biomarkers of immune activation circulating in blood and expressed on the surface of T cells and monocytes.
- Secondary efficacy analyses will determine 1) the difference between the change in the numbers of myelomonocytic cells from baseline to day 14 in Cohort 1 and the change in the numbers of myelomonocytic cells from day 14 to day 28 in Cohort 2 (to evaluate the effect of TB drugs on imatinib-induced myelopoesis); 2) the change in the numbers of myelomonocytic cells from baseline to day 28 in Cohort 1; 3) the change in the numbers of myelomonocytic cells from baseline to day 28 in Cohort 2; 4) the pooled change in both cohorts in the numbers of myelomonocytic cells in the blood between baseline and day 28; and 5) the relationship between imatinib exposures and change in the numbers

of myelomonocytic cells during the imatinib-exposed periods in each cohort separately and in the pooled cohorts.

- Finally, as exploratory analyses, we will evaluate the proteomic and transcriptomic changes associated with imatinib.

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

- Adult age ≥ 18 years & ≤ 55 years
- Body mass index (BMI) >18.5 kg/m^2
- At least 8 years formal education, with appropriate reading and comprehension skills
- Able and willing to provide written informed consent
- Males must agree to using contraception during the study and for 2 weeks after the last dose of study drug.
- If a female participant is of reproductive potential, the participant (and her partner) must agree to use of one of the following combinations of birth control during the study and for 2 weeks after the last dose of study drug (or tubal ligation as a single method):
  1) Use of a double-barrier method of contraception: condoms (male or female) and a diaphragm or cervical cap with spermicide;
  2) Use of an IUD and a barrier method: condoms (male or female, with or without spermicide) or a diaphragm or cervical cap with spermicide;
  3) Tubal ligation.
  Important Note: Due to documented effects of rifabutin on effectiveness of homonal contraceptives (16-18), these are not included as options here with the exception of an IUD. Women who are post-menopausal, defined as age greater than 45 and no menses for at least 1 year, or who have had a hysterectomy, are considered not of reproductive potential.

4.2 Exclusion Criteria

- Current or imminent treatment for significant infection
- Pregnant or breastfeeding
- HIV positive status as determined by an FDA-approved HIV assay

- Hepatitis B infection, as determined by an FDA-approved hepatitis B surface antigen assay
- Hepatitis C infection, as determined by an FDA-approved positive Hepatitis C antibody assay
- Known infection with Mycobacterium tuberculosis (MTB)
- History of allergy or hypersensitivity to imatinib, isoniazid or rifabutin.
- History of enrollment in other clinical trials with investigational agents within 8 weeks
- Cardiac arrhythmia requiring medication, or any clinically significant ECG abnormality
- Exam consistent with congestive heart failure (e.g., edema)
- Random blood glucose >140 mg/dL or history of unstable diabetes mellitus requiring hospitalization for hyper or hypoglycemia within the past year prior to start of screening
- Use of systemic corticosteroids within the past 28 days
- Any of the following readings from a complete blood count that fall outside the normal ranges as listed here:
  White blood cell count: 3.4 10E3/mclL – 11 10E3/mcL
  Hemoglobin: Female- 11.1 – 16.7 gm/dL, Male- 12.5 – 16.5 gm/dL
  Platelet count: 150-400 10E3/mcL
  Absolute neutrophil count: Female- 0.91-5.53 10E3/mcL, Male- 0.67-6.4110E3/mcL
  Absolute lympyocyte count: Female- 0.65-3.05 10E3/mcL, Male- 0.72-3.29 10E3/mcL
- Any of the following chemistry panel and liver function test readings that fall outside the normal ranges as listed here:
  Serum potassium: 3.5-5.4 mmol/L
  ALP: 34 – 104 unit/L
  ALT: 4 - 52 unit/L
  AST: 13 - 39 unit/L
  Total Bilirubin: 0.2 - 1.0 mg/dL
  Creatinine: Female- 0.60-1.32 mg/dL, Male- 0.7-1.3 mg/dL
- Cirrhosis of the liver, or any known active or chronic liver disease
- Current or past alcohol or elicit/recreational drug use, which in the expert judgment of the Investigator, will interfere with the participant's ability to comply with the protocol requirements.

- Any experimental medications for < 8 weeks prior to screening or anticipated use during the trial
- Current (within 30 days prior to the first dose of study drug) or anticipated use of antimetabolites; alkylating agents; or other drugs or herbal preparations (including St. John's wort), known to affect activity of the CYP3A4 enzyme pathway
- Consumption of grapefruit, grapefruit juice, or grapefruit-related citrus fruits (e.g., pomelos) within 7 days before assessment for eligibility
- Unwilling to avoid grapefruit or grapefruit-related citrus fruits/pomelo during the course of the study
- Unwilling to avoid alcohol for the duration of the study
- Unwilling to abstain from taking acetaminophen-containing medications during the 28-day study drug dosing period, due to increased risk of liver toxicity
- History of major medical disorders including metabolic, endocrine, hypothyroid, hepatic, renal, hematologic, pulmonary, gastrointestinal, autoimmune or cardiovascular disorders
- Uncontrolled hypertension (persistent measurements at or above 150/100)
- Participants who are, in the opinion of the Investigator, unable to comply with the dosing schedule and protocol evaluations
- Diarrhea defined as $\geq$ 4 stools per day
- Active involvement (by the participant or the participant's partner) in In Vitro Fertilization or another assisted reproductive technology procedure
- Emory students currently enrolled in a course taught by the PI or a Co-Investigator
- Emory employees currently working under supervision of the PI or a Co-Investigator

4.3 Participant Recruitment

Advertisements will be developed with basic information and a phone contact for interested persons. These will be posted with appropriate permissions on the Emory University campus and at Emory Healthcare primary care facilities. For potential volunteers who pass basic screening questions during the phone call (age, major comorbidities, COVID-19 screening questions), a formal screening visit at the GCRC unit will be arranged.

4.4 Duration of Study Participation

The duration of study participation will be up to 50 days, to account for up to 8 days of screening and 42 days of follow-up.

4.5 Total Number of Participants

Recruitment will end when 72 evaluable participants are enrolled. It is expected that approximately 80-85 participants may need to be enrolled in order to result in 72 evaluable participants.

4.6 Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

5 Study drugs

5.1 Description

Imatinib: Imatinib mesylate is a tyrosine kinase inhibitor that is approved by multiple regulatory agencies for the treatment of several malignancies, including Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML), at adult doses of 400-800 mg/day. The drug has a well-defined safety profile. It is well absorbed after oral administration, with a $t_{½}$ of 15 hr in normal participants, supporting once daily dosing. Doses of 400 mg/d produce mean plasma concentrations of approximately 1.1 mg/ml (9). The doses that we will study achieve concentrations shown in Figure 3. Imatinib is both a substrate for and an inhibitor of CYP3A4; it is however unclear if this is dose-dependent. In CML its primary target is BCR-Abl, a strongly expressed fusion protein with tyrosine kinase activity that results from the 9:22 chromosomal translocation. Inhibition of BCR-Abl in CML by imatinib arrests myeloid cell proliferation and restores normal apoptosis. In this study we will use imatinib mesylate at 50, 100, 200, and 400 mg orally daily. Imatinib is supplied as 100 mg and 400 mg tablets that are scored. Tablets will be split by a licensed research pharmacist for dosing.

Isoniazid: Isoniazid (isonicotinic acid hydrazine) is a potent antimycobacterial drug that is on the World Health Organization's (WHO) List of Essential Medicines. Isoniazid has been in use since 1954 to treat TB and since 1963 for the prevention of TB in latently infected individuals. Oral doses of isoniazid are rapidly and nearly completely absorbed and distributed throughout the body, resulting in a time to peak concentration of 1-2 hours and a bioavailability of 90-95%.

After absorption, the first step in isoniazid clearance is hepatic metabolism by acetylation and dehydrazination. Generic isoniazid is available as 100 and 300 mg tablets. The recommended dose is 300 mg (approximately 5 mg/kg) daily alone (for TB prevention and for drug susceptible TB) and 600 mg for MDR-TB treatment in the 9 months regimen in combination with other anti-tubercular therapies. Common side effects include gastrointestinal upset, rash, and occasionally fever. A rare but serious side effect is hepatotoxicity. Approximately 10 to 20% of patients experience transient serum aminotransferase elevations during TB treatment and approximately 5% have levels that rise 5 times or more above the upper limit of normal. Mild abnormalities typically resolve without dose adjustment or discontinuation. In less than 1% of those taking the drug, isoniazid can cause severe acute liver injury. Onset is usually characterized as a gradual worsening of nausea, anorexia, and abdominal discomfort, followed by dark urine and jaundice. The time to onset ranges from 2 weeks to 6 months or more and thus severe hepatic injury is very unlikely in those taking isoniazid for 14 days only. Monitoring patient symptoms and hepatic enzymes and prompt discontinuation if worrisome symptoms or signs develop are regularly employed to reduce hepatotoxicity risk. Importantly, isoniazid is an inhibitor of CYP3A4, the exact enzyme for which imatinib is both a substrate and an inhibitor. Polymorphisms at the *N*-acetyltransferase 2 gene (Nat2) affect the initial isoniazid acetylation rate – and represent an important factor for interpreting any AEs associated with isoniazid, as well as interpreting the potential for drug interaction between imatinib and isoniazid. In this study, the Nat2 acetylator status should be evident at the phenotypic level through the PK results for isoniazid. We will confirm this by batch analysis of Nat2 genetic polymorphisms at the end of the study, using buffy coat WBC samples collected from each participant.

Rifabutin: Rifabutin was approved for use to prevent disseminated Mycobacterium avium complex (MAC) disease in patients with HIV in the US in 1992 and is also on the WHO's List of Essential Medicines. Although rifampin is more commonly used because of cheaper cost, rifampin can be replaced with rifabutin in the case of concerns for drug-drug interactions from rifampin. Rifabutin comes as 150 mg capsules. Rifabutin has been associated with rash (4%), gastrointestinal intolerance (3%), and neutropenia (2%). Less than 1% of patients experience flu-like syndrome, hepatitis, hemolysis, arthralgia, myositis, and skin discoloration. Most of these adverse events have occurred in patients taking rifabutin for extended durations and tolerability of 14 days of the drug is expected to be very high. Uveitis may occur with elevated levels of rifabutin, which is a potential risk in this study when rifibutin is taken concurrently with imatinib.

Importantly, rifabutin is a mild inducer of CYP3A4, the exact enzyme for which imatinib is both a substrate and an inhibitor.

Please refer to the Package Inserts for additional information on the study medications listed above. The following sources will be used for the three drugs:

Imatinib – Apotex
https://www1.apotex.com/products/us/downloads/pil/imat_fctb_ins.pdf

Isoniazid - Teva
https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=9499f1cf-2f46-4047-8b71-90aee7dee854&type=display

Rifabutin - Greenstone
https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=c2026b67-4755-4236-96b6-a6b5e7399707&type=display

5.2 Intervention Regimen

See description of the study design in Section 3.1 above.

5.3 Study Product Acquisition/Distribution

Imatinib (Apotex), isoniazid (Teva), and rifabutin (Greenstone) will be supplied through the study and will be made available through the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC). The site pharmacist can obtain the study products for this protocol by following the instructions in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks in the section Study Product Management Responsibilities. Upon receipt of the drug the quantity and expiration dates will be verified to assure quantity and quality.

5.4 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. All unused study products must be returned to the NIAID CRPMC (or as otherwise directed) after the study is completed or terminated. The

procedures to be followed are provided in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks in the section Study Product Management Responsibilities.

5.5 Storage

We will store imatinib tablets at 25°C (77°F) at currently available research pharmacies in Emory; excursions will be permitted to 15°C-30°C (59°F-86°F) as per the package insert. We will protect tablets from moisture.

5.6 Preparation and Packaging

The clinical trials pharmacist will prepare treatment courses using pill containers after scoring tablets as necessary to achieve the desired doses.

5.7 Blinding

This study is not blinded in terms of participant assignment to study arms. However, research samples will be coded in a blinded fashion so that personnel reading assays will be blinded to treatment arm wherever practical/possible.

5.8 Administration and Accountability

A study nurse will watch participants take their assigned medication doses on days when they attend a study visit. Pill containers will be filled by the research pharmacists to provide participants with easy dosing on non-study days. Product reconciliation will be conducted on a regular basis and will include information on product administration, such as: date administered, amount administered and to which participants, product remaining, product damaged/destroyed and date of damage/destruction, product returned and date of return, etc. A standard form will be utilized to document this information throughout the study period.

5.9 Participant Compliance Monitoring

Participant compliance will be assessed by observing therapy on study visit days and by participant self-report and pill count during intervals between visits. Adherence will be tracked by noting whether the participant received/took the correct dose of the product using the above methods. The protocol adherence for each participant can be quantified for the 28-day dosing period using pill counts, using the formula #doses taken divided by number of prescribed days for an interval, x 100 (to get a percent adherence). Acceptable protocol-compliance is defined as taking $\geq$85% of all doses of study drugs and completed visits to day 28. All participants taking at least one dose of the study drug and who do not withdraw consent will be followed for the full 42-day period.

5.9.1 Return or Destruction of Investigational Product

The clinical trials pharmacists will complete a final reconciliation of the study drug after the last participant completes their last study visit. The trials pharmacist will investigate any discrepancies in drug supply. Drug remaining at the end of the study period will be disposed.

6 Study Procedures

6.1 Screening

Screening will include:

- Informed Consent
- Medical History and Medical Record Review
- Review of Inclusion and Exclusion Criteria
- HIV testing for those who do not report being HIV-infected
- HBV and HCV testing
- Vital Signs (HR, RR, BP, Temp)
- ECG
- Physical Exam, Weight, and Symptoms evaluation
- Height
- Urinalysis
- Urine collection for evaluation of drug metabolites (control reading for comparisons to visits 4 and 8)
- Pregnancy Test
- Review of Medications
- Clinical Laboratory Assessment (blood sample) for complete blood count with differential, manual differential, serum chemistries including liver function tests and serum creatinine
- Randomization after Consent (for Cohort 2 only)

Table 1: Schedule of Study Procedures

Study Phase	**Screening**	**Dosing Interval 1** **Cohort 1: imatinib** **Cohort 2: RBT+INH**				**Dosing Interval 2** **Cohort 1: imatinib+RBT+INH** **Cohort 2: imatinib+RBT+INH**					**Post-Treatment Follow-Up**
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Study Days	**-8 to 0**	**1**	**3**	**7**	**14**	**15***	**17**	**21**	**28**	**29***	**42**
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Enrollment (all participants) Randomization (Cohort 2)	X										
HIV, HCV, HBV testing	X										
Medical History and Record Review	X	X			X				X		X
Physical Assessment, Weight & Symptoms	X	X	X	X	X	X	X	X	X	X	X
Vital Signs: BP, HR, RR, Temperature	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Pregnancy Test	X	X			X				X		X
Medication Review	X	X			X				X		X
ECG	X				X			X	X		X
Clinical Laboratory Evaluation **	X	X		X	X			X	X		X
Dispense study drugs		X				X					
PK study					X	X			X	X	
Nat2 Screening		X									
Research Blood for immune cell subset analysis		X		X	X			X	X		X
Research Blood for RNA isolation		X			X				X		
Urinalysis and urine storage	X				**X**				**X**		
Adverse Event Review / Unanticipated Problems Assessment		X	X	X	X	X	X	X	X	X	X
Total blood draw volume	20ml	45ml		30ml	70ml	5ml		30ml	60ml	5ml	30ml

*Brief day 15 and day 29 visits are required to collect 24-hour post dose blood required for the day 14 and day 28 PK studies, respectively.

** Complete blood count with differential, manual differential, serum chemistries including liver function tests and serum creatinine.

INH=isoniazid; RBT=rifabutin; BP=Blood pressure; HR=heart rate; RR=respiratory rate; ECG=echocardiogram; PK=pharmacokinetic

6.2 Study Interventions

Each study visit 1 – 10 will be preceded by a phone call, within 24 hours before the visit, for COVID-19 potential exposure and symptom screening.

These questions are:

During the past 2 weeks, have you been in close contact with anyone known to have COVID-19 disease or who tested positive for the virus?
Do you have any of the following that started in the last 2 weeks, or have you had a COVID test within the last 14 days due to COVID-related symptoms?

- Fever greater than 100 F
- Shaking/chills
- Loss of taste/smell
- Cough

- Shortness of breath or difficulty breathing
- Sore throat
- Body/muscle aches
- Headache
- Diarrhea
- Rash

If the subject answers Yes to any of these questions the day before the Baseline visit (Visit 1), then the individual will be encouraged to seek virus testing, and study participation will be discontinued.

For visits 2-10, if a participant reports any body/muscle aches, headache, diarrhea, or rash, WITHOUT other symptoms that could indicate COVID-19 or likely exposure events, they will continue with the scheduled study visit since these symptoms could be due to side effects of the study drugs. The study team will arrange for such participants to be tested for SARS-CoV-2 through Emory Healthcare as soon as possible (but will not delay study visits while awaiting results). When the results are available (3-5 days after testing), if the virus test is negative, study visits will continue. If the virus test is positive, study participation will be discontinued.

For visits 2-10, if a participant answers Yes to the potential exposure questions, or Yes for the other symptoms (fever, shaking/chills, loss of taste/smell, couth, shortness of breath or difficulty breathing, sore throat), then the individual will be encouraged to seek virus testing, and study participation will be discontinued.

6.2.1 Visit 1 (Baseline, Day 1)

The baseline visit will occur within 8 days of screening. Procedures to be completed at the baseline visit include:

- Medical History and Medical Record Review
- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Pregnancy Test
- Review of Medications
- Clinical Laboratory Assessment (blood sample) for complete blood count with differential, manual differential, serum chemistries including liver function tests and serum creatinine
- Research Blood Collection including blood collection directly into RNA protection tubes for RNA sequencing. An aliquot of buffy coat white blood cells will be stored for batch analysis of Nat2 genetic polymorphisms at the end of the study as described in Section 5.1 - Isoniazid.
- Study Medication Dispensation
- Assessment for Adverse Effects/Unanticipated Problem Review

6.2.2 Visit 2 (Day 3)

This is a brief study visit for symptom check and vital signs. There is a 1-day visit window after day 3 for this visit (Day 3 or 4).

- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Assessment for Adverse Effects/Unanticipated Problem Review

6.2.3 Visit 3 (Day 7)

This is a full study visit. There is a 3-day window for this visit (Day 6, 7, or 8).

- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Clinical Laboratory Assessment (blood sample) for complete blood count with differential, manual differential, serum chemistries including liver function tests and serum creatinine
- Research Blood Collection
- Assessment for Adverse Effects/Unanticipated Problem Review

6.2.4 Visit 4 (Day 14)

This is a full study visit including PK. This is the last day of imatinib only (Cohort 1) or isoniazid + rifabutin only (Cohort 2) administration. There is no study visit window for this visit as it must occur on the last day of drug administration.

- Medical History and Medical Record Review
- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Pregnancy Test
- Review of Medications
- ECG

- Clinical Laboratory Assessment (blood sample) for complete blood count with differential, manual differential, serum chemistries including liver function tests and serum creatinine
- Research Blood Collection including blood collection directly into RNA protection tubes for RNA sequencing
- PK study comprising blood samples taken at 6 time points over approximately 24 hours. Samples will be collected at 0h (pre-dose), 0.5 hrs (+/- 5 min), 2 hrs (+/- 10 min), 4.0 hrs (+/- 10 min), 8.0 hrs (+/- 10 min), and 24 hrs (+/- 10 min). These sampling times were identified based on optimal sampling theory, using the SAMPLE program of ADAPT, and also taking into account collection on a realistic schedule for healthy volunteer participants. Of note, participants will go home after the 8 hour time-point and will return the next day (day 15) for a 24 hour blood draw that is required to determine trough drug levels.
- Urine collection for evaluation of drug metabolites
- Assessment for Adverse Effects/Unanticipated Problem Review

6.2.5 Visit 5 (Day 15)

This is a brief visit required for collection of the 24-hour blood sample for the PK study. There is no study visit window for this visit as it must occur the day after Visit 4. This is also the first day of imatinib combined with isoniazid + rifabutin administration.

- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Assessment for Adverse Effects/Unanticipated Problem Review
- PK assessment (one blood draw) at 24 hours after the previous day's study medication doses.
- Study Medication Dispensation

6.2.6 Visit 6 (Day 17)

This is a brief study visit for symptom check and vital signs. There is a 1-day window after day 17 for this visit (Day 17 or 18).

