A double-blinded, randomized, placebo-controlled dose escalation study to examine the microfilaricidal kinetics and safety of imatinib for the treatment of *Loa loa* (A pilot study)

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List of Abbreviations

AE	Adverse Event
AI	Associate Investigator
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BRB	Biostatistics Research Branch
CFR	Code of Federal Regulations
Cmax	Maximum concentration
CML	Chronic Myelogenous Leukemia
CRF	Case Report Form
CRFilMT	Centre de Recherche sur les Filarioses et Autres Maladies Tropicales
CRIMSON	Clinical Research Information Management System of the NIAID
DALY	Disability-Adjusted Life Year
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
FDA	Food and Drug Administration
FMPOS	Faculty of Medicine, Pharmacy and Odontostomatology
GCP	Good Clinical Practice
GXDn	Day n of Group X
IC50	Concentration Producing 50% Inhibition
ICER	Mali International Center for Excellence in Research
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
LF	Lymphatic Filariasis
LPD	Laboratory of Parasitic Diseases
MDA	Mass Drug Administration
MF	Microfilaria
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
OHRP	Office for Human Research Protections
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PO	Oral(ly)
qPCR	Quantitative Polymerase Chain Reaction
SAE	Serious Adverse Event
SERF	Safety Expedited Report Form
UP	Unanticipated Problem
UPnonAE	Unanticipated Problem that is not an Adverse Event
USTTB	University of Sciences, Techniques, and Technologies of Bamako

Protocol Summary

Full Title:	A double-blinded, randomized, placebo-controlled dose escalation study to examine the microfilaricidal kinetics and safety of imatinib for the treatment of *Loa loa* (A pilot study)
Short Title:	Imatinib in loaiasis
Clinical Phase:	Phase II pilot study
Conducted by:	LPD/NIAID/NIH
Principal Investigators:	Elise M. O'Connell, MD (NIH) and Joseph Kamgno, MD, PhD (CRFilMT and FMBS/UYI)
Accountable Investigator:	Thomas B. Nutman, MD
Sample Size:	N=20 total (placebo controls n=5, 200mg n=5, 400mg n=5, 600mg n=5)
Accrual Ceiling:	**200**
Study Population:	Otherwise healthy volunteers infected with *Loa loa* between the ages 18-65 from *Loa loa*-endemic regions of Cameroon
Accrual Period:	2 years of enrollment.
Study Design:	This is a double-blinded, randomized, placebo-controlled multi-armed dose escalation study in which increasing imatinib doses will be given to different subjects (each not to receive more than 1 dose).
Study Duration:	24 months Start Date: September, 2019 End Date: August, 2021
Study Agent/ Intervention Description:	Imatinib mesylate 200mg, 400mg, or 600mg, given one time orally
Primary Objective:	To model the short-term microfilaricidal kinetics of imatinib against *Loa loa* for use in designing follow-up studies.
Secondary Objectives:	To assess the safety of a single dose of imatinib in *Loa loa* infection
Exploratory Objectives:	To assess laboratory abnormalities associated with potential killing of *Loa loa* microfilariae; and to

determine the efficacy of single-dose imatinib as a microfilaricide at 1-, 3-, 6-, and 12-month time points.

Endpoints:

Primary:

Percent of baseline *Loa loa* microfilariae as determined by concentrated peripheral blood smear. Daily measurements will be taken the first week, followed by measurements at day 14 and day 21.

Secondary:

Tables of adverse events by treatment group including grades of AEs, as defined by CTCAE (Common Terminology Criteria for Adverse Events v5.0).

Exploratory:

Exploratory endpoints will include laboratory testing and complete blood count with white blood cell differential, as well as urine and stool assessment of coincident parasitic infections at multiple time points following imatinib used as a microfilaricide.