- Physical Exam, Weight, and Symptoms evaluation

- Vital Signs (HR, RR, BP, Temp)
- Assessment for Adverse Effects/Unanticipated Problem Review

6.2.7 Visit 7 (Day 21)

This is a full study visit. There is a 3-day window for this visit (Day 20, 21, or 22).

- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- ECG
- Clinical Laboratory Assessment (blood sample) for complete blood count with differential, manual differential, serum chemistries including liver function tests and serum creatinine
- Research Blood Collection
- Assessment for Adverse Effects/Unanticipated Problem Review

6.2.8 Visit 8 (Day 28)

This is a full study visit including PK. This is the last day of medication administration. There is no study visit window for this visit as it must occur on the last day of drug administration.

- Medical History and Medical Record Review
- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Pregnancy Test
- Review of Medications
- ECG
- Clinical Laboratory Assessment (blood sample) for complete blood count with differential, manual differential, serum chemistries including liver function tests and serum creatinine
- Research Blood Collection including blood collection directly into RNA protection tubes for RNA sequencing
- Urine collection for evaluation of drug metabolites
- Assessment for Adverse Effects/Unanticipated Problem Review

- PK study comprising blood samples taken at 6 time points over approximately 24 hours. Samples will be collected at 0h (pre-dose), 0.5 hrs (+/- 5 min), 2 hrs (+/- 10 min), 4.0 hrs (+/- 10 min), 8.0 hrs (+/- 10 min), and 24 hrs (+/- 10 min). Participants will go home after the 6 hour time-point and will return the next day (day 29) for a 24 hour blood draw that is required to determine trough drug levels.

6.2.9 Visit 9 (Day 29)

This is a brief visit required for collection of the 24-hour blood sample for the PK study. There is no study visit window for this visit as it must occur the day after Visit 8.

- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Assessment for Adverse Effects/Unanticipated Problem Review
- PK assessment (one blood draw) at 24 hours after the previous day's study medication doses.

6.2.10 Visit 10 (Day 42)

This is a post-drug follow-up visit and the final study visit. There is a 5 day window for this visit (Day 40, 41, 42, 43 or 44). Participants will be debriefed at this visit and will be told when they can obtain results of the study from the investigators.

- Medical History and Medical Record Review
- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Pregnancy Test
- Review of Medications
- ECG
- Clinical Laboratory Assessment (blood sample) for complete blood count with differential, manual differential, serum chemistries including liver function tests and serum creatinine
- Research Blood Collection
- Assessment for Adverse Effects/Unanticipated Problem Review

6.3 Unscheduled Visits

Visits occurring outside the visit windows will be considered unscheduled visits. At a minimum vital signs and medical history will be reviewed at these visits, in addition to recording, grading and reporting (as necessary) any adverse events. Any necessary clinical monitoring including physical exam and laboratory evaluation will also be done as necessary.

6.4 Participant Withdrawal and Discontinuation

Participants may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator. Specific criteria for Permanent and Premature Treatment Discontinuation include the following:

- Failure by the participant to attend 3 consecutive study visits and/or failure to comply with 4 or more doses of study drugs
- Protocol-defined drug-related toxicity of grade 3 or higher
- Requirement for prohibited concomitant medications
- Pregnancy or breast-feeding
- Request by participant to terminate treatment
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol

It will be documented whether or not each participant completes the clinical study. Participants who withdraw early, if willing, will have one final visit to collect investigational product and to follow up regarding adverse events. Participants may also be discontinued from the study for the following reasons:

- Request by the participant to withdraw
- Request of the primary care provider if she or he thinks the study is no longer in the best interest of the participant
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results
- At the discretion of the study supporter (NIH/NIAID/DAIDS), the IRB/Ethics Committee, Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), or other government agencies.

6.4.1 Data Collection and Follow-up for Withdrawn Participants

Participants who withdraw consent to participate in the study will be seen for one final visit if willing. During this visit they will be asked for permission to assess any possible AEs and will have a chance to debrief with study personnel.

6.5 Early Termination Visits

If a participant decides to leave the study early or is asked to leave by the investigator, a final close out visit will be performed if the participant is willing and the participant will be given a chance to debrief with the study team. The following will be done at the time of the early termination visits if the participant allows:

- Medical History and Medical Record Review
- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Pregnancy Test
- Review of Medications
- ECG
- Clinical Laboratory Assessment (blood sample) for complete blood count with manual differential, serum chemistries including liver function tests and serum creatinine
- Research Blood Collection including blood collection directly into RNA protection tubes for RNA sequencing
- Assessment for Adverse Effects/Unanticipated Problem Review

7 Study Evaluations and Measurements

Standard, validated tests and test instruments are not described.

7.1 Medical Record Review

The following variables will be abstracted from the medical chart (paper or electronic) or from the screening history and physical.

- Date of birth
- Sociodemographics
- Height
- Weight
- Any history of disease and dates of diagnosis and treatment

- Current or previous medication use

7.2 History and Physical Examination and ECG

Age, gender and race will be recorded. Participants will be screened for any signs of active infections or disease. A brief physical exam and a 12 lead ECG will be performed.

7.3 Vital Signs

Vital signs including BP, HR, RR, and temp will be determined in the sitting position using a Welch Allyn portable vital sign monitor (or equivalent device).

7.4 Laboratory Evaluations

Clinical blood sampling will be performed for the following laboratory evaluations:

- Hematology (hemoglobin, hematocrit, platelets, white blood cell count with manual differential)
- Liver Function
- Creatinine and electrolytes

7.5 Pregnancy Testing

A urine pregnancy test will be performed at the specified time points for all female participants of reproductive potential.

7.6 Efficacy Evaluations

7.6.1 Change from baseline in the absolute numbers of circulating myeloid blood cells and other immune parameters

Previous pre-clinical studies have shown that imatinib maximally reduces mycobacterial load in mice when administered at 66mg/kg/d, whereas both higher and lower doses proved much less effective (10). At this dose, imatinib causes sustained increases in the numbers of circulating PMNs and MNs (Figure 1) (2). Myelopoietic and antimycobacterial effects were directly correlated over a wide range of imatinib doses. Change from baseline in numbers of blood PMN and MN will serve as an efficacy endpoint to inform dose selection in a phase 2 trial. Additional immune parameters, such as cellular immune function, markers of immune activation, and function of circulating myeloid cells will be evaluated.

The peripheral white blood cell (WBC) count and manual differential report on the number and percentages of different cell types in blood. To determine the differential, a drop of blood is

thinly spread over a glass slide, air dried, and stained with a Romanofsky stain, most commonly using the May-Grunewald-Giemsa technique. Two hundred cells are then counted and classified. Machines have been developed to perform automated differential counts, but they are still inferior to manual techniques as far as reliability. The following subsets of leukocytes, as reported in the manual differential, would constitute the myeloid cells in blood; the absolute number of each subset can be determined by multiplying the percentage by the total leukocyte count (in the WBC count):

- SEGS (POLY) %
- BANDS %
- METAS %
- MYELOS %
- PROMYELOS %

The percentage and absolute numbers of Monocytes, Eosinsophils, Basophils, and Lymphcytes will be separately enumerated and recorded.

7.6.2 RNA sequencing

RNA sequencing will be performed using protocols described in our prior publications (19, 20), which we have also used for RNA sequencing of human and macaque TB lungs, as well as blood, at Emory. This test will be correlated with myelopoiesis, autophagy, adverse events, and drug concentrations, using such machine learning methods such as Random Forests, LASSO and MARS, described in our prior work (21, 22). This will be used to identify biomarkers and RNA signatures that can predict (i) response, (ii) adverse events, and (iii) drug-drug interactions in later clinical trials.

7.7 Safety Evaluations

CBCs, serum chemistries, symptoms, signs, and ECGs will be monitored for all participants during the study as described in the schedule of events.

8 Sample Size Justification and Analysis Methods

8.1 Sample Size Justification and Statistical Analysis

The primary objectives are to determine the effect of imatinib on the numbers of myelomonocytic cells in the blood, assessed as the change between baseline and day 14 of imatinib only administration in Cohort 1 and between day 14 and day 28 in Cohort 2, and the safety of imatinib. Secondary objectives include analysis of DDIs of imatinib with rifabutin and isoniazid with repeated PK measurements, bacterial killing, proteomic evaluations, and immune function evaluations. We will enroll 72 evaluable participants total, 12 across 4 study arms in Cohort 1 and 12 across 2 study arms in Cohort 2.

With 12 participants per dosage arm in the first cohort (N=48), we will have 80% power to reject the null hypothesis of no change versus the alternative hypothesis that imatinib induces an increase in the absolute numbers of myelomonocytic cells per uL of blood that is at least 0.41 of the standard deviation (SD) of the change for the cohort overall and 90% power to detect a 0.48 SD. The 24 participants with evaluable data in the 14 - 28 days (imatinib+TB drugs) in the second cohort will provide 80% power to detect a 0.60 SD in the change in the number of myelomonocytic cells on imatinib pooling the arms, and 90% power to detect a 0.69 SD. Our primary analysis of each Cohort will use a (separate) linear mixed model that pools data from all time points, thus we anticipate having more power by leveraging the within-person correlation between indivduals.

There is a chance that participants will not be enrolled on all doses. Given what is known about the safety profile of imatinib, we anticipate that at least one dose will be fully enrolled. By the same rationale above, we will have 80% (90%) power to detect an increase of at least 0.89 (1.03) of a SD of the mean number of myelomonocytic cells in a specific dosage strata (using 12 per stratum). We will also have sufficient power to detect differences in effects induced by different doses. For example, comparing dose groups with a two-sample t-test, with 12 participants per dosage stratum, we would have 80% power to detect a 2.3 x10^3 cells/uL difference between two arms in the change from baseline in the myelomoncytic cell count assuming a SD similar to that seen in a recent macaque study. In a preclinical study of imatinib in *Mtb*-infected antibiotic-treated treated macaques, the mean number of myelomonocytic cells increased from 1.47±0.96 in controls to 3.78±1.89 in imatinib treated animals, with a mean difference of 2.31 (all values indicate thousands of cells/uL). Thus we are adequately powered

to detect dose-specific differences on the order of what was seen in the macaques. Further, in a supportive analysis, we will also pool the arms in order to borrow strength across the doses to fit a dose-response curve.

Myelopoiesis will be determined by estimating the absolute number of myelomonocytic cells per uL of blood using the WBC and a manual differential, as noted above. We hypothesize that, on average, increases in myelopoiesis will occur (and the 95% CI for the change in myelopoiesis over time will exclude 0), with the maximum change being observed at day 14 of imatinib administration.

Cohort 1 Analysis

The same mixed model can be used for the analyses of all primary and secondary endpoints involving Cohort 1 comparisons, where data from all arms and time points are put into one model for the myelopoiesis count outcome. This approach should generally be a more powerful approach than the paired t-test for the change from baseline, as it is leveraging the within person correlation at all time points. Note that the screening value which occurred prior to Day 0 can be considered a duplicate observation for the baseline (Day 0) when fitting the model below.

Notation:
Let Yij represent the cell count for individual I at time j, where j=day 0,14,28.
Thus, Yi0= count at baseline, Yi14 = count at day 14, Yi28= count at day 28 for individual i.
Similarly, let $t14_{ij}$ = day14 indicator and $t28_{ij}$=day28 indicator, and $dosek_{ij}$ = dose k indicator for individual i, time j, where k=2,3,4. Let r_i be the random intercept term for person i and let $error_{ij}$ be the mean 0 independent error term for person i at time j.

Cohort 1 model:

$$Yij = b0 + b1\ t14_{ij} + b2\ t14_{ij}*dose2_{ij} + b3\ t14_{ij}*dose3_{ij} + b4\ t14_{ij}*dose4_{ij} + b5\ t28_{ij} + b6\ t28_{ij}*dose2_{ij} + b7\ t28_{ij}*dose3_{ij} + b8\ t28_{ij}*dose4_{ij} + r_i + error_{ij}$$

b0 = baseline myeolopoeis

b1 = day14 change from baseline for dose 1

b2 = difference between dose 2 and dose1 day14 change from baseline

b3 = difference between dose 3 and dose1 day14 change from baseline

b4 = difference between dose 4 and dose1 day14 change from baseline

(4 b1+b2+b3+b4)/4 is the average Day 14 change from baseline pooled across the 4 doses in, i.e. the primary endpoint for Cohort 1

b5 = day28 change from baseline for dose 1

b6 = difference between dose 2 and dose1 day28 change from baseline

b7 = difference between dose 3 and dose1 day28 change from baseline

b8 = difference between dose 4 and dose1 day28 change from baseline

b2 – b3 is the between dose difference in the day14 change from baseline for dose 2 and 3; similar comparisons can be for each distinct pair of doses for day14 change from baseline.

b8 – b7 is the between dose difference in the day28 change from baseline for dose 3 and 4.

b5 – b1 is the difference between day 28 and day 14 for dose 1.

b6 – b2 is the between dose difference for change between days 28 and 14 for doses 1 and 2.

Other comparisons of interest for Cohort 1 follow similarly.

Cohort 2 Analysis

Similar mixed model analyses can be done for Cohort 2; however, now only two doses are compared and the interpretation of the coefficients will change, as only TB drugs are given between Days 0-14, and imatinib is added starting on Day 15. The change from baseline at Day 14 can be interpreted as the effect of TB drugs on myelopoiesis. The difference between Day 28 and Day 14 can be interpreted as the effect of 14 days of imatinib on myelopoiesis in the presence of TB drugs. Dose 1 and Dose 2 denote the two selected doses from Cohort 1. Note that the screening value that occurred prior to Day 0 can again be a considered duplicate

observation for the baseline (Day 0) when fitting the model below. Assuming a similar notation as for the Cohort 1 model one has the

Cohort 2 model:

$Yij = a0 + a1\ t14_{ij} + a2\ t14_{ij}*Dose2_{ij} + a3\ t28_{ij} + a4\ t28_{ij}*Dose2_{ij} + r_i + error_{ij}$

a0 = average Day0 myeolopoeis
a1 = Day14 change from baseline for Dose 1
a2 = difference between Dose 2 and Dose1 Day14 change from baseline
a3 = day 28 change from baseline for Dose 1
a4 = difference between Dose 2 and Dose1 Day28 change from baseline

Some comparisons of interest
(a3-a1 +a4 +a3 –(a2+a1))/2 is the average change between Day 28 and Day 14 (imatinib baseline) pooled across the 2 doses, i.e. the primary endpoint for Cohort 2

a3 – a1 = change in myelopoiesis between Day 28 and Day 14 on Dose 1
a4 + a3 – (a2+a1) = change in myelopoiesis between Day 28 and Day 14 on Dose 2
a4 – a2 between dose difference in the change between Day 28 and Day 14

Pooled Cohort Analysis

We can use the estimates from the separately fitted Cohort 1 and Cohort 2 models provided above to compare the effect of 14 days of imatinib in the presence versus absence of TB drugs. This would be comparing the change from Day 0 to Day 14 for Cohort 1 to the change from Day 14 to Day 28 in Cohort 2. We consider this comparison for the selected doses, Dose 1 and Dose 2. Suppose Dose1=dose 3 and Dose 2= dose 4 then:

D1=(2b1+b2)/2 = the change from baseline to Day 14 averaged over Dose 1 and Dose 2 in Cohort 1.
D2=(a3-a1 +a4 +a3 –(a2+a1))/2 = the change from Day 28 to Day 14 averaged over Dose 1 and Dose 2 in Cohort 2.

D1-D2 = the between-Cohort difference in the change in myelopoiesis induced by 14 days of imatinib, i.e. the effect of TB drugs on the effect of 14 days of imatinib.

AE analysis

We will estimate proportion of clinical and laboratory adverse events, along with 95% exact Clopper-Pearson CI. AE rates will be summarized separately by dose and cohort, as well as combined across the cohorts for each dose, and then overall. All participants who take at least 1 dose will be included in assessments of safety.

8.1.1 Pharmacokinetic Analysis

Frozen plasma samples will be shipped on dry ice in batches to the laboratory of Dr. Charles Peloquin at the University of Florida in Gainesville for PK analyses

The main PK objective is:

To assess the impact of imatinib on isoniazid and rifabutin PK and the impact of isoniazid and rifabutin on the PK and PD of imatinib.

Within this main PK objective, specific PK analyses will aim to:

1. Identify pharmacokinetic parameter estimates, and concentration-time profiles of imatinib doses of 50, 100, 200, and 400 mg in healthy volunteers.
2. Identify if rifabutin and isoniazid standard doses are covariates of imatinib clearance, and if imatinib concentrations are covariates of rifabutin and isoniazid clearance and volume, using compartmental pharmacokinetic modeling.
3. Identify the pharmacokinetic/pharmacodynamic exposure-effect relationship between imatinib AUC or peak or trough and the change in the numbers of myelomonocytic cells in the blood between baseline and days 14 and 28 of therapy.

We will first evaluate the robustness of our sampling strategy. The percentage of imatinib concentrations measured that are below the limits of quantification in any of the participants at any of the time points identified by D-optimality will be calculated. A result of 0% indicates that

the optimal sampling strategy derived from sampling theory was likely to be optimal. Next, we will analyze all imatinib concentrations using ADAPT software of D'Argenio *et al* utilizing a compartmental PK analysis approach (23, 24). ADAPT software was developed using NIH funding, is open source, and has validated performance metrics, ensuring accuracy and robustness of findings from this software. We do not assume *a priori* how many compartments the imatinib PK model has; indeed some studies have described it as a one compartment model drug while others have found it is a two compartment model drug (8, 13, 25). We will examine one-, two-, and three-compartment models with first-order input and elimination. Estimation of PK parameters will be based on the MLEM algorithm in ADAPT, as described above. The best number of compartments will then be chosen by comparing Akaike's information criteria, Bayesian information criteria, and −2 negative log likelihood scores for each model; we also apply the rules of parsimony. Goodness of fit is evaluated by examining the predicted/observed plots prior to- and after- the Bayesian step. Potential problems by concentration are sought by examining run-of-sine plots. Measures of Bias (mean error and weighted mean error) will be examined, as well as measures of Precision (mean squared error, weighted mean squared error, Bias-adjusted mean squared error and Bias-adjusted mean weighted squared error). The mean pharmacokinetic parameters, mainly volume of central compartment and clearance will be calculated for each participant, and utilized to calculate the half-life, peak concentration, the 0-24h area under the concentration-time curve (AUC_{0-24}/MIC) and the percentage of time that concentration persists in either the concentration zone associated with autophagy or myelopoiesis for each participant. Urine will be collected, frozen and stored for possible assessment of drug metabolites at the time of the PK studies.

The precision in identifying both clearance and volume with PK sampling times we have chosen will be >95%, which means very little bias and error. The differences in clearance and volume (hence AUC and peak concentration) will therefore be driven by the interindividual variability (IIV) and doses given. There will be 12 participants for each imatinib dose group in Cohort 1 who complete the PK studies (evaluable for PK data). With a population of 12 per group, for 4 dose groups, the power in detecting a 25% difference in clearance (which drives the AUC), given the IIV, is 90% for the first cohort study. In Cohort 2, which has 2 dose groups of 12 participants each (total=24), given the IIV% of clearances (rifabutin, isoniazid and imatinib), the power would be greater than 90% to detect a 25% change in TB drug clearance (hence AUC) for the 24 patients comparing results before and after addition of imatinib.

8.1.1.2. Drug-drug pharmacokinetic interactions

We have recently introduced machine learning or artificial intelligence (AI) based algorithms to pharmacometrics to identify PK covariates, including genotypic, demographic, clinical, laboratory features, and concomitant medications chosen model was designated the base model (26, 27). We will examine the effect of rifabutin and isoniazid PK parameters, demographic features, laboratory values, and RNA-seq signatures, in each participant, on imatinib PK parameters and variability, and hence identify the DDIs if present. We will compare baseline pre-treatment blood samples with those taken after imatinib alone or after imatinib plus isoniazid and rifabutin. This will be performed using Salford Miner software. Moreover, algorithms such as MARS give a final output equation of the covariates which can be directly used to identify the optimal dose for use in the case that DDI are identified.

8.1.1.3. PK-PD interactions: myelopoiesis and immunologic response

We have also extensively used AI methods these methods to identify drug threshold concentrations associated with adverse events, and drug concentration thresholds associated with good microbial and clinical outcomes (28), (20, 21, 29), (30, 31), (32), (22). These methods are more accurate than mixed effects modeling, require smaller sample sizes, and are designed to handle both deep and wide data. We will examine the effect imatinib, and the effect of rifabutin and isoniazid PK parameters on imatinib immunological response. We will identify the imatinib concentration threshold associated with optimal hematopoiesis alone and in the presence of the anti-TB drugs rifabutin and isoniazid, using the MARS algorithm in Salford Miner software. Similarly, we will use the same approach to identifier predictors and imatinib concentrations associated with any adverse events.

8.1.1.4. PK-PD interactions: adverse events

The AI algorithm MARS will be used to identify predictors of imatinib, rifabutin, and isoniazid concentrations associated with any of these adverse events, following our methods in Modongo et al (32). Outcomes examined in relation to imatinib, isoniazid, or rifabutin concentrations will be any participant-reported adverse events, including diarrhea, ECG changes, changes in liver function tests, neutropenia, thrombocytopenia, anemia, changes in other serum chemistries, as well as other symptoms and signs.

8.1.2 Interim Analysis

Given imatinib is an FDA-approved drug with a known safety profile, we expect the doses used in this study to be well tolerated. After the first 6 participants in a dose group have completed the day 42 follow-up visit, the study team, the Data Safety Monitoring Board (DSMB), the Independent Safety Monitor, and the Sponsor will evaluate the safety data and determine whether it is safe to proceed to enrolling in the next dose group after the previous group is fully enrolled. Note that since 42-day follow-up is required for a participant that "counts" toward the 6 needed for formal safety analysis, if any of the first 6 participants in a dose group do not complete the study to day 42, we will need to include other participants who complete the day 42 visit in order to fulfill the requirement.

After Cohort 1 enrollment and data collection and analysis are complete, we will chose the doses with the most acceptable safety and efficacy profiles for study in Cohort 2. DSMB open meeting minutes and recommendations will be shared with the FDA.

8.1.3 Safety Analysis

All participants entered into the study who take at least one dose of imatinib and/or rifabutin + isoniazid will have detailed information collected on AEs for the overall study safety analysis. An Independent Safety Monitor (ISM) will review individual and summary reports of AEs in real time as they occur, as well as scheduled formal review of AEs and clinical laboratory results on a weekly basis during the study. SAEs will be reported to the Investigator within 24 hours of awareness of occurrence and the Investigator will then assess the events and report them to the Sponsor (DAIDS), the FDA and to the Emory IRB as described in Section 9.4. All SAEs will be reported to DAIDS in an expedited fashion, within 3 days of occurrence, in accordance with DAIDS requirements.

8.2 Participant Population(s) for Analysis

All-treated population: Any participants enrolled into the study who receive at least one dose of investigational product will be analyzed for myelopoiesis, safety, and other immune parameters.

Protocol-compliant population: Effects of imatinib on myelopoiesis and other immunologic parameters will also be assessed specifically in those with acceptable protocol-compliance for evaluable data – participants who have taken ≥85% of all doses of study drugs and completed visits to day 28.

9 Safety and Adverse Events

9.1 Definitions

9.1.1 Adverse Event

An **adverse event** is any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related.

9.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that:

- Is fatal
- Is life-threatening
- Requires or prolongs an inpatient hospital stay
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the participant, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

9.2 Recording and Grading of Adverse Events

At each contact with the participant during the study period, which includes every visit up to day 42, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, and grouped under one diagnosis.

AEs will be graded using the FDA Guidance Document, “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials Guidance for Industry,” September 2007, except when the specific AEs are not represented in this document. In these cases, we will also use the DAIDS table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, or the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017, as applicable. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event which we become aware of through a passive basis (participant reporting back to the study team, or through publicly available information), which occurs after the study period (after day 42) and is considered to be possibly related to the study intervention (suspected, unexpected serious adverse reactions, or SUSARs) or study participation will be recorded and reported immediately.

9.3 Relationship of AE to Study

The relationship of each adverse event to the study procedures will be characterized. The PI will make this determination and will classify adverse events as related or unrelated. “Related” will mean that there is a reasonable possibility that the AE may be related to the study agent(s). “Not Related” will mean that there is not a reasonable possibility that the AE is related to the study agent(s). When a SAE is assessed as “not related” to study agent(s), an alternative etiology, diagnosis, or explanation for the SAE should be provided. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated, as required. Any of the study drugs which a participant has taken (imatinib, rifabutin, isoniazid) will be assessed for relationship with the AE.

9.4 Reporting of Serious Adverse Events, and Unanticipated Problems

Requirements, definitions and methods for expedited reporting of adverse events are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids. This study will use the SAE form of expedited adverse event reporting, as defined in Version 2.0 of the DAIDS EAE Manual. The study products for which expedited reporting are required are imatinib, rifabutin, and isoniazid. The EAE reporting period for this study will be 42

days, which is the day of the final study visit. During these 42 days, all SAEs will be reported to DAIDS in an expedited fashion, within 3 days of occurrence, in accordance with DAIDS EAE Manual. Any of the study drugs which a participant has taken (imatinib, rifabutin, isoniazid) will be assessed for relationship with the SAE. In addition to the SAE Reporting Category identified above, other AEs that must be reported to DAIDS in an expedited manner are:

- Any gastrointestinal or liver toxicity of grade 3 or higher
- Any uveitis of grade 2 or higher
- Episodes of ventricular tachycardia or fibrillation, syncope, and seizure
- Grade 3 or higher QTcF prolongation
- Any Grade 4 event, including laboratory values
- Heart failure of grade 3 or higher

After the protocol-defined EAE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the DAIDS EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information). Of note, although pregnancy is not an AE, all pregnancies that occur during the study will be reported to DAIDS given the teratogenic potential of imatinib. Any pregnancy occurring during the study will be followed to assess any negative outcomes resulting from exposure to the study drugs. Reporting of pregnancies will not use the EAE system, but will be include a written clinical summary of the pregnancy including but not limited to the date discovered, any study or other medications taken during the pregnancy period, the expected due date, and eventual outcome. Pregnancies will be reported to DAIDS first within 7 business days after discovery, and monthly reports will follow until the end of the pregnancy period.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. At least two staff members at the Emory site will have a combination of Reporter and Submitter rights to DAERS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the

DAERS application itself. For questions about expedited reporting, please contact the DAIDS RSC Safety Office at (DAIDSRSCSafetyOffice@tech-res.com).

Written Investigational New Drug (IND) safety reports will be submitted to the FDA using FDA Form 3500A by DAIDS, for SUSARs within 15 calendar days of DAIDS determining that the information requires reporting. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The Investigator will also make an assessment of whether the event constitutes an unanticipated problem posing risks to participants or others (UP). This assessment will be provided to the Emory University IRB and DAIDS, which, in turn, will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

The Investigator is responsible for reviewing all IND Action Letters, Safety Reports and any other safety related Investigator Notifications and determining the action to be taken (i.e. prompt reporting to the IRB, consent change/modification, routine reporting, etc).

Co-investigators and the Investigator must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible. In narrative reports, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Participant number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

9.4.1 Follow-up report

If an AE has not resolved at the time of the initial report and new information arises that changes the Investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The Investigator is responsible for ensuring that all AE are followed until either resolved or stable.

9.5 Medical Monitoring and Toxicity Management

Martha Arellano, MD is a Professor of Hematology and Oncology with extensive experience administering imatinib to CML patients at Emory University Hospital. She is certified by the American Board of Internal Medicine in Hematology. She will serve as the Independent Safety Monitor (ISM) for this study. Dr. Arellano's role will be to help monitor the safety of participants and adjudicate adverse events that may be related to imatinib, rifabutin or INH. She has 9 years of experience as principal and co-investigator on multi-institutional clinical trials including trials evaluating transplantation for adults with acute leukemia. These collaborations have led to peer reviewed publications in high impact journals, such as *The Journal of Clinical Oncology*, *Cancer*, and *Lancet Oncology*. Her strong background in clinical investigation and experience as member, and now as vice chair of the Winship Data and Safety Monitoring Committee, make her exceptionally qualified to serve as the Independent Safety Monitor for the trial. The monitor will attest to the absence of relevant conflicts of interest as defined by NIAID and will be approved by all relevant regulatory bodies prior to beginning the study.

The ISM and the PI/co-PI will review safety data as enrollment progresses, assessing AE summaries in real-time and formally on a weekly basis for clinical significance and facilitating attribution to study medications (protocol Section 9.2 and Section 9.3). The ISM will provide information to the DSMB on frequency and severity of AEs.

For individual toxicity management, the PI will review all toxicity reports of grade 2 or higher in real time in order to decide on possible need for intervention or drug discontinuation. In general, a grade 2 AE thought to be related to a study drug that does not respond to non-pharmacologic intervention (e.g., salt restriction and elevation of legs for pedal edema) will lead to consideration for drug discontinuation, and any grade 3 or higher AE will cause discontinuation of study drugs. Participants taken off study drugs will be followed for safety if willing but will not participate in PK studies.

Plans for treatment of common side effects of imatinib are listed below, including symptom grading that warrants drug discontinuation.

The following 4 side effects / AEs will be graded using the FDA Guidance Document, "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials Guidance for Industry," September 2007.

- Low blood counts: Monitor blood counts more frequently for grade 1-2 leukopenia, anemia or thrombocytopenia. Discontinue study drugs if grade 3 or higher.

- Nausea and vomiting: Treat symptomatically with OTC medications for grade 1-2. Discontinue study drugs if grade 3 or higher.

- Diarrhea. Treat symptomatically with OTC medications for grade 1-2. Discontinue study drugs if grade 3 or higher.

- Fever: Treat symptomatically with OTC medications for grade 1-2. Discontinue study drugs if grade 3 or higher.

The following 3 side effects will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events - Corrected Version 2.1, July 2017

- Skin rash (skin reactions): Treat symptomatically with OTC medications for grade 1. Discontinue study drugs if grade 2 or higher.

- Muscle cramps and bone pain. Treat symptomatically with OTC medications for grade 1. Discontinue study drugs if grade 2 or higher. See “Pain (not associated with study agent injections and not specified elsewhere),” Page 21 of the DAIDS AE Grading Table.

- Hemorrhage (bleeding problems): Grade 1, N/A. Discontinue study drugs if grade 2 symptoms or higher, or decrease in Hgb > 1.5 g.

Edema is not listed in the FDA Guidance document or the DAIDS table, and will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, Nov 2017.

- Edema (swelling of the face, feet, hands): Treat symptomatically with salt restriction and limb elevation if possible for grade 1-2. Discontinue study drugs if grade 2 edema does not respond to non-pharmacologic treatment, or for higher grade edema.

9.5.1 Study Progress and Safety Monitoring Plan

The Division of AIDS guidance on study monitoring have been implemented to develop a protocol-specific Study Progress and Safety Monitoring Plan (SPSMP), which will be approved in writing by the assigned DAIDS Medical Monitor/Medical Officer before trial initiation. Briefly, the ISM, DAIDS representative, the DSMB, and the PI/study team will review all reports at least monthly, with AE reports generated every 2 weeks. The following reports will be generated: 1) Accrual update, 2) Progress report, 3) Delinquency report, 4) Periodic summary adverse event report, 5) Baseline characteristics report, 6) Data completeness report, 7) Outcomes summary report (completed, withdrew, etc), 8) Efficacy report (myelopoesis). The contents of the report will be as outlined in the DAIDS SPSMP protocol template, which can be

found at: (https://www.niaid.nih.gov/sites/default/files/studydatamonitor_plan.pdf) and which has been used to create a study-specific SPSMP. The reports created for this process will be provided to DAIDS at the frequency of each review as specified in the SPSMP.

A DAIDS-appointed DSMB will provide oversight and monitoring for the conduct of this study. The DSMB will conduct study-monitoring functions to ensure that the research produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. We expect that this trial will be risk classified by the scientific review committees as Moderate Risk, based on the history of use in healthy volunteers and the known adverse event profile and doses of the agents used. For studies deemed Moderate Risk, initial monitoring occurs within 1 year from the date of the first participant accrued, with 2 of the first 5 participants being reviewed. For this trial, this approach will apply to each imatinib dose cohort. The DSMB will review all aspects of the study, with a primary goal of assessment of participant safety, as well as compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the monitor(s) assigned to the DSMB may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. The monitor(s) will then prepare a final monitoring summary report.

Dr. Waller and the investigators, the ISM, the clinical research coordinator and the regulatory affairs coordinator will meet at least monthly to review and discuss study data to ensure participant safety. During the meetings the PI or co-I will review the eligibility criteria for each new participant. In addition, during these meetings the group will review all adverse events, random checks of case report form completion and a roadmap for each participant on the trial. All study personnel will be trained on the protocol by the PI or co-I. Study personnel will sign the training log prior to being included on delegation of authority log. All adverse events will be handled according to Section 9.4, which provides detailed instructions on reporting requirements.

The PI and the ISM will formally review clinical toxicity assessments with the DAIDS medical monitor every two weeks and after 6 participants have completed follow-up in a dose stratum. The PI and/or medical monitor will halt further enrollment at that dose level for formal review by the DSMB if any participant develops any emergent grade 3 or higher dose-limiting toxicity that

is definite, possible or probable in causal relationship to the study drug, in the opinion of the PI. If no such toxicity is observed after the first 6 participants in a dose stratum have completed follow-up, and a total of 12 participants are enrolled in the first stratum, then the next dose stratum will be opened for enrollment.

The safety rationale for opening accrual to a higher dose level, based upon findings from the first 6 participants at the previous lower dose level, is as follows: Rather than use a standard 3 + 3 dose escalation design, we will utilize a more conservative threshold for halting accrual. In this study, enrolling healthy volunteers, a frequency of >33% grade 3 or higher dose-limiting toxicity attributed to a study drug would warrant formal review by the DSMB. We propose to protect participant safety by performing a safety analysis after 6 participants have completed the day 42 follow-up visit, a sample size that gives us greater than 90% power to identify a safety signal and halt accrual at that dose level, based upon a true rate of grade 3 or higher toxicity of 33% (or greater).

9.6 Critical Event Identification and Reporting

In addition, we will report critical events (CEs) to DAIDS and other entities to which we are responsible, including IRBs. Critical events include the following classes of events: unanticipated problems involving risks to participants or others, serious noncompliance, continuing noncompliance, suspension or termination of EC/IRB approval, and suspected research misconduct. The time period for reporting CEs to DAIDS is from the date of study start up to the publication of all related manuscripts resulting from the study.

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study participants will be kept confidential and managed according to the principles of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

10.2 Data Collection and Management

All clinical and laboratory information required by this protocol is to be present in the source documents. All protocol-required visits are to be recorded on the CRFs and keyed into the database unless otherwise specified.

We will use Clinical Research IO, CRIO, as the study clinical data management system. The site data managers and clerks will be responsible for manually entering quantitative data, not already being collected routinely and required for the evaluation, into a study database. Site databases and the merged analytical datasets will be stored on password-protected, encrypted servers. Scheduled backups will be performed on a daily, weekly, and monthly basis. Personal identifiers will be suppressed from the analytic dataset prior to the data analysis phase of the study. Any paper registers, forms, or records that are reviewed in order to abstract data or cross-check missing data will not be removed from the secure, programmatic area where they are stored.

Data will be validated on entry, using range and consistency checks. Quality control procedures will include review of CRFs for completion and correctness. Logical data checks will also be performed on the data. Incomplete and incorrect data queries will be sent back to sites electronically for error resolution. Errors will be reviewed and corrected on a weekly basis. The study will be monitored by internal data monitors.

10.3 Records Retention

Study records (source documents, signed informed consent forms, IRB correspondence and approval letters, and screening logs) will be kept in a secure location accessible only to authorized study staff, investigators, and monitors. All records will be archived in a secure storage facility for at least ten years after the completion of the study.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

This study will be conducted under ICH E6 with good clinical practice compliance. Audits of the Emory site and study will be performed by the DAIDS-appointed Data and Safety Monitoring Board as described in Section 9.5.1. The Investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, site monitors, Office of Human Research Protections (OHRP), and other local, US, or international regulatory entities (e.g, FDA, EMA, and other regulatory agencies), and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by local, US, or international regulatory entities (e.g, EMA) and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the Investigator before commencement of this study.

12.1 Risks

The rationale for the dosing schedule is as follows: In Cohort 1, 14 days of imatinib exposure without TB drugs is required to observe an effect on myelopoiesis (the primary end-point). An additional 14 days of imatinib plus anti-TB drugs is proposed to allow imatinib levels to reach steady state after modulation of liver microsomal enzymes by rifabutin and isoniazid. In Cohort 2, 14 days of anti-TB drugs is sufficient to reach steady state, and an additional 14 days of anti-TB drugs with imatinib will allow us to observe imatinib effects on myelopoiesis with prior exposure to the anti-TB drugs.

The safety rationale for administration of imatinib for 28 days at the proposed doses in healthy volunteers is as follows: We do not expect that imatinib will cause significant AEs in healthy normal volunteers when given for this duration. While asymptomatic elevations in aminotransferase levels are often seen in patients within 2-8 weeks after starting imatinib, marked increases in ALT are usually only observed after 6 months of imatinib therapy. Importantly, the toxicity of imatinib is dose-related. We will minimize risk by starting with a very low dose (50 mg/day) and escalate carefully only after safety data on the lower dose has been reviewed for acceptability. The DSMB must recommend proceeding to the next dose level before it will be initiated. Volunteers will be very closely monitored for adverse events at a US cancer center setting highly experienced with imatinib therapy. Visits with a safety evaluation are at study days 1, 3, 7, 14, 15, 17, 21, 28, 29, and 42.

Imatinib is well tolerated in CML patients, and a maximal tolerated dose has not been defined, but >800mg/day is rarely used. Most adverse effects, even at the highest doses, are grade 1 (mild) or grade 2 (moderate). Most patients have a reduction in the Hgb level of 1 to 2 mg/dL; the hemoglobin level typically increased to base-line values or higher with continued therapy. Drug induced anemia during long-term administration has been rarely seen. Neutropenia occurs in chronic phase CML patients treated with imatinib at the onset of blast crisis, but is unlikely to occur in patients receiving low doses in the absence of hematological disease. Inhibition of normal hematopoiesis does not occur in Philadelphia chromosome negative patients, although further clinical assessment will be required to ensure this. Imatinib is an inhibitor of CYP2C9, CYP2D6 and CYP3A4. Thus, drugs metabolized through these enzymes, including rifabutin, in some patients could require alterations in dosing and/or dose interval. In the PK studies proposed, being on these drugs with major CYP enzyme interactions will serve as exclusion criteria. We will also monitor QT intervals with ECGs for all study participants. In summary, we expect these doses of imatinib to be very safe. Isoniazid and rifabutin are also medications with a well-known safety profiles. Toxicity may be idiosyncratic or dose-dependent. Because we are administering these drugs over only 14 to 28 days in healthy participants, we expect tolerability to be high.

12.2 Benefits

There are no direct benefits to the participants. Participants may however feel they experience the indirect benefit of participating in a research study aiming to identify a new treatment for TB.

12.3 Risk Benefit Assessment

Given the public health problem of TB, and the known safety profile of imatinib and the anti-TB drugs under study, we feel that the study has a favorable risk benefit ratio to society.

12.4 Informed Consent Process / HIPAA Authorization

Study nurses will obtain written informed consent in English from all potential participants. The consenting process will take place in a private space in the clinics where participants are recruited, to ensure confidentiality. Participants will be allowed to provide consent at the time of the consent discussion. Participants will be given time during the consent discussion to ask and have answered any questions. Informed consent will be documented in accordance with GCP standards.

13 Study Finances

13.1 Funding Source

This study is funded by a UH3 grant awarded to Dr. Daniel Kalman at Emory University, by the National Institutes of Allergy and Infectious Diseases / Division of AIDS.

13.2 Conflict of Interest

Emory investigators will for the Emory University Policy on Conflicts of Interest Related to Research. All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

13.3 Participant Stipends or Payments

Emory participants will be reimbursed at a rate of $175 for the Day 1 visit, $75 for each brief visit (7 visits), plus $300 for each PK study visit (2 visits) for a total of $1300 for the entire study.

14 Publication Plan

Dr. Shaw will perform the primary statistical data analyses. Drs. Bisson, Wallis, Waller, Kalman, Giver, Harvey, Gumbo and Shaw and other investigators who meet authorship requirements will all contribute to timely publication of the results. The primary draft manuscript will be done by Drs. Bisson and Waller and will be reviewed by all authors within 3 months after the analysis is completed.