Percent of baseline *Loa loa* microfilariae over time: 1, 3 months (and if needed 6 and 12 months)

Précis

With the discovery that people experiencing severe treatment reactions following mass drug administration (MDA) with ivermectin for onchocerciasis and lymphatic filariasis control were co-infected with *Loa loa,* there has been a need for new filaricidal drugs. Currently, *Loa loa* infection, considered relatively non-pathogenic, is not treated in endemic areas. However, because treatment for *Loa loa* can result in toxicity in people who are being concurrently treated for onchocerciasis and lymphatic filariasis, finding a new treatment for *Loa loa* has become a priority. Imatinib has recently been shown to be microfilaricidal *in vitro* at concentrations physiologically achievable after a single oral dose in humans. The current standard in loiasis treatment outside of endemic areas is to treat those with low microfilarial (MF) levels (less than approximately 8,000MF/mL) with diethylcarbamazine (DEC). However, at high MF concentrations (>20,000 MF/mL) serious side effects including encephalopathy and death have occurred with administration of DEC or ivermectin, a widely distributed microfilaricide throughout Africa. In endemic areas, this risk is avoided by not treating loiasis altogether. The adverse reactions are believed to be due release of a large antigen load due to rapid killing of large numbers of MF. The rapidity of killing is believed to be the main driver of these reactions seen at high MF counts. The purpose of this study is to assess how imatinib acts as a slow microfilaricide at levels (<2,500 MF/mL) that have been safely treated previously with DEC and ivermectin. We aim to perform a dose escalation study to identify the minimum single oral dose that will be effective as a slow microfiaricidal drug against *Loa loa*. If imatinib is found to be effective and have kinetics which favor slow microfilarial killing, then this can serve as the basis for a larger study in which patients with very high microfilarial loads would be treated, as this is the at risk population in current MDA campaigns. This is a double blind, randomized, pilot phase 2 dose-escalation trial. Subjects will receive a dose of imatinib at 200, 400 or 600 (n = 5 each). Symptoms and blood microfilarial concentration will be assessed at baseline, daily for the first 7 days, then weekly for the next 21 days, then at 3, 6, and 12 months. These will be compared against an untreated placebo-controlled group of 5 subjects who will have the same data collected at these respective days.

1 Background Information and Scientific Rationale

1.1 Background Information

The World Health Organization has the goal of eliminating lymphatic filariasis (LF) caused by the filarial parasites *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori,* and onchocerciasis, caused by the filarial species *Onchocerca volvulus,* by the year 2020. Approximately 157 million individuals are infected with organisms that cause either LF or onchocerciasis, together being responsible for ~6.3 million disability-adjusted life years (DALYs).[1] To this end, millions of doses of ivermectin and albendazole have been distributed throughout Africa through mass drug administration (MDA) campaigns. Of enormous concern for the MDA programs for LF and onchocerciasis in Central and West Africa is co-incident *Loa loa* infection in which Loa-infected individuals with very high levels of microfilariae (MF) have had severe neurological adverse events (AEs) including encephalopathy and death following ivermectin administration[2]. This has led to a cessation of ivermectin-based MDA in areas where *Loa loa* is present. Considered to be relatively non-pathogenic, *Loa loa* occasionally causes transient angioedema and eyeworm (subconjunctival migration of an adult parasite); extremely rarely it can cause renal and/or cardiac dysfunction.[3] In Loa-endemic areas, no treatment for loiasis is given because of the concern for severe reactions with currently available drugs. The reason we are seeking a treatment is so that lymphatic filariasis and onchocerciasis can be safely treated after *Loa loa* microfilariae are safely eliminated from the bloodstream.