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16 Attachment

Study Informed Consent Form

17 Appendix

17.1 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from

automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

17.2 Case Report Forms (CRFs)

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

17.3 GEORGIA CTSA CLINICAL RESEARCH CENTER FACILITY AT EMORY UNIVERSITY

GEORGIA CTSA - GCRC site at Emory University Hospital (EUH): The EUH GCRC site houses inpatient and outpatient areas, administrative offices, participant waiting area and laboratories. The two areas combined encompass a total of 11,893 square feet. The Inpatient Research Unit includes fully equipped private rooms and a nursing station. At the far end of the GCRC inpatient unit, the Serious Communicable Disease Unit (SCDU) has three rooms that are capable of providing appropriate isolation and intensive care for patients with highly contagious, serious infectious diseases. Each room has an anteroom that has net negative air pressure in relation to the hallway. The patient rooms have net negative air pressure in relation to the anteroom. Each patient room has over 20 air changes per hour with laminar airflow over the patient beds. All air from the rooms is HEPA filtered and directly exhausted to the outside after being filtered. The rooms were successfully used to treat 4 Ebola patients during the 2014-2015 epidemic. Currently they are used to conduct research on various communicable diseases through Georgia CTSA. In addition to the 3 ICU level isolation rooms, the 8 additional rooms in the unit can be used to care for patients with a lesser degree of illness. Participants check in with the staff at the nursing stations. The participant waiting area seats 9 people. The outpatient research unit is immediately adjacent to the inpatient unit and houses a nursing station, 6 private research bays for study participants and several procedure rooms. GCRC research

nurses and technicians are available on a daytime 8-hr shift to perform research activities such as IV placement, timed urine and blood collection, study drug administration, etc.

The Human Performance Unit includes three private outpatient rooms separate from the above described outpatient care area with (1) a treadmill equipped for VO_2Max testing, EKG for exercise stress testing, (2) and ultrasound system for the assessment of flow mediated dilatation and carotid artery intimal medial thickness, and (3) an infusion room.

GCRC Administrative Unit: The administrative suite is adjacent to the EUH-GCRC research nursing units and houses the offices of the GCRC Program Director and site specific Co-Director, Research Nursing Director, Administrative Director, the GCRC scheduling coordinator and Program Coordinators.

GCRC Core Laboratory: The main GCRC Core Laboratory is located adjacent to the EUH GCRC unit and staff includes research technicians with long-standing experience in processing and storage of timed blood, urine and tissue samples. The unit employs the Georgia CTSA-wide state-of-the art Nautilus Laboratory Information Management System (LIMS) for de-identified sample tracking, storage and management. Lab resources include a main Laboratory office, a large sample bench processing and aliquoting area for use by GCRC and investigator staff, general and refrigerated centrifuges and microcentrifuges and 11 [-80^{o}C], 3 [-20^{o}C] and 2 [4^{o}C] freezers for sample storage. All freezers/refrigerators are equipped with CO_2 back-up system. All three core laboratories hold CLIA waivers.

17.4 Emory University Investigational Drug Service

The pharmacy that will serve the study is the Emory University Investigational Drug Service (IDS) - http://www.ocr.emory.edu/ids/index.html
The IDS is currently involved in a number of NIAID/DAIDS studies, demonstrating the capacity of the IDS to initiate, conduct, participate in, and support NIAID/DAIDS funded research.

Staffing:

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Susan Rogers, Director, B.S., RPH, sroger2@emory.edu, 404 712-7485

Access:

Access to IDS is limited to IDS employees only. All have keys to the area.

Continual access to electrical power:

IDS is located in Emory Clinic Building A which has a backup generator that provides continual power in case of power outages

Controlled room temperature:
Room temperature is controlled and monitored continually via an electronic monitoring system, Tempalert.

Study product preparation:
Study products are prepared in the pharmacy which is a clean, safe and secure setting. All study product is properly labeled by name and protocol # and is stored according to the labeling requirements.

Equipment:
IDS is equipped with appropriate space and equipment for proper handling and preparation of study product.

Clean water:
IDS has a sink for water supply in the dose preparation area of the Pharmacy.

Equipment maintenance:
IDS maintains equipment for storage, temperature monitoring and preparation of study product and doses. IV hoods are inspected every six months. Temperature monitoring equipment is calibrated annually.

Emergency plan:
IDS maintains backup refrigerators and freezers in case of power equipment failure

Importation:
IDS complies with all international regulations for shipping

Destruction:
IDS can destroy locally through the University's Environmental Health and Safety Office. All study product is destroyed via incineration.

Pharmacy Accountability Records:
IDS uses Vestigo software for all aspects of drug inventory, billing, and accountability
http://www.mccreadiegroup.com/vestigo/

Study Product Acquisition Plan:
Imatinib, isoniazid and rifabutin will be purchased from the manufacturers and dispensed through the IDS pharmacy using standard procedures.

IMPACT-TB*: A phase II clinical trial of the safety, pharmacokinetics and hematologic effects of imatinib on myelopoiesis in adults when given with and without isoniazid and rifabutin

*Imatinib mesylate per oral as a clinical therapeutic for TB

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PREFACE TO THIS AMENDED PROTOCOL:

In a previous version of this protocol that included imatinib dosing for 2 weeks, followed by imatinib together with rifabutin and isoniazid for another 2 weeks, we found 50mg imatinib to be the maximum tolerated dose when given with these drugs, and an unacceptably high rate of toxicity at imatinib 100mg when given as combination therapy. These data suggest further imatinib dosing with rifabutin and isoniazid should not be conducted at 100mg or higher. However, these data do not negate the potential of imatinib as a host-directed therapy for TB, as dosing at 100mg imatinib was safe when given alone during days 1-14. Our current goal is to determine if imatinib dosed alone has beneficial effects. If so, additional studies evaluating drug-drug interactions with agents other than isoniazid and rifabutin will be pursued. Hence, the amended protocol here is specific for volunteer studies using imatinib alone.

SIGNATURE PAGE

Protocol Title: IMPACT-TB*: A phase II clinical trial of the safety, pharmacokinetics and hematologic effects of imatinib on myelopoiesis in adults when given with and without isoniazid and rifabutin

*Imatinib mesylate per oral as a clinical therapeutic for TB

DAIDS Protocol Number: Aim 1
DAIDS-ES ID 38518

DAIDS Protocol Version History:
Protocol Aim 1, Version 5.0, June 22, 2022
Protocol Aim 1, Version 4.0, September 13, 2021
Protocol Aim 1, Version 3.0, July 12, 2019
Protocol Aim 1, Version 2.0, March11, 2019

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Investigator name	Signature	Date signed

NIH Grant Number	NIH4UH3AI122320 - 03
Investigational Product:	Imatinib
Protocol Number: **IRB Number:**	DAIDS-ES ID 38518 IRB00103001
IND/ IDE Number:	IND 143386
IND Sponsor	DAIDS
ClinicalTrials.gov Number	NCT03891901

Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, the site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Initial Registration

Site-specific informed consent forms (ICFs) will be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification will be retained in the site's regulatory files.

Amendment Registration Language

Upon receiving final IRB/EC and any other applicable RE approval(s) for a study amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. Site-specific ICF(s) will not be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification from the DAIDS PRO that approves the site specific ICFs and indicates successful completion of the amendment protocol registration process. A copy of the final amendment Registration Notification issued by the DAIDS PRO should be retained in the site's regulatory files.

Table of Contents

List of Abbreviations

AE.....adverse event
ART .....antiretroviral therapy
CI .....confidence interval
Cmax .....maximum concentration
CML……chronic myelogenous leukemia
CRF .....case report form
DAIDS.....Division of AIDS of NIAID
DDI .....drug-drug interactions
FDA .....US Food and Drug Administration
GCP.....good clinical practice
HDT .....host-directed therapy
INH……..isoniazid
IIV……interindividual variability
LTBI……latent TB infection
MDR .....multidrug-resistant
MGIT……..Mycobacteria growth indicator tube
Mm …… *Mycobacterium marinum*
MN .....monocytes
Mtb……..*Mycobacterium tuberculosis*
OCR…… Office of Clinical Research
OHRP……Office for Human Research Protections
PD.....pharmacodynamics
PK.....pharmacokinetics
PMN.....polymorphonuclear cells
qD……...once daily
RBT……rifabutin
SAE .....serious adverse event
SUSAR .....suspected unexpected serious adverse reaction
T½ .....elimination half life
TB .....tuberculosis
Tmax.....time to maximum concentration
WBA……...whole blood bactericidal assay
XDR……...extensively drug-resistant

Study Summary

Title	IMPACT-TB*: A phase II clinical trial of the safety, pharmacokinetics and hematologic effects of imatinib on myelopoiesis in adults when given with and without isoniazid and rifabutin *Imatinib mesylate per oral as a clinical therapeutic for TB
Short Title	Imatinib Dosing Trial
IRB Number	IRB00103001
Protocol Number	DAIDS-ES ID 38518
Phase	Phase 2 evaluating safety, immunologic and microbiologic efficacy and pharmacokinetics (PK)
Methodology	Open label, sequential dose escalation design
Study Duration	Up to 50 days, including up to 8 days of screening, 28 days of imatinib alone, and 14 days of post-drug follow-up.
Study Center	Winship Cancer Institute of Emory University And Georgia Clinical & Translational Science Alliance (Georgia CTSA) Georgia CTSA Clinical Research Center Emory University Hospital 1364 Clifton Rd. Atlanta, Georgia 30322 United States

Objectives	Primary: • To determine the effects of different doses of imatinib on myelopoiesis in adults when given alone • Primary Safety Objective: To determine the safety of different doses of imatinib Secondary: • To determine the effects of different doses of imatinib on *ex vivo* bacillary killing in adults when given alone • To assess the PK and PD of imatinib in relation to myelopoesis and *ex vivo* bacillary killing • To determine the effects of imatinib on cellular immune function and on circulating biomarkers of immune activation and on T cells and monocytes • To assess proteomic and transcriptomic changes associated with imatinib administration
Number of Participants	48 participants total, including 16 enrolled in a previous protocol version and 32 to be enrolled in this amended protocol. The additional 32 participants will receive 28 days of imatinib alone at one of 3 doses
Main Inclusion and Exclusion Criteria	The study will enroll healthy adult volunteers as defined in the protocol.
Investigational Product	Participants will receive imatinib mesylate at 100, 200, or 400 mg per day.
Duration of administration	Volunteers will receive imatinib for a total of 28 days.
Reference therapy	None

Statistical Methodology

Immunologic effects

The primary outcome is the change in the numbers of myelomonocytic cells in the blood between baseline and day 14 of the study. The change in these cells will be estimated with mixed models, combining all dose groups, with interactions between dose and each time point. Secondary efficacy analyses will also use mixed models to determine the relationship between imatinib exposures and change in the numbers of myelomonocytic cells at each dose separately and in the pooled dose strata. Similar analyses will be used to assess bacillary killing, as determined by the Whole Blood Bactericidal Assay (WBA), using bacille Calmette-Guerin (BCG), at day 14.

Safety

The incidence of all adverse events and in particular grade 3 or 4 adverse events and SAEs during all follow-up time will be determined using point estimates and 95% CIs.

Pharmacokinetic analysis

Pharmacokinetic (PK) parameters, including absorption, distribution, and metabolism, will be determined using S-ADAPT software utilizing a compartmental PK analysis approach and summarized by treatment regimen.

Study design

Dose-escalation trial with PK components

Power and Sample Size Analysis

At completion of the study, 48 participants with evaluable data will provide 90% power to detect a 0.48 SD in the change in the number of myelomonocytic cells on imatinib. Within each dose stratum, we will have 90% power to detect a 1.03 SD change.

Safety Evaluations

Clinical and laboratory adverse events including ECG changes will be monitored prospectively while on study drug and at 14 days after completion of imatinib.

Study Progress and Safety Monitoring Plan

The Independent Safety Monitor, PI and study team, Data Safety Monitoring Board (DSMB), and Sponsor will be responsible for monitoring the data quality and the ongoing safety of participants. Twelve participants will be enrolled into each dosage arm in an ascending manner, starting with the 100 mg imatinib dose. A safety analysis will be performed by the team and the DSMB after complete safety data are available from 6 participants within a stratum. If safe, and after a total of 12 participants are enrolled for the first stratum, then the next higher dose will begin enrolling participants. Enrollment will proceed in this manner until the sample size has been reached. Formal safety analysis will then occur using the data from all dose groups.

1. BACKGROUND AND STUDY RATIONALE

This document is a clinical research protocol and the described study will be conducted in compliance with the protocol, Good Clinical Practice standards, Good Clinical Laboratory Practice standards, associated federal regulations, NIAID/DAIDS funding agency requirements, and all applicable University research requirements. The study is being performed in the United States, at Emory University in Atlanta, and will therefore also comply with all US federal research requirements. All episodes of noncompliance will be documented.

Introduction

Therapeutic agents capable of improving treatment of all forms of TB are urgently needed. The cancer drug imatinib limits mycobacterial infections in culture and animal models by reducing both entry into macrophages and augmenting phagolysosomal fusion (autophagy), which may facilitate antigen presentation and pathogen killing (1). Additionally, imatinib induces increases in myeloid cells (myelopoiesis), and an innate immune response to infection that mimics so-called “emergency hematopoiesis,” a response that *Mycobacterium tuberculosis* (*Mtb*) appears to suppress (2). Importantly, these mechanisms can be induced in animal models by oral doses substantially lower than those used in people to combat cancer. The dose-dependence has important implications for TB clinical studies in humans, as it suggests that imatinib could improve TB treatment using doses that impart minimal if any toxicity.

This trial will evaluate the safety, immunologic effects and PK properties of several doses of imatinib when given alone in order to inform subsequent phase 2 studies evaluating the microbiologic effects of adjunctive imatinib at an optimized dose in patients with pulmonary TB or latent TB infection (LTBI). A full consideration of exposure-efficacy data and exposure-safety data from this study in healthy volunteers will be undertaken in collaboration with the DSMB and DAIDS prior to making recommentations for subsequent studies.

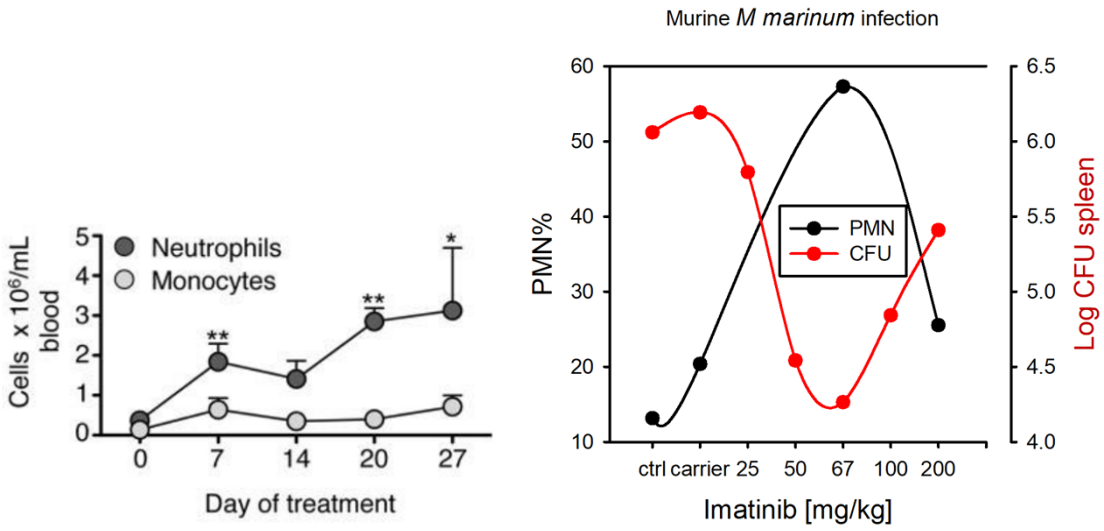
1.1 Background and Relevant Literature

With existing anti-tubercular drug therapies, treatment of drug-susceptible TB takes at least 6 months and success rates for multi-drug resistant tuberculosis (MDR-TB) and extensively drug resistant TB (XDR-TB) are a dismal 50 and 20%, respectively, highlighting the urgent need for new TB drugs (3). We have identified imatinib mesylate, a cancer drug used to treat humans with chronic myelogenous leukemia (CML) or gastrointestinal stromal tumors (GISTs), as a

potential “host- directed therapeutic (HDT)” for drug resistant TB infections and TB/HIV co-infections. Imatinib inhibits c-Abl tyrosine kinase (TK), which is dysregulated in CML, as well as related TKs (e.g. c-Kit). Data from tens of thousands of human patients indicate that imatinib is generally well tolerated, with few severe adverse events and little toxicity, especially at low doses (4-7). In animal models, imatinib facilitates clearance of *Mtb* by disrupting the cellular mechanisms that *Mtb* uses for entry and survival in host cells (1). Also, at doses substantially lower than those used for CML, imatinib stimulates “emergency hematopoiesis,” a host immune response to infection that mobilizes myeloid cell populations, but which is suppressed by *Mtb* (2). As an HDT, imatinib acts synergistically with antibiotics, is effective against antibiotic-resistant mycobacteria, and may be less likely to engender resistance compared to traditional anti-bacterial agents. Our proposal seeks to: determine the safety profile, immunologic effects, and PK properties of imatinib when given to volunteers. These studies will directly inform dosing for subsequent studies that will determine PK interactions with relevant TB treatments and the safety and microbiologic efficacy of imatinib when used as an adjunctive therapy in TB infection and disease. **We will conduct this initial study in Atlanta at Emory University in order to facilitate timely completion of the study, which will aid in the rapid evaluation of imatinib in future studies.**

1.2 Imatinib mesylate

Imatinib mesylate is a tyrosine kinase inhibitor that is approved by multiple regulatory agencies for the treatment of several malignancies, including Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML), at adult doses of 400 - 800 mg/d (4, 5). The drug has a well-defined safety profile. It is well absorbed after oral administration, with a t½ of 15 hr, supporting once daily dosing (8). Doses of 400 mg/d produce mean plasma concentrations of approximately 1.1 mg/L (average male, 1.8 m^2) (9). Imatinib is both a substrate for and an inhibitor of CYP3A4. In CML its primary target is Bcr-Abl, a strongly expressed fusion protein with tyrosine kinase activity that results from the 9:22 chromosomal translocation. Inhibition of Bcr-Abl in CML by imatinib arrests myeloid cell proliferation and restores normal apoptosis.



Figures 1a and 1b. Effect of low dose imatinib on blood PMNs and MNs in mice and relationship between myelopoesis and mycobacterial growth. From (2).

Two distinct mechanisms of action of imatinib pertain to its potential role in TB. The first is a direct, pharmacologic effect on macrophage function. In normal individuals, therapeutic concentrations of imatinib inhibit c-Abl1, c-Kit and related tyrosine kinases. *Mtb* uses one or more of these enzymes to inhibit phagolysosome fusion, thereby evading innate host defenses. Treatment of *Mtb*-infected macrophages with imatinib blocks this pathogenic mechanism by altering intracellular trafficking, promoting vesicle acidification and restricting *Mtb* growth [1, 10]. In addition, low imatinib concentrations induce differentiation of hematopoietic stem cells and progenitors in the bone marrow, augmenting myelopoiesis but not lymphopoiesis, and increasing numbers of myeloid cells in blood and spleen of mice (Figure 1a) (2). Whereas progenitor differentiation relies on partial inhibition of c-Kit by imatinib, myeloid lineage commitment depends upon inhibition of other PTKs. Myelopoiesis in turn is associated with improved control of mycobacterial growth (Figure 1b). Thus, imatinib at low doses mimics “emergency myelopoiesis”, a physiological innate immune response to systemic infection. At higher doses, effects on myelopoiesis are still evident but exodus of mature myeloid cells from the bone marrow into the periphery does not occur.

1.2.1 Preclinical Data on the effect of imatinib on Mtb infection

In one representative experiment, C57Bl/6 mice treated with low dose imatinib by continuous infusion were infected with a large inoculum of *Mtb*. Treatment continued for 28 days, after

which animals were sacrificed. *Mtb*-CFU counts were significantly lower in imatinib treated animals, of whom approximately one third had completely cleared the infection, a reduction of more than 7 logs (Figure 2a) (10). In a recent, ongoing experiment, macaques were infected with *Mtb* by the aerosol route. After 6 weeks, 2 cohorts began treatment with either 3 antimicrobial drugs used for MDR-TB treatment (moxifloxacin, ethambutol and pyrazinamide), or the 3 drugs plus imatinib 30 mg/kg/d. A 3rd cohort received no treatment. Animals underwent bronchoalveolar lavage (BAL) and immunologic evaluation after 3 additional weeks. Those treated with antimicrobials alone had a mean of $2x10^4$ CFU in BAL fluid, whereas those also treated with imatinib had no detectable bacilli (Figure 2b). In addition, serum concentrations of C-reactive protein, a marker of inflammation, had normalized in imatinib-treated animals, whereas they had remained markedly abnormal in the other cohorts (Figure 2c). This suggests that contrary to what one would expect in increasing autophagy and myelopoiesis, there was actually decreased inflammation. Indeed, lung pathology was also reduced with imatinib treatment when the drug was administered alone following reactivation with SIV, or when administered together with antibiotics (Figure 2d).

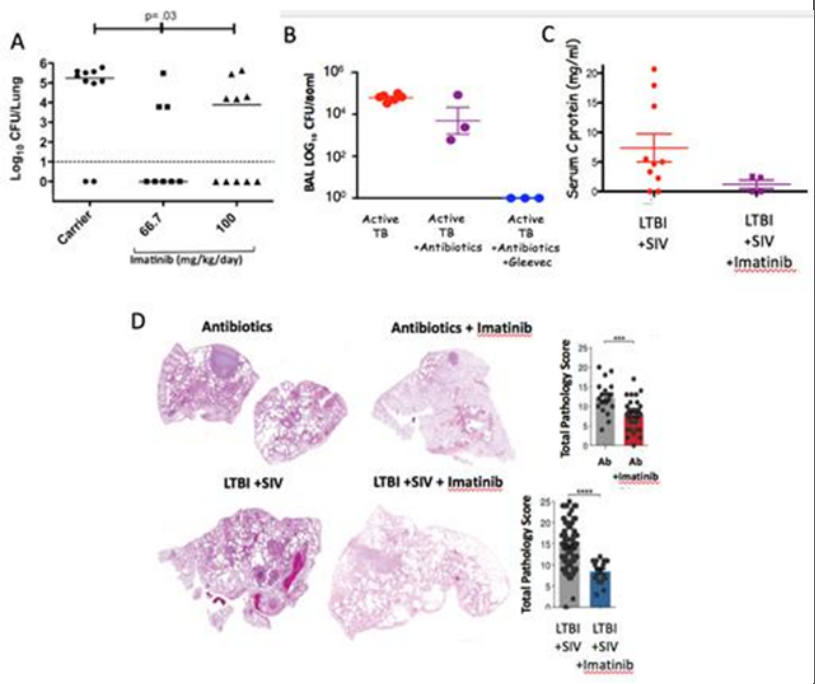


Figure 2. *Effects of imatinib of TB infection in mice and non human primates (NHPs).* ***A.*** *CFUs from lung following aerosol Mtb infection in mice. Control animals were administered placebo or imatinib at 66 or 100 mg/kg/d for 28d. Note that 80% of animals showed reductions of at least 2 orders of magnitude and in some animals Mtb was below detectable levels (from Napier et al., 2011).* ***B.*** *BAL CFUs in NHPs infected with high inoculum of Mtb (200CFU) for ~6 weeks, and then treated for three weeks with either antibiotic regimen (ethambutol (15mg/kg), pyrazinamide (20mg/kg) and moxifloxacin (40mg/kg)), or antibioitcs plus imatinib (30mg/kg/d).* ***C.*** *Serum CRP from animals infected with low inoculum of Mtb to induce a latent TB infction (LTBI), and then infected with SIV, which causes TB reactivation. Imatinib treatment commenced when animals showed signs of active disease; imatinib-treated animals were sacrificed pairwise when a control animal succumbed.* ***D.*** *Lung histology (H&E) and pathology scores from the antibiotic experiment (B) or the SIV reactivation experiment (C).*

1.2.2 Clinical Data on the effect of imatinib on Mtb infection to Date

There currently is limited clinical data on the effects of imatinib on TB treatment outcomes in humans. No trials have been performed, but individuals on imatinib for treatment of CML who developed TB anecdotally had successful treatment outcomes (11, 12).

1.2.2.1 Human Pharmacokinetics

Human population PK of imatinib have been identified by Scmidli et al in 371 patients and are also a one compartment model: clearance of 14 L/hr with an inter-individual variability (IIV) of 32% and a volume of 252 L (13). These data are also consistent with population PK data from Widmer et al using data from 59 patients with CML or GIST (8).

1.2.2.2 Clinical Studies in Adults and Children

There have been no clinical studies of adjunctive imatinib for TB treatment in adults or children.

1.3 Dose Rationale

The optimal dose for adjunctive imatinib therapy in TB is unknown, necessitating a trial evaluating the safety, PK and PD relationships of multiple doses. We have used data from our NHP experiments to inform dosing for the proposed study. Specifically, we will aim to replicate drug concentrations associated with myeloid responses and *Mtb* killing in the NHP model. Based on the myeloid respone data, macaques treated with 10 mg/kg had no increase in myelomonocytic cell percentages by day 7, while in 2 animals treated with 30 mg/kg, one had an increase in the percentage of myelomonocytic cells and the other did not. In the macaque treated with 60 mg/kg there was a myelomonocytic cell response. The drug concentrations achieved by 30 mg/kg and 60 mg/kg in NHP were thus used to model the dosing target for human TB patients.

We utilized S-ADAPT for identifying PK parameters. The macaque concentrations with treatment of 30 mg/kg were best explained by a one-compartment model based on both Akaike Information criteria (score of 0.45 versus 6.51) and Bayesian Information criteria (score of 2.58 versus 9.54) when compared to a two-compartment model. The final clearance estimate was 23.95 L/hr, volume of 110.1 L, and absorption constant (K_a) of 0.22 per hour. This translates to a half-life of 3.19 hours in the macaques. The peak concentration was 1.35 mg/L at 4 hours and a trough of 0.05 mg/L at 24 hours (just prior to next dose). From this, we can calculate that the macaques treated with 30 mg/kg achieved a 0-24 hours area under the concentration-time curve (AUC_{0-24}) of 9.19 mg*hr/L. By scaling, doses of 60 mg/kg would achieve an AUC_{0-24} of

18.37 mg*hr/L, peak of 2.70 mg/L and trough of 0.1 mg/L. These sets of concentrations give us the target floor and ceiling concentrations to aim for in patients.

We performed Monte Carlo Experiments (MCE) of 5,000 patients each to identify the concentrations achieved by imatinib doses of 50 mg, 100, 150 mg, and 200 mg administered daily. The domain input were the PK parameter estimates and covariance matrix from Scmidli et al in 371 patients; these were entered into subroutine PRIOR of ADAPT. Results are shown in

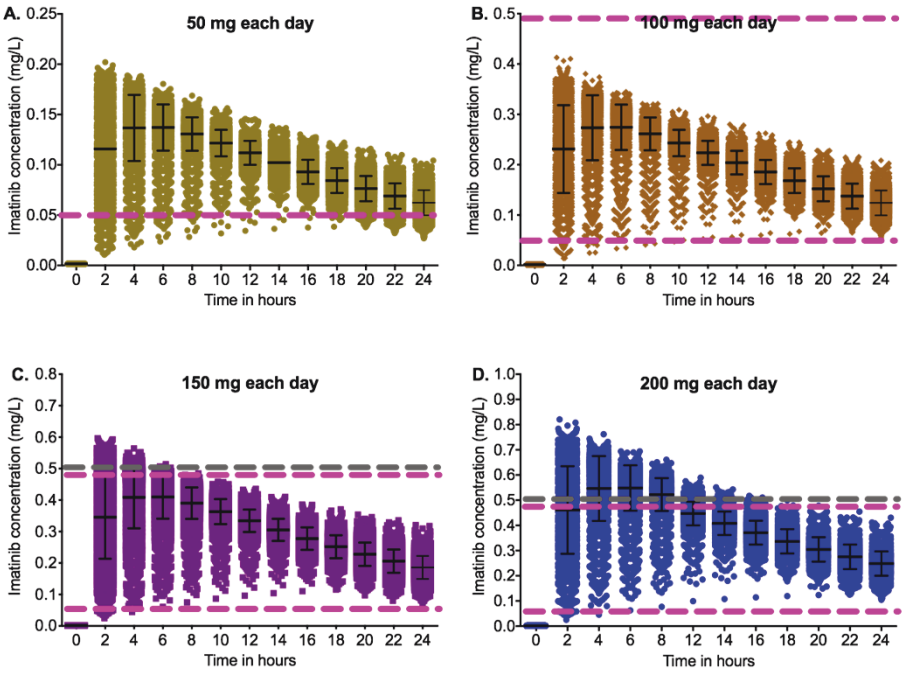


Figure 3. Model of PK/PD of imatinib in humans based on responses in non-human primates.

Figure 3, which also shows where concentrations for each would fall in relationship to the concentrations of 0.05-0.49 mg/L (pink lines) that have been associated with myelopoiesis, and 0.5-1.97 mg/L (grey lines) that have been associated with autophagy. In addition, the doses of 150 mg/day and 200 mg/day would also be able to fulfill the range on peak of 2.70 mg/L and a trough of 0.05 mg/L identified in the macaques that achieved both myelopoiesis and anti-TB effect. We have completed dosing with 50 mg imatinib. Hence, we will continue with 100 - 200 mg/day, as well as a higher dose of 400 mg/day to account for possible under-estimation of the effects in humans. Thus, we propose doses of 100 mg/day, 200 mg/day, and 400 mg/day to be tested in human volunteers.

1.4 Possible Drug-Drug Interactions with TB Therapy

Standard treatment of drug-susceptible TB involves two months of isoniazid, a rifamycin such as rifampin or rifabutin, pyrazinamide and ethambutol, followed by four months of isoniazid and a

rifamycin. Isoniazid inhibits CYP3A4, which could increase the concentrations of imatinib when given together (14). Both rifampin and rifabutin are inducers of cytochrome P450 enzymes, including CYP3A4. Although rifampin is the most commonly used rifamycin in TB treatment globally, in a single-dose PK study of 14 healthy human subjects rifampin reduced the mean imatinib C_{max}, AUC_{0-24} and $AUC_{0-\infty}$ by 54% (90% CI: 48–60%), 68% (64–70%) and 74% (71–76%), respectively. Rifabutin is substantially less potent in terms of inducing CYP3A and other drug-metabolizing enzymes compared to rifampin (15). In the first 16 volunteers enrolled in a previous version of this protocol that included imatinib dosing between day 14 and day 28 together with rifabutin and isoniazid, we found 50mg to be the maximum tolerated dose when given with these drugs, and an unacceptably high rate of toxicity at imatinib 100mg when given as combination therapy. These data suggest further imatinib dosing with rifabutin and isoniazid should not be conducted at 100mg or higher. However, these data do not negate the potential of imatinib as a host-directed therapy for TB, as dosing at 100mg imatinib was safe when given alone during days 1-14. New drug regimens for drug-resistant TB involve medications other than rifabutin and isoniazid, and imatinib may have benefits when given with these agents, which include oxazolidinones, nitroimidazoles, fluoroquinolones, and bedaquiline. Drug-drug interactions with these agents could occur, and studies examining these interactions would be justified if imatinib demonstrates beneficial effects at safe doses in humans, including myelopoesis and bacillary killing using the WBA assay. Therefore, our current goal is to determine if imatinib dosed alone has beneficial effects. If so, additional studies evaluating drug-drug interactions with agents other than isoniazid and rifabutin will be pursued.

1.5 Conduct of Study: Emory University, Office of Clinical Research

The protocol team at Emory receives guidance from the Emory Office of Clinical Research (OCR) in the design of protocol-related documents including Standard Operating Procedures, Data Management Plan, and Clinical Quality Management Plan. The OCR also provides guidance for clinical coordination and regulatory management, helping to ensure compliance with Good Clinical Practice (GCP), Emory University Institutional Review Board (IRB), US Food and Drug Administration (FDA), and other regulatory agencies (e.g., the OHRP) and NIAID/DAIDS (the Sponsor). Further information about the Emory OCR is found at: https://www.ocr.emory.edu/

1.6 Conduct of Study: Georgia Clinical & Translational Science Alliance (CTSA), Georgia CTSA Clinical Research Center (GCRC)

The study will be carried out using facilities of the Georgia CTSA GCRC located within the Emory University Hospital Clinical Research Site, with personnel based in the GCRC Nursing Staff and Core Laboratory.

http://georgiactsa.org/discovery/clinical-sites/emory-university.html

http://georgiactsa.org/discovery/nursing.html

Please see protocol Appendix Section 17.3 for further details.

1.7 Conduct of Study: Emory University Investigational Drug Service

The pharmacy that will serve the study is the Emory University Investigational Drug Service (IDS) - http://www.ocr.emory.edu/ids/index.html

The IDS is currently involved in a number of NIAID/DAIDS studies, demonstrating the capacity of IDS to initiate, conduct, participate in, and support NIAID/DAIDS funded research. Please see Protocol Section 17.4 for required IDS information.

1.8 Conduct of Study: Emory Medical Laboratory (EML)

Standard medical laboratory tests will be conducted by the Emory Medical Laboratory (EML). The EML is a fully accredited and licensed clinical laboratory. EML participates in the College of American Pathologists (CAP) Laboratory Accreditation Program and has CLIA (Clinical Laboratory Improvement Amendments) certification through CMS (Centers of Medicare and Medicaid Services). Emory Medical Laboratory also is licensed by the state of Georgia.

EML Lab Reference Ranges and CLIA certificate are found at the website.

http://www.emoryhealthcare.org/centers-programs/medical-laboratory/index.html

1.9 Protocol Review, Finalization, and Approval Processes

The protocol will undergo a review, approval and set-up phase with the Georgia CTSA GCRC during the first 2 months of funding, as well as the Protocol Registration process with NIAID/DAIDS. A protocol-specific Manual of Operational Procedures in accordance with NIAID/DAIDS requirements will also be prepared and approved during this timeframe, incorporating procedures needed for this study and existing SOPs from the Winship CTO, Georgia CTSA GCRC and Core Lab, IDS Pharmacy, and Emory University Medical Laboratory.

2 Study Objectives

The overall objective of the study is to determine safe and immunologically effective doses of imatinib that will subsequently be advanced to future studies. Given toxicity of imatinib when given at 100mg with rifabutin and isoniazid, the objectives are amended to focus on evaluating potential beneficial effects of imatinib when given alone. If beneficial effects are seen, drug-drug interactions with relevant anti-tubercular therapies will be evaluated in future trials.

2.1 Primary Objective

- To determine the effects of different doses of imatinib on myelopoiesis in adults when given alone
- Primary Safety Objective: To determine the safety of different doses of imatinib in adults

2.2 Secondary Objectives

- To determine the effects of different doses of imatinib on *ex vivo* bacillary killing in adults when given alone
- To assess the PK and PD of imatinib in relation to myelopoesis and *ex vivo* bacillary killing
- To determine the effects of imatinib on cellular immune function and on circulating biomarkers of immune activation and on T cells and monocytes
- To assess proteomic and transcriptomic changes associated with imatinib administration

3 Investigational Plan

3.1 General Design

This is an open label trial evaluating the safety, PK and immunologic effects (PD) of different doses of imatinib in healthy adult volunteers. In this revised protocol, 32 participants will be enrolled in a dose-escalting fashion to receive one of three imatinib doses alone for 28 days. Because 4 participants received imatinib at 100mg in a previous protocol, 8 participants will receive 100mg daily under this revised protocol, to complete dosing of 12 participants at 100mg imatinib daily. Safety evaluation to day 42 follow-up will be conducted for the first 6 participants in the 100mg stratum (4 previous participants, plus 2 more enrolled through this amended protocol) while the remaining 6 participants are continuing to accrue to the study. Once the safety evaluation for the first 6 participants is finalized, and enrollment of a total of 12 participants in the 100mg stratum is complete, we will begin enrolling 12 participants in the next

dose stratum (200 mg/daily). Enrollment will proceed in this fashion, with safety evaluation after the first 6 participants at each dose. In this manner, 12 participants will be allocated to each imatinib dose, proceeding from 100mg to 200mg and finally from 200mg to 400mg daily.

3.1.1 Screening Phase

The in-person screening evaluations will occur on days -8 to 0. Upon arrival at the GCRC for the in-person screening visit, the participant's temperature will be taken and participants will be asked to provide written informed consent. If consent is provided, demographic and medical history and medical record review will be conducted and an HIV test will be performed. Testing for HBV and HCV will also be performed. Inclusion and exclusion criteria will be examined. For women of reproductive potential, a pregnancy test will be performed. Physical exam with vital signs, medication review, lab safety tests, urinalysis, and a 12-lead ECG will be performed. These activities may be spread over multiple visits within the indicated time window. Participants who consent and who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled.

3.1.2 Study Intervention Phase

The doses of imatinib used here are the same or lower than those used routinely and safely in CML patients, and we do not expect any Grade 3 or Grade 4 adverse events (AEs). Hence, safety evaluations for this imatinib-only amended protocol will consist of e-mailed adverse event reports to DAIDS, followed by communication from DAIDS to the DSMB. Any Grade 3 or Grade 4 adverse events will be reported to DAIDS in real time.

We will enroll using a sequential dose-escalation design. Specifically, we will enroll 2 more participants in the imatinib 100 mg qD arm, which brings brings enrollment in this group to 6 participants. We will conduct a safety review of adverse events after these 6 participants given imatinib 100mg complete day 42 follow-up. Enrollment of the second 6 participants in the 100mg dose group will continue while safety review of the first 6 participants is conducted by the DSMB via e-mail. The plan to continue enrollment during this review period is based on the known safety profile of imatinib in CML patients who take 400 to 800mg daily. If after the first 6 participants at 100mg complete the 42-day study follow-up there are no treatment emergent grade 3 or 4 adverse events considered to be related to imatinib treatment, and there are no serious adverse events or other safety concerns among these first six volunteers as well as volunteers 7 - 12 in the opinion of the investigators, the Independent Safety Monitor, the DSMB,

and the Sponsor that would prevent dose escalation (also documented through e-mail communication), we will commence enrollment of the 12 participants in the next dose group (200mg qD arm). We will again conduct a safety review of adverse events via e-mail after the first 6 participants in the group complete day 42 followup while continuing with the next 6 participants in the group as above, following the same procedures before starting the 400mg imatinib group. After 6 participants complete day 42 followup in the 400 mg qD arm, we will review safety data and PK/PD data while enrollment in the 400 mg/day group continues. If the safety criteria above are met, we will complete enrollment of remaining participants in the 400 mg qD arm. This approach will proceed until there are 12 participants with evaluable myelopoiesis data in each dose arm and the sample size of 48 participants (16 in the previous protocol version plus 32 in this version) is fulfilled. All enrolled participants will be evaluable for safety and toxicity assessments if they have taken at least one dose of a study drug. Note that in this protocol version, given imatinib dosing only occurs for 28 days, 42-day followup is required for a participant to “count” toward the 6 needed for followup assessment. Therefore, if any of the first 6 participants in a dose group do not complete the study to day 42, we will need to include other participants who complete the day 42 visit to fulfill the requirement. Similarly, because study endpoints require data collection up to day 14, if a participant drops out prior to day 14, we will enroll another participant to complete the required complement of 12 participants with protocol-compliant evaluable data (has taken $\geq$85% of all doses of study drugs and completed visits to day 14) per dose group (see Section 8.1 and Section 8.2).

After assignment to a group, each participant will be assessed for baseline data according to Table 1 prior to their first imatinib dose. They will then take their first imatinib dose. Participants will then come back at various times during the 28-day period of imatinib-only dosing (see Section 6 on Study Procedures). During this time, safety assessments will be performed and blood will be collected for lab assays. Participants will be given imatinib in pre-filled pill containers at visit 1 (day 1) as indicated on the schedule of events. There will also be an intensive PK study performed on day 14. On this day, participants will have an IV placed to minimize discomfort related to phlebotomy at repeated time-points after dosing. Participants will return to complete the last PK blood draw on day 15. Additional visits at days 21 and 28 will include safety and efficacy assessments. Volunteers will then discontinue all study drug and will complete one additional follow-up visit at day 42, 14 days after receiving their last dose, for safety.