Recently, *in vitro* data has shown that the human stages of *B. malayi* (MF, L3, adult) are susceptible to imatinib-induced filaricidal effects, thought to be due to inhibiting an abl-like protein expressed by this filaria which has a high homology to the human c-Abl protein, to which it was designed to bind.[4] Moreover, the concentration producing 50% inhibition (IC50) found *in vitro* for MF (6.06 μM) and L3 (11.27 μM) were lower than the observed maximum concentration (Cmax, 13.3 μM) *in vivo* following a single 600mg oral dose of imatinib.[5] Three dimensional modeling of the protein which is found in *Loa loa* shows that imatinib would likely bind to the abl-like protein in the same way.[4] Sequence analysis of this abl-like protein found in *L. loa, B. malayi, O. volvulus,* and *W. bancrofti,* show >98% identity between each other at the projected drug binding site.[4] The probability of Loa-related treatment side effects following ivermectin administration increases proportionally to the microfilarial loads (non-neurologic side effects seen with >8,000 MF/mL,[6] neurologic side effects seen with >30,000 MF/mL)[2] Severe side effects begin within 3 days following medication administration[7, 8] and do not appear to change with simply using a lower dose of ivermectin.[9] Moreover, when treated with ivermectin, MF appear to reliably decrease post treatment by 70-100% day 1 following treatment (Herrick et al, 2017), with a slight increase to 65% by day 3 [10], then falling again thereafter [10].

1.2 Imatinib

Imatinib is a small molecule inhibitor which was US Food and Drug Administration (FDA)-approved for chronic myelogenous leukemia (CML) in 2001 which acts on the protein product of the Philadelphia chromosome, Bcr-Abl. Single dose administration in healthy volunteer studies (imatinib 400mg) have shown a remarkable safety profile although headaches, nausea/vomiting and diarrhea have been reported.[5, 11]

1.3 Rationale

Given the high homology of the protein between *Loa loa* abl-like protein, and human c-Abl, which imatinib targets, as well as *in vitro* data suggesting that imatinib will have microfilaricidal effects at achievable physiologic doses,[4] this study aims to answer the question of whether imatinib has significant microfilaricidal effects *in vivo*. Additionally, this presents both the opportunity to explore a drug which may treat this disease, as well as provide a very safe model by which we can predict the safety and efficacy of this drug on *Loa loa* by assessing the rapidity in which microfilariae are killed.

In studies observing treatment reactions in patients with high levels of *Loa loa* microfilaremia, side effects of fever, pruritus, headaches, and arthralgias were seen in the first 24-36 hours.[10] Within the first 3 days following treatment hematuria, proteinuria, decrease in alkaline phosphatase, increase in white blood cell counts, and dramatic changes in eosinophil counts are seen proportional to the degree of pre-treatment microfilaremia levels.[10, 12] Thus, we plan to evaluate clinical symptoms daily for the first 7 days, expecting to find any clinical manifestations pertaining to a treatment reaction to begin prior to day 4 following drug administration. Likewise, we will check all of the above mentioned laboratory tests daily during for the first 7 days, and again would expect any abnormalities related to a treatment reaction to begin prior to day 4 following drug administration. One dose of imatinib has not been associated with clinically significant laboratory abnormalities or any of the above side effects.[5, 11, 13]

The primary objective of this study is to model the microfilaricidal effects of imatinib in the short-term (days) and long term (weeks-months). Following a dose of ivermectin a 70-100% decrease in MF is seen by day 1[14]. Based on both efficacy and microfilarial decline we can then pick the most promising appearing imatinib dose in order to design a larger trial evaluating efficacy.

Microfilarial levels will be checked daily for the first week, then weekly for the next 3 weeks in order to track the kinetics of the microfilaricidal properties as it is currently unknown when the nadir will occur. Likewise, while imatinib may *in vitro* have some sterilizing effects on the adult female worms [15], whether this happens *in vivo* is unknown. Although these subjects live in *Loa loa* endemic areas, the time from infection to appearance of MF in the blood is over 3 months.[16] Thus, blood microfilariae seen at month 3 following imatinib would indicate persistent female fertility and not reinfection. A 6 month blood draw is scheduled to assess for durability of the response with the acknowledgement that

reinfection may occur. Subjects who have previously experienced side effects or lab abnormalities following microfilarial killing at high levels of Loa loa microfilaremia (>10,000MF/mL) in the first 3 days can experience fevers, headaches, fatigue, confusion, arthralgias, and pruritus,[10, 12] which is why we will be interviewing and performing a focused physical exam on enrolled subjects daily for the first week, and thereafter if the subjects indicate new symptoms. Additionally, during these days some subjects may develop proteinuria, hematuria, changes in alkaline phosphatase or the white blood cell differential, and so safety labs, including CBC with differential, liver enzymes, creatinine, and urinalysis will be throughout the first week, then weekly (CBC and MF smear) for 3 more weeks, then at 3, 6, and 12 months (see Appendix "A: schedule of evaluations").

2 Study Objectives

2.1 Primary Objective:
To model the short-term microfilaricidal kinetics of imatinib against *Loa loa* for use in designing follow-up studies.

2.2 Secondary Objectives
To assess the safety of single dose of imatinib in *Loa loa*

2.3 Exploratory Objectives
To assess laboratory abnormalities associated with potential killing of *Loa loa* microfilariae; and to determine the efficacy of single-dose imatinib as a microfilaricide at 1-, 3-, 6-, and 12-month time points.

3 Study Design

3.1 Description of the Study Design
This is a randomized, double blind, placebo-controlled dose escalation pilot study. Increasing doses of imatinib will be given to different subjects (each not to receive more than 1 dose), and MF change following imatinib will be compared to blinded placebo-receiving subjects' MF concentrations. Halting criteria are described in section 11.6.

Dose Escalation Schedule:

Group 1 (7 subjects: 5 drug, 2 placebo): 200mg oral (po) imatinib mesylate given day 0 of group 1 (G1D0), side effects monitored daily. If no halting criteria (SAE

or grade 3 or higher AE by CTCAE v5.0) are met by G1D4[1], group 2 can begin the study.

Group 2 (7 subjects: 5 drug, 2 placebo): 400mg po imatinib mesylate given G2D0, side effects monitored daily. If no halting criteria (SAE or grade 3 or higher AE by CTCAE v5.0) are met by G2D4, group 3 begins the study.

Group 3 (6 subjects: 5 drug, 1 placebo): 600mg po imatinib mesylate given

G3D0, side effects monitored daily.

Study Endpoints

3.2 Primary Endpoint

Percent of baseline Loa loa microfilariae as determined by concentrated peripheral blood smear. Daily measurements will be taken the first week, followed by measurements at day 14 and day 21.

3.3 Secondary Endpoints

Tables of AEs by treatment group including grades of AEs, as defined by CTCAE (Common Terminology Criteria for Adverse Events v5.0).

Percent of baseline *Loa loa* microfilariae over time (up to 12 months).

3.4 Exploratory Endpoints

Exploratory endpoints will include laboratory testing and complete blood count with white blood cell differential, as well as urine and stool assessment of coincident parasitic infections at multiple time points following imatinib used as a microfilaricide.

Percent of baseline *Loa loa* microfilariae over time: 1, 3 months (and if needed 6 and 12 months)

4 Study Population

4.1 Rationale for Subject Selection

Since this is a pilot phase II clinical trial and there is a potential risk for unknown AEs, only adults without pre-existing medical conditions, and without chronic medication use will be enrolled. Women of childbearing age and breastfeeding

[1]For group 1 only, if 5/7 subjects have safely passed Day 4, then the remaining 2 subjects can be enrolled at the same time as group 2.

women will likewise be excluded due to potentially harmful effects of imatinib to the fetus/infant as detailed below.

4.2 Recruitment Plan

The Centre de Recherche sur les Filarioses et Autres Maladies Tropicales (CRFilMT) has played a major role in mapping *Loa loa* infection in Cameroon. As such, many of the districts near Yaoundé are hyperendemic for *Loa loa*. Subjects will be recruited through the district health officers who are responsible for particular districts. This pilot study will be conducted in Mbalmayo, a *Loa loa* hyperendemic region in which there is a small but well-equipped hospital and outpatient clinic, and where the entire census has recently been performed as part of a larger epidemiologic study.