Meal Timing for all participants: We will instruct participants to take drugs on an empty stomach. Our data on the first 16 participants dosed at 50 and 100mg of imatinib indicate that this results in expected PK exposures and is consistent with care of TB-infected patients, who are commonly instructed to take their anti-TB drugs after fasting. Breakfast may be eaten 1 hour after taking the study drugs. On study visit days, participants may eat a small breakfast at home at least 2 hours before the scheduled time of study drug administration (e.g. 7am), anticipating that the study drugs will be administered at the GCRC at 9am. On the PK study day (visit 4), a meal or snack will be provided 1 hour after study drug administration at the GCRC.

3.1.3 Follow Up Phase

Participants will be followed for an additional 14 days after study drug administration. All participation in the study should be complete by day 50 after enrollment.

3.1.4 Allocation to Interventional Group

Imatinib dose allocation will occur in an ascending manner, with safety evaluations before proceeding to the next higher dose as described in Section 3.1.2.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

- The primary endpoint is the change in the number of myelomonocytic cells in the blood between baseline and day 14 of imatinib (imatinib alone).
- The primary safety endpoint will be grade 3 or 4 events and SAEs. All AEs regardeless of grade will be recorded and monitored. Safety will be primarily determined by the percent of participants on study who experience a grade 3 or 4 AE or a serious adverse event (SAE) that are considered related to the study drug. An SAE is defined as any untoward medical occurrence that meets any of the following criteria:
    - Results in death, or is life-threatening
    - Results in participant hospitalization or prolongation of existing hospitalization
    - Results in persistent or significant disability/incapacity
    - Is a congenital anomaly/birth defect

Other medically important conditions will also be assessed. These conditions include important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the definition above.

3.2.2 Secondary Study Endpoints

- Evaluation of the PK parameters.
- Additional research endpoints related to immunologic effects will include measures of cellular immune function and biomarkers of immune activation circulating in blood and expressed on the surface of T cells and monocytes.
- Secondary efficacy analyses will determine 1) the difference between the change in the numbers of myelomonocytic cells from baseline to day 14; 2) the relationship between imatinib exposures and change in the numbers of myelomonocytic cells during the imatinib-exposed periods; and 3) the relationship between imatinib dose and blood levels and the BCG-killing activity of day 14 leukocytes in the WBA .
- Finally, as exploratory analyses, we will evaluate the proteomic and transcriptomic changes associated with imatinib.

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

- Adult age $\geq$ 18 years & $\leq$ 55 years
- Body mass index (BMI) >18.5 kg/m^2
- At least 8 years formal education, with appropriate reading and comprehension skills
- Able and willing to provide written informed consent
- Males must agree to using contraception during the study and for 2 weeks after the last dose of study drug.
- If a female participant is of reproductive potential, the participant (and her partner) must agree to use of one of the following combinations of birth control during the study and for 2 weeks after the last dose of study drug (or tubal ligation as a single method):
  1) Use of a double-barrier method of contraception: condoms (male or female) and a diaphragm or cervical cap with spermicide;
  2) Use of an IUD (hormonal or non-hormonal) and a barrier method: condoms (male or female, with or without spermicide) or a diaphragm or cervical cap with spermicide;

3) Use of hormone-based contraceptives (pill, patch, implant, ring, or injectable) and a barrier method: condoms (male or female, with or without spermicide) or a diaphragm or cervical cap with spermicide;

4) Tubal ligation.

Women who are post-menopausal, defined as age greater than 45 and no menses for at least 1 year, or who have had a hysterectomy, are considered not of reproductive potential.

4.2 Exclusion Criteria

- Current or imminent treatment for significant infection
- Pregnant or breastfeeding
- HIV positive status as determined by an FDA-approved HIV assay
- Hepatitis B infection, as determined by an FDA-approved hepatitis B surface antigen assay
- Hepatitis C infection, as determined by an FDA-approved positive Hepatitis C antibody assay
- Known infection with Mycobacterium tuberculosis (MTB)
- History of allergy or hypersensitivity to imatinib.
- History of enrollment in other clinical trials with investigational agents within 8 weeks
- Cardiac arrhythmia requiring medication, or any clinically significant ECG abnormality
- Exam consistent with congestive heart failure (e.g., edema)
- Random blood glucose >140 mg/dL or history of unstable diabetes mellitus requiring hospitalization for hyper or hypoglycemia within the past year prior to start of screening
- Use of systemic corticosteroids within the past 28 days
- Any of the following readings from a complete blood count that fall outside the normal ranges as listed here:
  White blood cell count: 3.4 10E3/mclL – 11 10E3/mcL
  Hemoglobin: Female- 11.1 – 16.7 gm/dL, Male- 12.5 – 16.5 gm/dL
  Platelet count: 150-400 10E3/mcL
  Absolute neutrophil count: Female- 0.91-5.53 10E3/mcL, Male- 0.67-6.4110E3/mcL
  Absolute lympyocyte count: Female- 0.65-3.05 10E3/mcL, Male- 0.72-3.29 10E3/mcL
- Any of the following chemistry panel and liver function test readings that fall outside the normal ranges as listed here:
  Serum potassium: 3.5-5.4 mmol/L
  ALP: 34 – 104 unit/L
  ALT: 4 - 52 unit/L

AST: 13 - 39 unit/L
Total Bilirubin: 0.2 - 1.0 mg/dL
Creatinine: Female- 0.60-1.32 mg/dL, Male- 0.7-1.3 mg/dL

- Cirrhosis of the liver, or any known active or chronic liver disease
- Current or past alcohol or elicit/recreational drug use, which in the expert judgment of the Investigator, will interfere with the participant's ability to comply with the protocol requirements.
- Any experimental medications for < 8 weeks prior to screening or anticipated use during the trial
- Current (within 30 days prior to the first dose of study drug) or anticipated use of antimetabolites; alkylating agents; or other drugs or herbal preparations (including St. John's wort), known to affect activity of the CYP3A4 enzyme pathway
- Consumption of grapefruit, grapefruit juice, or grapefruit-related citrus fruits (e.g., pomelos) within 7 days before assessment for eligibility
- Unwilling to avoid grapefruit or grapefruit-related citrus fruits/pomelo during the course of the study
- Unwilling to avoid alcohol for the duration of the study
- Unwilling to abstain from taking acetaminophen-containing medications during the 28-day study drug dosing period, due to increased risk of liver toxicity
- History of major medical disorders including metabolic, endocrine, hypothyroid, hepatic, renal, hematologic, pulmonary, gastrointestinal, autoimmune or cardiovascular disorders
- Uncontrolled hypertension (persistent measurements at or above 150/100)
- Participants who are, in the opinion of the Investigator, unable to comply with the dosing schedule and protocol evaluations
- Diarrhea defined as $\geq$ 4 stools per day
- Active involvement (by the participant or the participant's partner) in In Vitro Fertilization or another assisted reproductive technology procedure
- Emory students currently enrolled in a course taught by the PI or a Co-Investigator
- Emory employees currently working under supervision of the PI or a Co-Investigator

4.3 Participant Recruitment

Advertisements will be developed with basic information and a phone contact for interested persons. These will be posted with appropriate permissions on the Emory University campus and at Emory Healthcare primary care facilities. For potential volunteers who pass basic screening questions during the phone call (age, major comorbidities), a formal screening visit at the GCRC unit will be arranged.

4.4 Duration of Study Participation

The duration of study participation will be up to 50 days, to account for up to 8 days of screening and 42 days of follow-up.

4.5 Total Number of Participants

Recruitment will end when 48 evaluable participants are enrolled, including 16 enrolled in the last version of the protocol and 32 enrolled in this version. It is expected that approximately 52-60 participants may need to be enrolled in order to result in 48 evaluable participants.

4.6 Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

5 Study Drug

5.1 Description

Imatinib: Imatinib mesylate is a tyrosine kinase inhibitor that is approved by multiple regulatory agencies for the treatment of several malignancies, including Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML), at adult doses of 400-800 mg/day. The drug has a well-defined safety profile. It is well absorbed after oral administration, with a $t_{½}$ of 15 hr in normal participants, supporting once daily dosing. Doses of 400 mg/d produce mean plasma concentrations of approximately 1.1 mg/ml (9). The doses that we will study achieve concentrations shown in Figure 3. Imatinib is both a substrate for and an inhibitor of CYP3A4; it is however unclear if this is dose-dependent. In CML its primary target is BCR-Abl, a strongly expressed fusion protein with tyrosine kinase activity that results from the 9:22 chromosomal translocation. Inhibition of BCR-Abl in CML by imatinib arrests myeloid cell proliferation and restores normal apoptosis. In this amended protocol we will use imatinib mesylate at 100, 200, and 400 mg orally daily. Imatinib is supplied as 100 mg tablets.
Please refer to the Package Insert for additional information on the study medication. Imatinib will be obtained from Apotex.
https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=0291eca5-7a1d-4a79-30be-252224d96509&type=display

5.2 Intervention Regimen

See description of the study design in Section 3.1 above.

5.3 Study Product Acquisition/Distribution

Imatinib (Apotex) will be supplied through the study and will be made available through the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC). The site pharmacist can obtain the study products for this protocol by following the instructions in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks in the section Study Product Management Responsibilities. Upon receipt of the drug the quantity and expiration dates will be verified to assure quantity and quality.

5.4 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. All unused study products must be returned to the NIAID CRPMC (or as otherwise directed) after the study is completed or terminated. The procedures to be followed are provided in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks in the section Study Product Management Responsibilities.

5.5 Storage

We will store imatinib tablets at 25°C (77°F) at currently available research pharmacies in Emory; excursions will be permitted to 15°C-30°C (59°F-86°F) as per the package insert. We will protect tablets from moisture.

5.6 Preparation and Packaging

The clinical trials pharmacist will prepare treatment courses using pill containers and instructions necessary to achieve the desired doses.

5.7 Blinding

This is an open-label study, and is not blinded in terms of participant assignment to study arms.

5.8 Administration and Accountability

A study nurse will watch participants take their assigned medication doses on days when they attend a study visit. Pill containers will be filled by the research pharmacists to provide participants with easy dosing on non-study days. Product reconciliation will be conducted on a regular basis and will include information on product administration, such as: date administered, amount administered and to which participants, product remaining, product damaged/destroyed and date of damage/destruction, product returned and date of return, etc. A standard form will be utilized to document this information throughout the study period.

5.9 Participant Compliance Monitoring

Participant compliance will be assessed by observing therapy on study visit days and by participant self-report and pill count during intervals between visits. Adherence will be tracked by noting whether the participant received/took the correct dose of the product using the above methods. The protocol adherence for each participant can be quantified for the 28-day dosing period using pill counts, using the formula #doses taken divided by number of prescribed days for an interval, x 100 (to get a percent adherence). Acceptable protocol-compliance is defined as taking ≥85% of all doses of study drugs and completed visits to day 28. All participants taking at least one dose of the study drug and who do not withdraw consent will be followed for the full 42-day period.

5.9.1 Return or Destruction of Investigational Product

The clinical trials pharmacists will complete a final reconciliation of the study drug after the last participant completes their last study visit. The trials pharmacist will investigate any discrepancies in drug supply. Drug remaining at the end of the study period will be disposed.

6 Study Procedures

6.1 Screening

Screening will include:

- Informed Consent
- Medical History and Medical Record Review
- Review of Inclusion and Exclusion Criteria
- HIV testing for those who do not report being HIV-infected
- HBV and HCV testing
- Vital Signs (HR, RR, BP, Temp)
- ECG
- Physical Exam, Weight, and Symptoms evaluation
- Height
- Visual acuity test using Snellen chart
- Urinalysis
- Urine collection for evaluation of drug metabolites
- Pregnancy Test
- Review of Medications
- Clinical Laboratory Assessment (blood sample) for complete blood count, manual differential, serum chemistries including liver function tests and serum creatinine

Table 1: Schedule of Study Procedures

Study Phase	**Screening**	**Imatinib dosing**							**Post-Treatment Follow-Up**
Visit Number		**1**	**2**	**3**	**4**	**5***	**6**	**7**	**8**
Study Days	**-8 to 0**	**1**	**3**	**7**	**14**	**15**	**21**	**28**	**42**
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Enrollment (all participants)	X								
HIV, HCV, HBV testing	X								
Medical History and Record Review	X	X			X			X	X
Physical Assessment, Weight & Symptoms	X	X	X	X	X	X	X	X	X
Visual Acuity/Snellen Chart	X			X			X		X
Vital Signs: BP, HR, RR, Temperature	X	X	X	X	X	X	X	X	X
Height	X								
Pregnancy Test	X	X			X			X	X
Medication Review	X	X			X			X	X
ECG	X				X		X	X	X
Clinical Laboratory Evaluation **	X	X		X	X		X	X	X
Dispense study drug		X							
PK study					X	X			
Research Blood for immune cell subset analysis		X		X	X		X	X	X
Research Blood for RNA isolation		X			X			X	
WBA		X			X				
Urinalysis and urine storage	X				X			X	
Adverse Event Review / Unanticipated Problems Assessment		X	X	X	X	X	X	X	X
Total blood draw volume	20ml	30ml		25ml	55ml	5ml	25ml	28ml	25ml

*A brief day 15 visit is required to collect 24-hour post dose blood required for the day 14 PK study.

** Complete blood count, manual differential, serum chemistries including liver function tests and serum creatinine.

BP=Blood pressure; HR=heart rate; RR=respiratory rate; ECG=echocardiogram; PK=pharmacokinetic

6.2 Study Interventions

At the time of this protocol amendment, Emory University Hospital and the GCRC are no longer requiring clinical trials to screen participants for COVID-19 symptoms. Therefore, we have removed sections pertaining to these screening procedures. However, development of COVID-19 will result in study discontinuation as in Section 6.4. If routine COVID-19 screening becomes necessary again in the future, we will comply with EUH and GCRC requirements.

6.2.1 Visit 1 (Baseline, Day 1)

The baseline visit will occur within 8 days of screening. Procedures to be completed at the baseline visit include:

- Medical History and Medical Record Review
- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Pregnancy Test
- Review of Medications
- Clinical Laboratory Assessment (blood sample) for complete blood count, manual differential, serum chemistries including liver function tests and serum creatinine
- Research Blood Collection including blood collection directly into RNA protection tubes for RNA sequencing.
- Study Medication Dispensation
- Assessment for Adverse Effects/Unanticipated Problem Review
- WBA

6.2.2 Visit 2 (Day 3)

This is a brief study visit for symptom check and vital signs. There is a 1-day visit window after day 3 for this visit (Day 3 or 4).

- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Assessment for Adverse Effects/Unanticipated Problem Review

6.2.3 Visit 3 (Day 7)

This is a full study visit. There is a 3-day window for this visit (Day 6, 7, or 8).

- Physical Exam, Weight, and Symptoms evaluation

- Visual acuity test using Snellen chart
- Vital Signs (HR, RR, BP, Temp)
- Clinical Laboratory Assessment (blood sample) for complete blood count, manual differential, serum chemistries including liver function tests and serum creatinine
- Research Blood Collection
- Assessment for Adverse Effects/Unanticipated Problem Review

6.2.4 Visit 4 (Day 14)

This is a full study visit including PK. There is no study visit window for this visit.

- Medical History and Medical Record Review
- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Pregnancy Test
- Review of Medications
- ECG
- Clinical Laboratory Assessment (blood sample) for complete blood count, manual differential, serum chemistries including liver function tests and serum creatinine
- Research Blood Collection including blood collection directly into RNA protection tubes for RNA sequencing
- PK study comprising blood samples taken at 6 time points over approximately 24 hours. Samples will be collected at 0h (pre-dose), 0.5 hrs (+/- 5 min), 2 hrs (+/- 10 min), 4.0 hrs (+/- 10 min), 8.0 hrs (+/- 10 min), and 24 hrs (+/- 10 min). These sampling times were identified based on optimal sampling theory, using the SAMPLE program of ADAPT, and also taking into account collection on a realistic schedule for healthy volunteer participants. Of note, participants will go home after the 8 hour time-point and will return the next day (day 15) for a 24 hour blood draw that is required to determine trough drug levels.
- Urine collection for evaluation of drug metabolites
- Assessment for Adverse Effects/Unanticipated Problem Review
- WBA sample collection at 0h (pre-dose), 0.5 hrs (+/- 5 min), 2 hrs (+/- 10 min), 4.0 hrs (+/- 10 min).

6.2.5 Visit 5 (Day 15)

This is a brief visit required for collection of the 24-hour blood sample for the PK study. There is no study visit window for this visit as it must occur the day after Visit 4.

- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Assessment for Adverse Effects/Unanticipated Problem Review
- PK assessment (one blood draw) at 24 hours after the previous day's study medication doses.

6.2.6 Visit 6 (Day 21)

This is a full study visit. There is a 3-day window for this visit (Day 20, 21, or 22).

- Physical Exam, Weight, and Symptoms evaluation
- Visual acuity test using Snellen chart
- Vital Signs (HR, RR, BP, Temp)
- ECG
- Clinical Laboratory Assessment (blood sample) for complete blood count, manual differential, serum chemistries including liver function tests and serum creatinine
- Research Blood Collection
- Assessment for Adverse Effects/Unanticipated Problem Review

6.2.7 Visit 7 (Day 28)

This is a full study visit. This is the last day of medication administration. There is no study visit window for this visit as it must occur on the last day of drug administration.

- Medical History and Medical Record Review
- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Pregnancy Test
- Review of Medications
- ECG

- Clinical Laboratory Assessment (blood sample) for complete blood count, manual differential, serum chemistries including liver function tests and serum creatinine
- Research Blood Collection including blood collection directly into RNA protection tubes for RNA sequencing
- Urine collection for evaluation of drug metabolites
- Assessment for Adverse Effects/Unanticipated Problem Review

6.2.8 Visit 8 (Day 42)

This is a post-drug follow-up visit and the final study visit. There is a 5-day window for this visit (Day 40, 41, 42, 43, 44). Participants will be debriefed at this visit and will be told when they can obtain results of the study from the investigators.

- Medical History and Medical Record Review
- Physical Exam, Weight, and Symptoms evaluation
- Visual acuity test using Snellen chart
- Vital Signs (HR, RR, BP, Temp)
- Pregnancy Test
- Review of Medications
- ECG
- Clinical Laboratory Assessment (blood sample) for complete blood count, manual differential, serum chemistries including liver function tests and serum creatinine
- Research Blood Collection
- Assessment for Adverse Effects/Unanticipated Problem Review

6.3 Unscheduled Visits and Tele-Medicine Visits

Visits occurring outside the visit windows will be considered unscheduled visits. At a minimum vital signs and medical history will be reviewed at these visits, in addition to recording, grading and reporting (as necessary) any adverse events. Any necessary clinical monitoring including physical exam and laboratory evaluation will also be done as necessary.

Some study visits may be conducted by tele-medicine, in place of in-person visits, if the visits are amenable to this format.

6.4 Participant Withdrawal and Discontinuation

Participants may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator. Specific criteria for Permanent and Premature Treatment Discontinuation include the following:

- Positive SARS-CoV-2 antigen or PCR test
- Any documented serious viral or bacterial infection (COVID-19, influenza, cytomegalovirus, adenovirus, strep throat, etc.)
- Any infection that requires treatment or is associated with significant symptons (fever, shortness of breath, muscle aches, headache)
- Failure by the participant to attend 3 consecutive study visits and/or failure to comply with 2 or more doses of study drugs
- Protocol-defined drug-related toxicity of grade 3 or higher
- Requirement for prohibited concomitant medications
- Pregnancy or breast-feeding
- Request by participant to terminate treatment
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol

It will be documented whether or not each participant completes the clinical study. Participants who withdraw early, if willing, will have one final visit to collect investigational product and to follow up regarding adverse events. Participants may also be discontinued from the study for the following reasons:

- Request by the participant to withdraw
- Request of the primary care provider if she or he thinks the study is no longer in the best interest of the participant
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results
- At the discretion of the study supporter (NIH/NIAID/DAIDS), the IRB/Ethics Committee, Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), or other government agencies.

6.4.1 Data Collection and Follow-up for Withdrawn Participants

Participants who withdraw consent to participate in the study will be seen for one final visit if willing. During this visit they will be asked for permission to assess any possible AEs and will have a chance to debrief with study personnel.