4.3 Subject Inclusion Criteria

1. Age $\geq$ 18 years old and $\leq$ 65 years
2. *Loa loa* microfilaremia >500 MF/mL and <2500 MF/mL at screening visit.
3. Subject has the capacity to understand the potential risks and benefits and consents to protocol indicated blood draws and follow up visits

Participation of Women:
Contraception:
Imatinib is a pregnancy category D drug (see package insert). Spontaneous abortions and infant congenital anomalies have been reported during postmarketing surveillance. Females of childbearing potential will be excluded.

4.4 Subject Exclusion Criteria

1. Women under 45 years of age, or over 45 years of age with a menstrual period in the preceding 12 months.
2. Currently breastfeeding
3. Currently taking daily medications
4. Known chronic medical conditions, including but not limited to diabetes, renal failure, liver disease, seizure disorder, HIV, malignancy, psychiatric disorder, or any conditions which within the investigators' judgement are deemed to be clinically significant.
5. *W. bancrofti* serologic positivity against Wb123
6. *O. volvulus* serologic positivity against Ov16
7. HIV by history or clinical signs of HIV/AIDS (e.g. oral thrush, oral/skin lesions of Kaposi's sarcoma, etc.)
8. Any of the following lab abnormalities: Creatinine >1.5, Platelets <100,000/mL, Hemoglobin <12g/dL, alanine aminotransferase or aspartate aminotransferase >60 U/L, total bilirubin >1.7mg/dL, absolute neutrophil count equal to or less than 1500/mm^3.

9. Any condition that, in the opinion of the PI, may substantially increase the risk of participation, including any contraindication to imatinib.

Co-enrollment Guidelines: Co-enrollment in other trials is restricted, other than enrollment on observational studies. Study staff should be notified of co-enrollment as it may require the approval of the PI.

4.5 Justification for Exclusion of Special Populations

Exclusion of Women:

- **Pregnancy:** Women who are still menstruating over the preceeding year OR are less than age 45 years old are excluded from this study because the effects of imatinib on the developing human fetus are potentially teratogenic or abortifacient without a clear benefit to the mother.
- **Breastfeeding:** Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with imatinib, women who are breastfeeding will be excluded.

Exclusion of Children:

Because there are no data regarding AEs in adults for this indication to judge the potential risk in children, children are excluded from this study.

Exclusion of subject ≥ 65 years:

Because we want subjects without significant comorbidities at this phase, subjects older than 65 years will be excluded. The data on the safety at this phase will give indication for the inclusion of these subjects for the next phase.

5 Study Agent/Interventions

5.1 Disposition and Dispensation

Study agent and placebo will be a vitamin (folic acid) provided by the NIH Central Pharmacy and shipped to the study site according to standard pharmacy procedures. An unblinded pharmacist member of the study team (who will not be involved in collecting subject information) will be responsible for randomization and distribution of the drug and placebo.

5.2 Formulation and Packaging

Imatinib is available in the US as an orange oblong tablet in the strength of 400mg with a central score and is packaged in a bottle. For the 100mg tablet, it is provided as a round yellow/orange tablet with a central score. For the purposes of blinding these pills will be removed from the bottles and provided (up to 3 tabs depending on what arm of the study) to the subjects in an envelope. Placebo folic acid pills are yellow/orange oblong and round, although not identical, are similar in appearance. They will be packaged in envelopes and delivered in the same

way to subjects in such a manner that the subject will not be able to identify that the placebo pills are slightly different than imatinib.

5.3 Study Agent Storage and Stability

Imatinib should be stored at a controlled room temperature of 25°C (77°F), with excursions permitted between 15 and 30°C (59 and 86°F). It should be protected from moisture. Procedures for ensuring this range of temperature are maintained are already in place at the pharmacy and will be continued with daily logs and a mercury thermometer.

5.4 Preparation, Administration, and Dosage of Study Agent

A physician at the study site will remain unblinded throughout the study and be in charge of medication blinding and dispensation, and maintaining study supplies/inventory list. This physician will be independent of any study assessments. To maintain blinding, any discussion of the treatment assignment between the clinicians and this physician is prohibited until the study is unblinded, except as may be required to address an immediate serious adverse event (SAE) that may be affected by this information.

Dose Groups:

Group 1 (7 subjects: 5 drug, 2 placebo): 200mg oral (po) imatinib mesylate given day 0 of group 1 (G1D0).

Group 2 (7 subjects: 5 drug, 2 placebo): 400mg po imatinib mesylate given G2D0.

Group 3 (6 subjects: 5 drug, 1 placebo): 600mg po imatinib mesylate given G3D0.

5.5 Assessment of Subject Compliance with Study Agent

The study drug is administered as a single dose in the presence of a member of the research team.

5.6 Concomitant Medications and Procedures

Subjects on scheduled daily medications are excluded. Other non-emergency medications taken within the first 4 days following study drug administration should be discussed with study team prior to administration.

6 Study Schedule

Also see Appendix A: Schedule of Evaluations

6.1 Screening (Days −14 to −1)

A brief interview will be conducted, and if no exclusion criteria are initially met by history, informed consent will be obtained. No research related procedure will be conducted until informed consent is obtained. Then subjects will then undergo a

clinical assessment and physical exam, have blood drawn for concentration and assessment of *Loa loa* infection via blood smear, dried blood spots for qPCR (to be used if needed), and storage for future studies. All subjects will have blood taken to assess for *O. volvulus* (by Ov16 testing) and *W. bancrofti* (WB123 serology) using the SD Bioline Oncho/LF IgG4™ RDT, as well as to perform a complete blood count, blood chemistry (creatinine, potassium, sodium), and hepatic panel (alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase, and bilirubin). If the subject meets the eligibility criteria, then they will proceed to baseline.

6.2 Baseline and Randomization (Day 0)

On Study Day 0, subjects will undergo blood microfilariae count, complete blood count with white cell differential, chemistries (Alkaline phosphatase, ALT, AST, bilirubin, creatinine, sodium, potassium), and urinalysis. If subjects are willing, urine, and stool specimens will also be collected for possible future analyses. A blood spot will also be collected for later *Loa loa* microfilarial quantification by qPCR. A baseline evaluation of symptoms will be conducted, as well as history and physical exam (including vital signs).

After baseline evaluation, subjects will be randomized to either treatment or placebo for the current test group (i.e. randomization of 6 [group 3] to 7 [groups 1 and 2] subjects will occur with each drug escalation minimum of 4 days following the previous dose, up to 14 days later). Each group will be allocated a collection of sealed envelopes such that 2 randomly selected subjects from each of groups 1 and 2 will receive placebo and 1 subject will receive placebo from group 3. Randomization is being generated by the statistician and randomization codes supplied by him to the on-site pharmacist, both whom are unblinded. Each group will have 5 subjects receive imatinib. Subjects will be given the drug dose assigned to their group or placebo on day 0, and a small volume of blood will be drawn 2-4 hours following study drug administration to test for peak imatinib levels.

6.3 Study Phase (Days 1 to 28)

On D1 (approximately 24 hours later), blood to test an imatinib level will again be drawn. For all subjects, daily D1 through D7, and thereafter every 7 days D14 to D28, blood smears for microfilariae, blood spots for *Loa loa* qPCR, complete blood count with differential, will be performed, as will a symptom assessment (see Appendix C), a targeted history and physical exam, and assessment for any drug toxicity. Chemistries (alkaline phosphatase, ALT, AST, bilirubin, creatinine, sodium, potassium) will be performed 4 out of the first 7 days, Serum will be collected and stored.The targeted physical exam will be performed on D21 and thereafter only if symptoms are reported. Urinalysis will be conducted daily D1-D7 to assess for proteinuria and hematuria.

If no halting criteria are met by D4 following drug administration (grade 3 or above CTCAE or SAE), the subsequent group will undergo randomization and a higher dose will be given. If halting criteria are met after a higher dose of drug has been given, halting rules (see Section 11.7) will be followed with suspension in enrollment and further doses held until it is deemed safe to continue or it is decided the study should discontinue.