6.5 Early Termination Visits

If a participant decides to leave the study early or is asked to leave by the investigator, a final close out visit will be performed if the participant is willing and the participant will be given a chance to debrief with the study team. The following will be done at the time of the early termination visits if the participant allows:

- Medical History and Medical Record Review
- Physical Exam, Weight, and Symptoms evaluation
- Vital Signs (HR, RR, BP, Temp)
- Pregnancy Test
- Review of Medications
- ECG
- Clinical Laboratory Assessment (blood sample) for complete blood count with manual differential, serum chemistries including liver function tests and serum creatinine
- Research Blood Collection including blood collection directly into RNA protection tubes for RNA sequencing
- Assessment for Adverse Effects/Unanticipated Problem Review

7 Study Evaluations and Measurements

Standard, validated tests and test instruments are not described.

7.1 Medical Record Review

The following variables will be abstracted from the medical chart (paper or electronic) or from the screening history and physical.

- Date of birth
- Sociodemographics
- Height
- Weight
- Any history of disease and dates of diagnosis and treatment
- Current or previous medication use

7.2 History and Physical Examination and ECG

Age, gender and race will be recorded. Participants will be screened for any signs of active infections or disease. A brief physical exam and a 12 lead ECG will be performed.

7.3 Vital Signs

Vital signs including BP, HR, RR, and temp will be determined in the sitting position using a Welch Allyn portable vital sign monitor (or equivalent device).

7.4 Laboratory Evaluations

Clinical blood sampling will be performed for the following laboratory evaluations:

- Hematology (hemoglobin, hematocrit, platelets, white blood cell count with manual differential)
- Liver Function
- Creatinine and electrolytes

7.5 Pregnancy Testing

A urine pregnancy test will be performed at the specified time points for all female participants of reproductive potential.

7.6 Efficacy Evaluations

7.6.1 Change from baseline in the absolute numbers of circulating myeloid blood cells and other immune parameters

Previous pre-clinical studies have shown that imatinib maximally reduces mycobacterial load in mice when administered at 66mg/kg/d, whereas both higher and lower doses proved much less effective (10). At this dose, imatinib causes sustained increases in the numbers of circulating PMNs and MNs (Figure 1) (2). Myelopoietic and antimycobacterial effects were directly correlated over a wide range of imatinib doses. Change from baseline in numbers of blood PMN and MN will potentially serve as an efficacy endpoint in future phase 2 trials. Additional immune parameters, such as cellular immune function, markers of immune activation, and function of circulating myeloid cells will be evaluated.

The peripheral white blood cell (WBC) count and manual differential report on the number and percentages of different cell types in blood. To determine the differential, a drop of blood is thinly spread over a glass slide, air dried, and stained with a Romanofsky stain, most commonly

using the May-Grunewald-Giemsa technique. Two hundred cells are then counted and classified. Machines have been developed to perform automated differential counts, but they are still inferior to manual techniques as far as reliability. The following subsets of leukocytes, as reported in the manual differential, would constitute the myeloid cells in blood; the absolute number of each subset can be determined by multiplying the percentage by the total leukocyte count (in the WBC count):

- SEGS (POLY) %
- BANDS %
- METAS %
- MYELOS %
- PROMYELOS %

The percentage and absolute numbers of Monocytes, Eosinsophils, Basophils, and Lymphcytes will be separately enumerated and recorded.

7.6.2 Whole blood bactericidal activity (WBA)

The protocol will use the WBA assay to confirm the infection-clearing potential of white blood cells before and after imatinib dosing. WBA is a candidate biomarker for assessment of protective antimycobacterial immunity and chemotherapy. Cultures consist of equal 300 µL volumes of heparinized blood and tissue culture medium, to which *BCG* is added. Of note this test can be used in participants, such as those enrolled here, who do not have TB disease. Essentially all bacilli are quickly ingested by PMN and mononuclear cells. After 4 days incubation, bacilli are recovered, and the extent of growth or killing determined by inoculation into the Mycobacteria Growth Indicator Tube (MGIT) system and monitoring time to positivity. Cell numbers and drug concentrations in whole blood cultures reflect those *in vivo* at the time of phlebotomy. Immune control of intracellular mycobacterial growth in whole blood culture is inferior in TST-negative persons and in young children, is enhanced by vitamin D and by primary but not secondary BCG vaccination, is impaired by chemokine receptor or TNF blockade, T cell depletion or HIV infection, and is restored by antiretroviral therapy (16-27). WBA during TB treatment is superior in the intensive *vs* continuation phase, is superior for standard *vs* MDR regimens, and correlates with 2 month culture status (28-31). WBA will be measured prior to imatinib dosing (day 1, baseline) and at day 14 of imatinib dosing. Measurement of WBA has accelerated the development of new TB drugs and vaccines (Figure

4) (32-35). The WBA experiments will help us understand the relationships between increases in myeloid cell numbers and *Mtb* killing capacity and will help inform dose selection in a subsequent Phase 2 trial in participants with TB.

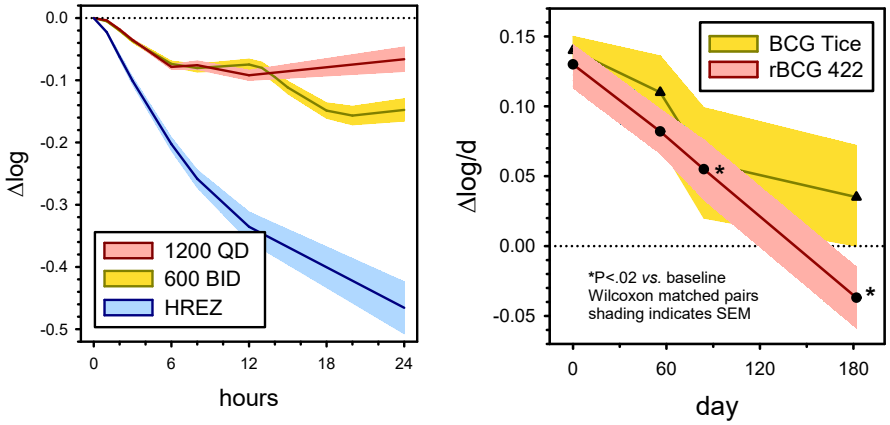


Figure 4. WBA of novel TB drugs (sutezolid, left) (36) and vaccines (rBCG 422, right) (35).

7.6.3 RNA sequencing

RNA sequencing will be performed using protocols described in our prior publications (37, 38), which we have also used for RNA sequencing of human and macaque TB lungs, as well as blood, at Emory. This test will be correlated with myelopoiesis, autophagy, adverse events, and drug concentrations, using such machine learning methods such as Random Forests, LASSO and MARS, described in our prior work (39, 40). This will be used to identify biomarkers and RNA signatures that can predict (i) response, (ii) adverse events, and (iii) drug-drug interactions in later clinical trials.

7.7 Safety Evaluations

CBCs, serum chemistries, symptoms, signs, and ECGs will be monitored for all participants during the study as described in the schedule of events.

8 Sample Size Justification and Analysis Methods

8.1 Sample Size Justification and Statistical Analysis

The primary objectives are to determine the effect of imatinib on the numbers of myelomonocytic cells in the blood, assessed as the change between baseline and day 14 of

imatinib only administration. Secondary objectives include analysis of PK measurements, bacterial killing, proteomic evaluations, and immune function evaluations. We will enroll a total of 48 evaluable participants total, 12 across 4 doses of imatinib (50, 100, 200 and 400mg). 12 participants were already enrolled at the 50 mg dose, and 4 at the 100mg dose in the previous version of the protocol.

With 12 participants per dosage arm (N=48), we will have 80% power to reject the null hypothesis of no change versus the alternative hypothesis that imatinib induces an increase in the absolute numbers of myelomonocytic cells per uL of blood that is at least 0.41 of the standard deviation (SD) of the change for the cohort overall and 90% power to detect a 0.48 SD. Our primary analysis will use a linear mixed model that pools data from all time points, thus we anticipate having more power by leveraging the within-person correlation between indivduals.

There is a chance that participants will not be enrolled on all doses. Given what is known about the safety profile of imatinib, we anticipate that at least one dose will be fully enrolled. By the same rationale above, we will have 80% (90%) power to detect an increase of at least 0.89 (1.03) of a SD of the mean number of myelomonocytic cells in a specific dosage strata (using 12 per stratum). We will also have sufficient power to detect differences in effects induced by different doses. For example, comparing dose groups with a two-sample t-test, with 12 participants per dosage stratum, we would have 80% power to detect a 2.3 x10^3 cells/uL difference between two arms in the change from baseline in the myelomoncytic cell count assuming a SD similar to that seen in a recent macaque study. In a preclinical study of imatinib in *Mtb*-infected antibiotic-treated treated macaques, the mean number of myelomonocytic cells increased from 1.47±0.96 in controls to 3.78±1.89 in imatinib treated animals, with a mean difference of 2.31 (all values indicate thousands of cells/uL). Thus we are adequately powered to detect dose-specific differences on the order of what was seen in the macaques. Further, in a supportive analysis, we will also pool the arms in order to borrow strength across the doses to fit a dose-response curve.

Myelopoiesis will be determined by estimating the absolute number of myelomonocytic cells per uL of blood using the WBC and a manual differential, as noted above. We hypothesize that, on

average, increases in myelopoiesis will occur (and the 95% CI for the change in myelopoiesis over time will exclude 0).

The same mixed model can be used for the analyses of all primary and secondary endpoints where data from all arms and time points are put into one model for the myelopoiesis count outcome. This approach should generally be a more powerful approach than the paired t-test for the change from baseline, as it is leveraging the within person correlation at all time points.

Notation: Note that day 28 terms, not shown here, can also be included similarly for those with 28-day imatinib only dosing.
Let Yij represent the cell count for individual I at time j, where j=day 0,14.
Thus, Yi0= count at baseline, Yi14 = count at day 14 for individual i.
Similarly, let $t14_{ij}$ = day14 indicator and $dosek_{ij}$ = dose k indicator for individual i, time j, where k=2,3,4. Let r_i be the random intercept term for person i and let $error_{ij}$ be the mean 0 independent error term for person i at time j.

$$Yij = b0 + b1\ t14_{ij} + b2\ t14_{ij}*dose2_{ij} + b3\ t14_{ij}*dose3_{ij} + b4\ t14_{ij}*dose4_{ij} + r_i + error_{ij}$$

b0 = baseline myeolopoeis
b1 = day14 change from baseline for dose 1
b2 = difference between dose 2 and dose1 day14 change from baseline
b3 = difference between dose 3 and dose1 day14 change from baseline
b4 = difference between dose 4 and dose1 day14 change from baseline

(4 b1+b2+b3+b4)/4 is the average Day 14 change from baseline pooled across the 4 doses in, i.e. the primary endpoint

b2 – b3 is the between dose difference in the day14 change from baseline for dose 2 and 3; similar comparisons can be for each distinct pair of doses for day14 change from baseline.

AE analysis

We will estimate proportion of clinical and laboratory adverse events, along with 95% exact Clopper-Pearson CI. AE rates will be summarized separately by dose and then overall. All participants who take at least 1 dose will be included in assessments of safety.

8.1.1 Pharmacokinetic Analysis

Frozen plasma samples will be shipped on dry ice in batches to the laboratory of Dr. Charles Peloquin at the University of Florida in Gainesville for PK analyses

The main PK objective is:

To assess imatinib PK and the relationship between PK and PD effects (immunologic and bacillary killing in WBA).

Within this main PK objective, specific PK analyses will aim to:

1. Identify pharmacokinetic parameter estimates, and concentration-time profiles of imatinib doses of 50, 100, 200, and 400 mg in healthy volunteers. Imatinib PK data was already obtained for 12 participants at the 50mg dose, and 4 at the 100mg dose in the previous version of the protocol.
2. Identify the pharmacokinetic/pharmacodynamic exposure-effect relationship between imatinib AUC or peak or trough and i) the change in the numbers of myelomonocytic cells in the blood between baseline and days 14 of therapy and ii) WBA.

We will first evaluate the robustness of our sampling strategy. The percentage of imatinib concentrations measured that are below the limits of quantification in any of the participants at any of the time points identified by D-optimality will be calculated. A result of 0% indicates that the optimal sampling strategy derived from sampling theory was likely to be optimal. Next, we will analyze all imatinib concentrations using ADAPT software of D'Argenio *et al* utilizing a compartmental PK analysis approach (41, 42). ADAPT software was developed using NIH funding, is open source, and has validated performance metrics, ensuring accuracy and robustness of findings from this software. We do not assume *a priori* how many compartments the imatinib PK model has; indeed some studies have described it as a one compartment model drug while others have found it is a two compartment model drug (8, 13, 43). We will examine one-, two-, and three-compartment models with first-order input and elimination. Estimation of

PK parameters will be based on the MLEM algorithm in ADAPT, as described above. The best number of compartments will then be chosen by comparing Akaike's information criteria, Bayesian information criteria, and −2 negative log likelihood scores for each model; we also apply the rules of parsimony. Goodness of fit is evaluated by examining the predicted/observed plots prior to- and after- the Bayesian step. Potential problems by concentration are sought by examining run-of-sine plots. Measures of Bias (mean error and weighted mean error) will be examined, as well as measures of Precision (mean squared error, weighted mean squared error, Bias-adjusted mean squared error and Bias-adjusted mean weighted squared error). The mean pharmacokinetic parameters, mainly volume of central compartment and clearance will be calculated for each participant, and utilized to calculate the half-life, peak concentration, the 0-24h area under the concentration-time curve (AUC_{0-24}/MIC) and the percentage of time that concentration persists in either the concentration zone associated with autophagy or myelopoiesis for each participant. Urine will be collected, frozen and stored for possible assessment of drug metabolites at the time of the PK studies.

The differences in clearance and volume (hence AUC and peak concentration) will be driven by the interindividual variability (IIV) and doses given. There will be 12 participants for each imatinib dose group who complete the PK studies (evaluable for PK data). With a population of 12 per group, for 4 dose groups, the power in detecting a 25% difference in clearance (which drives the AUC), given the IIV, is 90%.

8.1.1.1. Drug-drug pharmacokinetic interactions

* While DDIs between imatinib, isoniazid, and rifabutin are no longer a focus of the study, the following language has been left in the protocol as these associations may be analyzed in participants enrolled in the previous protocol in the 50 and 100mg arms. We have recently introduced machine learning or artificial intelligence (AI) based algorithms to pharmacometrics to identify PK covariates, including genotypic, demographic, clinical, laboratory features, and concomitant medications (44, 45). We will examine the effect of rifabutin and isoniazid PK parameters, demographic features, laboratory values, and RNA-seq signatures, in each participant, on imatinib PK parameters and variability, and hence identify the DDIs if present. We will compare baseline pre-treatment blood samples with those taken after imatinib alone or after imatinib plus isoniazid and rifabutin. This will be performed using Salford Miner software.

Moreover, algorithms such as MARS give a final output equation of the covariates which can be directly used to identify the optimal dose for use in the case that DDI are identified.

8.1.1.2. PK-PD interactions: myelopoiesis and immunologic response

* While DDIs between imatinib, isoniazid, and rifabutin are no longer a focus of the study, the following language has been left in the protocol as these associations may be analyzed in participants enrolled in the previous protocol in the 50 and 100mg arms. We have also extensively used AI methods these methods to identify drug threshold concentrations associated with adverse events, and drug concentration thresholds associated with good microbial and clinical outcomes (46), (38, 39, 47), (48, 49), (50), (40). These methods are more accurate than mixed effects modeling, require smaller sample sizes, and are designed to handle both deep and wide data. We will examine the effect imatinib, and the effect of rifabutin and isoniazid PK parameters on imatinib immunological response. We will identify the imatinib concentration threshold associated with optimal hematopoiesis alone and in the presence of the anti-TB drugs rifabutin and isoniazid, using the MARS algorithm in Salford Miner software. Similarly, we will use the same approach to identifier predictors and imatinib concentrations associated with any adverse events.

8.1.1.3. PK-PD interactions: adverse events

* While DDIs between imatinib, isoniazid, and rifabutin are no longer a focus of the study, the following language has been left in the protocol as these associations may be analyzed in participants enrolled in the previous protocol in the 50 and 100mg arms. The AI algorithm MARS will be used to identify predictors of imatinib, rifabutin, and isoniazid concentrations associated with any of these adverse events, following our methods in Modongo et al (50). Outcomes examined in relation to imatinib, isoniazid, or rifabutin concentrations will be any participant-reported adverse events, including diarrhea, ECG changes, changes in liver function tests, neutropenia, thrombocytopenia, anemia, changes in other serum chemistries, as well as other symptoms and signs.

8.1.2 Interim Analysis

Given imatinib is an FDA-approved drug with a known safety profile, we expect the doses used in this study to be well tolerated. After the first 6 participants in the 200mg dose group have completed the day 28 follow-up visit, the study team, the Data Safety Monitoring Board (DSMB),

the Independent Safety Monitor, and the Sponsor will evaluate the safety data and determine via email whether it is safe to proceed to enrolling in the 400mg dose group after the previous group is fully enrolled. Note that since 42-day follow-up is required for a participant that "counts" toward the 6 needed for follow-up safety analysis, if any of the first 6 participants in a dose group do not complete the study to day 42, we will need to include other participants who complete the day 42 visit in order to fulfill the requirement.

8.1.3 Safety Analysis

All participants entered into the study who take at least one dose of imatinib will have detailed information collected on AEs for the overall study safety analysis. An Independent Safety Monitor (ISM) will review individual and summary reports of AEs in real time as they occur, as well as scheduled formal review of AEs and clinical laboratory results on a weekly basis during the study. SAEs will be reported to the Investigator within 24 hours of awareness of occurrence and the Investigator will then assess the events and report them to the Sponsor (DAIDS), the FDA and to the Emory IRB as described in Section 9.4. All SAEs will be reported to DAIDS in an expedited fashion, within 3 days of occurrence, in accordance with DAIDS requirements.

8.2 Participant Population(s) for Analysis

All-treated population: Any participants enrolled into the study who receive at least one dose of investigational product will be analyzed for myelopoiesis, safety, and other immune parameters.

Protocol-compliant population: Effects of imatinib on myelopoiesis and other immunologic parameters will also be assessed specifically in those with acceptable protocol-compliance for evaluable data – participants who have taken ≥85% of all doses of study drug and completed visits to day 14.

9 Safety and Adverse Events

9.1 Definitions

9.1.1 Adverse Event

An **adverse event** is any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related.

9.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that:

- Is fatal
- Is life-threatening
- Requires or prolongs an inpatient hospital stay
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the participant, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

9.2 Recording and Grading of Adverse Events

At each contact with the participant during the study period, which includes every visit up to day 42, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, and grouped under one diagnosis.

AEs will be graded using the FDA Guidance Document, “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials Guidance for Industry,” September 2007, except when the specific AEs are not represented in this document. In these cases, we will also use the DAIDS table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, or the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017, as applicable. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the

study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event which we become aware of through a passive basis (participant reporting back to the study team, or through publicly available information), which occurs after the study period (after day 42) and is considered to be possibly related to the study intervention (suspected, unexpected serious adverse reactions, or SUSARs) or study participation will be recorded and reported immediately.

Note: Page 9 of the 2007 FDA Guidance Document describes two methods of AE grading for low hemoglobin. The first method is based on lab value ranges. The second is based on decreased readings compared to the subject's baseline reading, with Grade 1 AE assigned for "Any decrease – 1.5" gm/dL change from baseline value. For purposes of this study, hemoglobin readings in this category will not be recorded as Grade 1 AEs. All other criteria for low hemoglobin AE, as described in the FDA document, remain in effect. If a hemoglobin reading is classified as AE using both methods of grading, only one AE will be reported (as the higher grade if different grades are obtained using the two methods).

9.3 Relationship of AE to Study

The relationship of each adverse event to the study procedures will be characterized. The PI will make this determination and will classify adverse events as related or unrelated. "Related" will mean that there is a reasonable possibility that the AE may be related to the study agent(s). "Not Related" will mean that there is not a reasonable possibility that the AE is related to the study agent(s). When a SAE is assessed as "not related" to study agent, an alternative etiology, diagnosis, or explanation for the SAE should be provided. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated, as required. The study drug which a participant has taken will be assessed for relationship with the AE.

9.4 Reporting of Serious Adverse Events, and Unanticipated Problems

The DAIDS-assigned Medical Monitors will be alerted to any new Grade 3 or Grade 4 AEs in real time via email. This is in addition to the formal AE reporting requirements below.