6.4 Follow-up and Final Study Visits

Subjects will be assessed at 3 months (+/- 7 days) following drug administration, and 6 and 12 months (any day of the 6^{th} and 12^{th} month) following drug administration. At those times, a blood for microfilarial quantification, blood spots for *Loa loa* PCR, and complete blood count with differential will be performed, as will a symptom assessment, and assessment for any drug toxicity. A targeted physical exam will be performed only if symptoms are reported. Subjects will have the options to provide urine and stool samples at these time points for further future analyses.

6.5 Early Termination Visit

Subjects who withdraw from the study are not required to complete additional visits. These subjects, similarly to those that do complete the trial will be given a dose of DEC following confirmation peripheral blood smear is <5000MF/mL.

6.6 Final disposition for participant

At the end of the study, after confirmation by concentrated blood smear that peripheral blood contains <5000MF/mL, all the participants will receive one dose (300 mg) of diethylcarbamazine (DEC) to reduce *Loa loa* microfilarial levels.

7 Study Procedures/Evaluations

7.1 Clinical Evaluations

A medical history and physical examination to assess potential signs and symptoms of *Loa loa* infection will be performed as part of the baseline evaluation. Clinical evaluations at subsequent time points will be targeted and focus on the assessment of new symptoms, signs or untoward medical events. All of these assessments are both for research as well as clinical safety purposes. This includes assessing for complications related to microfilarial death (headache, arthralgia, confusion) as well as medication side effect (headache, nausea, vomiting, diarrhea). Vital signs, including blood pressure, heart rate, and body temperature will be measured as part of all physical examinations, according to standard nursing practice.

7.2 Laboratory Evaluations

7.2.1 Clinical and Laboratory Evaluations and Specimen Collection

Blood for routine laboratory testing and for research studies will be obtained by venipuncture. Serum samples will be collected and stored at -80 deg C.

To ensure safety and efficacy in *Loa loa* microfilariae killing only in enrolling subjects, they will be screened for co-infection serology to Wb123 (for W. bancrofti) and to Ov16 (for *O. volvulus*) and excluded if positive.

Concentrated peripheral blood smears and blood spots for PCR will be collected mid-day (10am-2pm). Blood smears will be processed in real time, and qPCR on blood spots will be performed at a later time as a verification of what is seen in the peripheral smear (particularly at low MF levels).

Complete blood count with differential and urinalysis will be performed daily during week 1 and blood chemistries and hepatic panel will be performed 4 days during week 1 when other drugs have had the most impact on these parameters, then all but urinalysis (which will not be continued) will be progressively more spaced out as the likelihood of finding abnormalities decreases over time from a microfilaricide. Serum will be collected for future studies pertaining to immune function and/or co-pathogen identification.

If subjects are willing stool and urine will be collected for future studies pertaining to co-pathogens and/or diagnostic test development.

7.2.2 Specimen Preparation, Handling and Shipping

Serum samples will be aliquoted and frozen at the CRFilMT and stored at both the CRFiLMT or at the NIH at -80^{o}C for future use. Blood spots, stool, and urine will be stored at CRFilMT or at NIH for for future use.

8 Potential Risks and Benefits

8.1 Potential Risks

8.1.1 Imatinib

Imatinib is a small molecule inhibitor which was FDA approved for CML in 2001 which acts on the protein product of the Philadelphia chromosome, Bcr-Abl. Single dose administration in healthy volunteer studies (imatinib 400mg) have shown a good safety profile, with headache (53%), nausea (13-43%), vomiting (13%), and diarrhea (3%).[5, 11] Although in the case of daily dosing for malignancy possible side effects include edema, cytopenias, rash, and extremely rarely, death, these have not been reported in healthy volunteers with one dose of medication. Therefore, these AEs are very unlikely to occur in this study.