Requirements, definitions and methods for expedited reporting of adverse events are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS RSC website at

https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids. This study will use the SAE form of expedited adverse event reporting, as defined in Version 2.0 of the DAIDS EAE Manual. The study product for which expedited reporting is required is imatinib. The EAE reporting period for this study will be 42 days, which is the day of the final study visit. During these 42 days, all SAEs will be reported to DAIDS in an expedited fashion, within 3 days of occurrence, in accordance with DAIDS EAE Manual. The study drug a participant has taken (imatinib) will be assessed for relationship with the SAE. In addition to the SAE Reporting Category identified above, other AEs that must be reported to DAIDS in an expedited manner are:

- Any gastrointestinal or liver toxicity of grade 3 or higher
- Any uveitis of grade 2 or higher
- Episodes of ventricular tachycardia or fibrillation, syncope, and seizure
- Grade 3 or higher QTcF prolongation
- Any Grade 4 event, including laboratory values
- Heart failure of grade 3 or higher

After the protocol-defined EAE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the DAIDS EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information). Of note, although pregnancy is not an AE, all pregnancies that occur during the study will be reported to DAIDS given the teratogenic potential of imatinib. Any pregnancy occurring during the study will be followed to assess any negative outcomes resulting from exposure to the study drug. Reporting of pregnancies will not use the EAE system, but will be include a written clinical summary of the pregnancy including but not limited to the date discovered, any study or other medications taken during the pregnancy period, the expected due date, and eventual outcome. Pregnancies will be reported to DAIDS first within 7 business days after discovery, and monthly reports will follow until the end of the pregnancy period.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. At least two staff members at the Emory site will have a combination of Reporter and Submitter rights to DAERS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at

https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself. For questions about expedited reporting, please contact the DAIDS RSC Safety Office at (DAIDSRSCSafetyOffice@tech-res.com).

Written Investigational New Drug (IND) safety reports will be submitted to the FDA using FDA Form 3500A by DAIDS, for SUSARs within 15 calendar days of DAIDS determining that the information requires reporting. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The Investigator will also make an assessment of whether the event constitutes an unanticipated problem posing risks to participants or others (UP). This assessment will be provided to the Emory University IRB and DAIDS, which, in turn, will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

The Investigator is responsible for reviewing all IND Action Letters, Safety Reports and any other safety related Investigator Notifications and determining the action to be taken (i.e. prompt reporting to the IRB, consent change/modification, routine reporting, etc).

Co-investigators and the Investigator must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible. In narrative reports, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Participant number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

9.4.1 Follow-up report

If an AE has not resolved at the time of the initial report and new information arises that changes the Investigator's assessment of the event, a follow-up report including all relevant new

or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The Investigator is responsible for ensuring that all AE are followed until either resolved or stable.

9.5 Medical Monitoring and Toxicity Management

Martha Arellano, MD is a Professor of Hematology and Oncology with extensive experience administering imatinib to CML patients at Emory University Hospital. She is certified by the American Board of Internal Medicine in Hematology. She will serve as the Independent Safety Monitor (ISM) for this study. Dr. Arellano's role will be to help monitor the safety of participants and adjudicate adverse events that may be related to imatinib. She has 9 years of experience as principal and co-investigator on multi-institutional clinical trials including trials evaluating transplantation for adults with acute leukemia. These collaborations have led to peer reviewed publications in high impact journals, such as *The Journal of Clinical Oncology*, *Cancer*, and *Lancet Oncology*. Her strong background in clinical investigation and experience as member, and now as vice chair of the Winship Data and Safety Monitoring Committee, make her exceptionally qualified to serve as the Independent Safety Monitor for the trial. The monitor will attest to the absence of relevant conflicts of interest as defined by NIAID and will be approved by all relevant regulatory bodies prior to beginning the study.

The ISM and the PI/co-PI will review safety data as enrollment progresses, assessing AE summaries in real-time and formally on a weekly basis for clinical significance and facilitating attribution to study medication (protocol Section 9.2 and Section 9.3). The ISM will provide information to the DSMB on frequency and severity of AEs.

For individual toxicity management, the PI will review all toxicity reports of grade 2 or higher in real time in order to decide on possible need for intervention or drug discontinuation. In general, a grade 2 AE thought to be related to a study drug that does not respond to non-pharmacologic intervention (e.g., salt restriction and elevation of legs for pedal edema) will lead to consideration for drug discontinuation, and any grade 3 or higher AE will cause discontinuation of study drug. Participants taken off study drug will be followed for safety if willing but will not participate in PK studies.

For manual differential ALC and ANC lab values classified as Grade 3 - Grade 4 AEs, the study team will request that the Emory Medical Lab re-check the counts using the same specimen.

This will provide the needed confirmation of the low count, or indication that the first count was a lab error, allowing the team to make better informed action decisions.

Plans for treatment of common side effects of imatinib are listed below, including symptom grading that warrants drug discontinuation.

The following 4 side effects / AEs will be graded using the FDA Guidance Document, “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials Guidance for Industry,” September 2007.

- Low blood counts: Monitor blood counts more frequently for grade 1-2 leukopenia, anemia or thrombocytopenia. Discontinue study drugs if grade 3 or higher.
- Nausea and vomiting: Treat symptomatically with OTC medications for grade 1-2. Discontinue study drugs if grade 3 or higher.
- Diarrhea. Treat symptomatically with OTC medications for grade 1-2. Discontinue study drugs if grade 3 or higher.
- Fever: Treat symptomatically with OTC medications for grade 1-2. Discontinue study drugs if grade 3 or higher.

The following 3 side effects will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events - Corrected Version 2.1, July 2017

- Skin rash (skin reactions): Treat symptomatically with OTC medications for grade 1. Discontinue study drug if grade 2 or higher.
- Muscle cramps and bone pain. Treat symptomatically with OTC medications for grade 1. Discontinue study drug if grade 2 or higher. See “Pain (not associated with study agent injections and not specified elsewhere),” Page 21 of the DAIDS AE Grading Table.
- Hemorrhage (bleeding problems): Grade 1, N/A. Discontinue study drug if grade 2 symptoms or higher, or decrease in Hgb > 1.5 g.

Edema is not listed in the FDA Guidance document or the DAIDS table, and will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, Nov 2017.

- Edema (swelling of the face, feet, hands): Treat symptomatically with salt restriction and limb elevation if possible for grade 1-2. Discontinue study drug if grade 2 edema does not respond to non-pharmacologic treatment, or for higher grade edema.

9.5.1 Study Progress and Safety Monitoring Plan

The Division of AIDS guidance on study monitoring have been implemented to develop a protocol-specific Study Progress and Safety Monitoring Plan (SPSMP), which will be approved

in writing by the assigned DAIDS Medical Monitor/Medical Officer before trial initiation. Briefly, the ISM, DAIDS representative, and the PI/study team will review all reports at least monthly, with AE reports generated every 2 weeks. The following reports will be generated: 1) Accrual update, 2) Progress report, 3) Delinquency report, 4) Periodic summary adverse event report, 5) Baseline characteristics report, 6) Data completeness report, 7) Outcomes summary report (completed, withdrew, etc), 8) Efficacy report (myelopoesis). The contents of the report will be as outlined in the DAIDS SPSMP protocol template, which can be found at: (https://www.niaid.nih.gov/sites/default/files/studydatamonitor_plan.pdf) and which has been used to create a study-specific SPSMP. The reports created for this process will be provided to DAIDS at the frequency of each review as specified in the SPSMP. The DSMB will receive these reports at the planned imatinib dose group 6- and 12- participant completion points as described in Section 3.1.2.

A DAIDS-appointed study monitoring team will provide oversight and monitoring for the conduct of this study. This DAIDS-appointed team will conduct study-monitoring functions to ensure that the research produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. We expect that this trial will be risk classified by the scientific review committees as Moderate Risk, based on the history of use in healthy volunteers and the known adverse event profile and doses of the agents used. For studies deemed Moderate Risk, initial monitoring occurs within 1 year from the date of the first participant accrued, with 2 of the first 5 participants being reviewed. For this trial, this approach will apply to each imatinib dose cohort. The monitor(s) will review all aspects of the study, with a primary goal of assessment of participant safety, as well as compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the monitor(s) assigned by DAIDS may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. The monitor(s) will then prepare a final monitoring summary report.

Dr. Waller and the investigators, the ISM, the clinical research coordinator and the regulatory affairs coordinator will meet at least monthly to review and discuss study data to ensure participant safety. During the meetings the PI or co-I will review the eligibility criteria for each new participant. In addition, during these meetings the group will review all adverse events, random checks of case report form completion and a roadmap for each participant on the trial.

All study personnel will be trained on the protocol by the PI or co-I. Study personnel will sign the training log prior to being included on delegation of authority log. All adverse events will be handled according to Section 9.4, which provides detailed instructions on reporting requirements.

The PI and the ISM will formally review clinical toxicity assessments with the DAIDS medical monitor every two weeks and after 6 participants have completed follow-up in a dose stratum. The PI and/or medical monitor will halt further enrollment at that dose level for formal review by the DSMB if any participant develops any emergent grade 3 or higher dose-limiting toxicity that is definite, possible or probable in causal relationship to the study drug, in the opinion of the PI. If no such toxicity is observed after the first 6 participants in a dose stratum have completed follow-up, and a total of 12 participants are enrolled in the first stratum, then the next dose stratum will be opened for enrollment.

The safety rationale for opening accrual to a higher dose level, based upon findings from the first 6 participants at the previous lower dose level, is as follows: Rather than use a standard 3 + 3 dose escalation design, we will utilize a more conservative threshold for halting accrual. In this study, enrolling healthy volunteers, a frequency of >33% grade 3 or higher dose-limiting toxicity attributed to a study drug would warrant formal review by the DSMB. We propose to protect participant safety by performing a safety analysis after 6 participants have completed the day 42 follow-up visit, a sample size that gives us greater than 90% power to identify a safety signal and halt accrual at that dose level, based upon a true rate of grade 3 or higher toxicity of 33% (or greater).

9.6 Critical Event Identification and Reporting

In addition, we will report critical events (CEs) to DAIDS and other entities to which we are responsible, including IRBs. Critical events include the following classes of events: unanticipated problems involving risks to participants or others, serious noncompliance, continuing noncompliance, suspension or termination of EC/IRB approval, and suspected research misconduct. The time period for reporting CEs to DAIDS is from the date of study start up to the publication of all related manuscripts resulting from the study.

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study participants will be kept confidential and managed according to the principles of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

10.2 Data Collection and Management

All clinical and laboratory information required by this protocol is to be present in the source documents. All protocol-required visits are to be recorded on the CRFs and keyed into the database unless otherwise specified.

We will use Clinical Research IO, CRIO, as the study clinical data management system. The site data managers and clerks will be responsible for manually entering quantitative data, not already being collected routinely and required for the evaluation, into a study database. Site databases and the merged analytical datasets will be stored on password-protected, encrypted servers. Scheduled backups will be performed on a daily, weekly, and monthly basis. Personal identifiers will be suppressed from the analytic dataset prior to the data analysis phase of the study. Any paper registers, forms, or records that are reviewed in order to abstract data or cross-check missing data will not be removed from the secure, programmatic area where they are stored.

Data will be validated on entry, using range and consistency checks. Quality control procedures will include review of CRFs for completion and correctness. Logical data checks will also be performed on the data. Incomplete and incorrect data queries will be sent back to sites electronically for error resolution. Errors will be reviewed and corrected on a weekly basis. The study will be monitored by internal data monitors.

10.3 Records Retention

Study records (source documents, signed informed consent forms, IRB correspondence and approval letters, and screening logs) will be kept in a secure location accessible only to authorized study staff, investigators, and monitors. All records will be archived in a secure storage facility for at least ten years after the completion of the study.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

This study will be conducted under ICH E6 with good clinical practice compliance. Audits of the Emory site and study will be performed by the DAIDS-appointed study-monitoring team as described in Section 9.5.1. The Investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, site monitors, Office of Human Research Protections (OHRP), and other local, US, or international regulatory entities (e.g, FDA, EMA, and other regulatory agencies), and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by local, US, or international regulatory entities (e.g, EMA) and applicable University compliance and quality assurance offices.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity (51). The site will make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. Potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, direct access to Electronic Medical Record (EMR), and Medidata Rave Imaging Solution. Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

12 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning

the conduct of the study will be made in writing to the Investigator before commencement of this study.

12.1 Risks

The rationale for the dosing schedule is as follows: 14 days of imatinib exposure is required to observe an effect on myelopoiesis (the primary end-point), and 28 days will provide additional information on safety. We do not expect that imatinib will cause significant AEs in healthy normal volunteers when given for this duration. While asymptomatic elevations in aminotransferase levels are often seen in patients within 2-8 weeks after starting imatinib, marked increases in ALT are usually only observed after 6 months of imatinib therapy. Importantly, the toxicity of imatinib is dose-related. We will minimize risk by starting with a very low dose (50 mg/day) and escalate carefully only after safety data on the lower dose has been reviewed for acceptability. The DSMB must recommend proceeding to the next dose level before it will be initiated. Volunteers will be very closely monitored for adverse events at a US cancer center setting highly experienced with imatinib therapy. Visits with a safety evaluation are at study days 1, 3, 7, 14, 15, 21, 28 and 42.

Imatinib is well tolerated in CML patients, and a maximal tolerated dose has not been defined, but >800mg/day is rarely used. Most adverse effects, even at the highest doses, are grade 1 (mild) or grade 2 (moderate). Most patients have a reduction in the Hgb level of 1 to 2 mg/dL; the hemoglobin level typically increased to base-line values or higher with continued therapy. Drug induced anemia during long-term administration has been rarely seen. Neutropenia occurs in chronic phase CML patients treated with imatinib at the onset of blast crisis, but is unlikely to occur in patients receiving low doses in the absence of hematological disease. Inhibition of normal hematopoiesis does not occur in Philadelphia chromosome negative patients, although further clinical assessment will be required to ensure this. In summary, we expect these doses of imatinib to be very safe.

12.2 Benefits

There are no direct benefits to the participants. Participants may however feel they experience the indirect benefit of participating in a research study aiming to identify a new treatment for TB.

12.3 Risk Benefit Assessment

Given the public health problem of TB, and the known safety profile of imatinib and the anti-TB drugs under study, we feel that the study has a favorable risk benefit ratio to society.

12.4 Informed Consent Process / HIPAA Authorization

The Principal Investigator or an authorized clinical Co-Investigator will obtain written informed consent in English from all potential participants. The consenting process will take place in a private space in the clinics where participants are recruited, to ensure confidentiality. Participants will be allowed to provide consent at the time of the consent discussion. Participants will be given time during the consent discussion to ask and have answered any questions. Informed consent will be documented in accordance with GCP standards.

13 Study Finances

13.1 Funding Source

This study is funded by a UH3 grant awarded to Dr. Daniel Kalman at Emory University, by the National Institutes of Allergy and Infectious Diseases / Division of AIDS.

13.2 Conflict of Interest

Emory investigators will for the Emory University Policy on Conflicts of Interest Related to Research. All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

13.3 Participant Stipends or Payments

Emory participants will be reimbursed at a rate of $50 for the screening visit, $125 for visit 1, $75 for each brief visit (6 visits), plus $300 for the PK study visit, for a total of $925 for the entire study.

14 Publication Plan

Dr. Shaw will perform the primary statistical data analyses. Drs. Bisson, Wallis, Waller, Kalman, Giver, Harvey, Gumbo and Shaw and other investigators who meet authorship requirements will all contribute to timely publication of the results. The primary draft manuscript will be done by Drs. Bisson and Waller and will be reviewed by all authors within 3 months after the analysis is completed.

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16 Attachment

Study Informed Consent Form

17 Appendix

17.1 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

17.2 Case Report Forms (CRFs)

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

17.3 GEORGIA CTSA CLINICAL RESEARCH CENTER AT EMORY UNIVERSITY

GEORGIA CTSA - GCRC site at Emory University Hospital (EUH): The EUH GCRC site houses inpatient and outpatient areas, administrative offices, participant waiting area and laboratories. The two areas combined encompass a total of 11,893 square feet. The Inpatient Research Unit includes fully equipped private rooms and a nursing station. At the far end of the GCRC

inpatient unit, the Serious Communicable Disease Unit (SCDU) has three rooms that are capable of providing appropriate isolation and intensive care for patients with highly contagious, serious infectious diseases. Each room has an anteroom that has net negative air pressure in relation to the hallway. The patient rooms have net negative air pressure in relation to the anteroom. Each patient room has over 20 air changes per hour with laminar airflow over the patient beds. All air from the rooms is HEPA filtered and directly exhausted to the outside after being filtered. The rooms were successfully used to treat 4 Ebola patients during the 2014-2015 epidemic. Currently they are used to conduct research on various communicable diseases through Georgia CTSA. In addition to the 3 ICU level isolation rooms, the 8 additional rooms in the unit can be used to care for patients with a lesser degree of illness. Participants check in with the staff at the nursing stations. The participant waiting area seats 9 people. The outpatient research unit is immediately adjacent to the inpatient unit and houses a nursing station, 6 private research bays for study participants and several procedure rooms. GCRC research nurses and technicians are available on a daytime 8-hr shift to perform research activities such as IV placement, timed urine and blood collection, study drug administration, etc.

The Human Performance Unit includes three private outpatient rooms separate from the above described outpatient care area with (1) a treadmill equipped for VO_2Max testing, EKG for exercise stress testing, (2) and ultrasound system for the assessment of flow mediated dilatation and carotid artery intimal medial thickness, and (3) an infusion room.

GCRC Administrative Unit: The administrative suite is adjacent to the EUH-GCRC research nursing units and houses the offices of the GCRC Program Director and site specific Co-Director, Research Nursing Director, Administrative Director, the GCRC scheduling coordinator and Program Coordinators.

GCRC Core Laboratory: The main GCRC Core Laboratory is located adjacent to the EUH GCRC unit and staff includes research technicians with long-standing experience in processing and storage of timed blood, urine and tissue samples. The unit employs the Georgia CTSA-wide state-of-the art Nautilus Laboratory Information Management System (LIMS) for de-identified sample tracking, storage and management. Lab resources include a main Laboratory office, a large sample bench processing and aliquoting area for use by GCRC and investigator staff, general and refrigerated centrifuges and microcentrifuges and 11 [-80^{o}C], 3 [-20^{o}C] and 2 [4^{o}C]

freezers for sample storage. All freezers/refrigerators are equipped with CO_2 back-up system. All three core laboratories hold CLIA waivers.

17.4 Emory University Investigational Drug Service

The pharmacy that will serve the study is the Emory University Investigational Drug Service (IDS) - http://www.ocr.emory.edu/ids/index.html

The IDS is currently involved in a number of NIAID/DAIDS studies, demonstrating the capacity of the IDS to initiate, conduct, participate in, and support NIAID/DAIDS funded research.

Staffing:

Esther Park, Pharm.D., esther.sue.park@emory.edu, 404 727-0028

Jianguo Xu,Ph.D., jxu5@emory.edu, 404 727-0036

Rebecca Gonzalez, Pharm.D., rebecca.feng@emory.edu, 404 778-0672

Susan Rogers, Director, B.S., RPH, sroger2@emory.edu, 404 712-7485

Access:

Access to IDS is limited to IDS employees only. All have keys to the area.

Continual access to electrical power:

IDS is located in Emory Clinic Building A which has a backup generator that provides continual power in case of power outages

Controlled room temperature:
Room temperature is controlled and monitored continually via an electronic monitoring system, Tempalert.

Study product preparation:
Study products are prepared in the pharmacy which is a clean, safe and secure setting. All study product is properly labeled by name and protocol # and is stored according to the labeling requirements.

Equipment:
IDS is equipped with appropriate space and equipment for proper handling and preparation of study product.

Clean water:
IDS has a sink for water supply in the dose preparation area of the Pharmacy.

Equipment maintenance:
IDS maintains equipment for storage, temperature monitoring and preparation of study product and doses. IV hoods are inspected every six months. Temperature monitoring equipment is calibrated annually.

Emergency plan:
IDS maintains backup refrigerators and freezers in case of power equipment failure

Importation:
IDS complies with all international regulations for shipping

Destruction:
IDS can destroy locally through the University's Environmental Health and Safety Office. All study product is destroyed via incineration.

Pharmacy Accountability Records:
IDS uses Vestigo software for all aspects of drug inventory, billing, and accountability
http://www.mccreadiegroup.com/vestigo/

Study Product Acquisition Plan:
Imatinib will be acquired through the CRPMC and dispensed through the IDS pharmacy using standard procedures.