Imatinib is classified as a pregnancy category D drug (package insert) based on animal and human data. There are postmarket reports of spontaneous abortions and birth defects from women who have taken imatinib for treatment of malignancy. Risk appears to be greatest during the first trimester during organogenesis (which protein kinases play a key role in) [17, 18]. Major organogenesis occurs from days 13-56 of gestation [19], however using a low serum beta-HCG cutoff (10IU/l) detects essentially all pregnancies by day 11-12 [20-22], thus minimizing these risks by excluding women with detectable levels at screening or baseline. However, given the exploratory nature of this study, all women of childbearing age will be excluded from this study.

Imatinib is excreted in breastmilk, therefore women who are breastfeeding are excluded from this study.

There are no risks associated with the placebo.

8.1.2 Blood draws

The potential risks of the needlestick for blood drawing include pain, fainting, infection and bruising, or a small hematoma. The bruising may last up to 72 hours. Any hematomas will be treated with local pressure. Infection from the needle puncture is rare, but if this does occur, appropriate treatment will be given. The total amounts of blood drawn are shown in Appendix B.

8.1.3 Microfilarial Death

Rapid killing of high microfilarial loads in *Loa loa* have been associated with pruritus, rash, asthma-like respiratory complications, angioedema, hypotension, and, extremely rarely, neurologic complications and death. This study has specifically been designed to avoid these complications; given the low *Loa loa* microfilarial loads this is not expected to be a problem.

8.2 Potential Benefits

Participants may not directly benefit from imatinib therapy. However, subjects may receive some benefit if imatinib is able to clear the *Loa loa* infection. Subjects may also benefit from enhanced access to medical care and intensive active surveillance for *Loa loa* infection since they will be getting laboratory testing performed both at baseline and throughout the trial. Any illness that may have been caused by the study drug will be treated without cost to the participants. The information obtained in this study will improve the understanding of the use of imatinib in treating people with *Loa loa* infection. Subjects may benefit from treatment with a single dose of DEC.

9 Research Use of Stored Human Samples, Specimens or Data

- **Intended Use:** Samples and data collected under this protocol may be used to study parasite infections. No genetic testing will be performed. Any other research or experimental treatments will be done under this or

other protocols for which separate signed informed consent documents will be obtained.

- **Storage:** Access to stored samples will be limited using a locked room or freezer, in both Cameroon and Bethesda. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- **Tracking:** Samples and data acquired during this study will be tracked using the NIH Biological Specimen Inventory System.
- **Disposition at the Completion of the Protocol:**
    - In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. In that case, Institutional Review Board (IRB) approval must be sought prior to any sharing of samples and/or data. Any clinical information shared about the sample would similarly require prior IRB approval.
    - At the completion of the protocol (termination), samples and data will either be destroyed, or after IRB approval, transferred to another existing protocol.
- **Reporting the Loss or Destruction of Samples/Specimens/Data to the IRB:**
    - Any loss or unanticipated destruction of samples or data (for example, due to freezer malfunction) that meets the definition of Protocol Deviation and/or compromises the scientific integrity of the data collected for the study, will be reported to the NIAID IRB.
    - Additionally, subjects may decide at any point not to have their samples stored. In this case, the principal investigator will destroy all known remaining samples and report what was done to both the subject and to the IRB. This decision will not affect the subject's participation in this protocol or any other protocols at NIH.

10 Remuneration Plan for Subjects

The subjects will be reimbursed for participation in this study and as compensation for their time. Subjects will be paid 10 000 cfa ($19) for each outpatient or inpatient visit since it would lead to an entire day of missed work.

11 Assessment of Safety

AEs and other reportable events are defined in NIH Human Research Protections Program (HRPP) Policy 801.

11.1 Toxicity Scale

The Investigator will grade the severity of each AE according to the "Common Terminology Criteria for Adverse Events (CTCAE)" (v 5.0) which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
Subjects with documented vital sign, symptom, physical exam, or laboratory evidence of pre-existing conditions that are intermittent in nature and that re-occur to the same degree they occurred at baseline/screening will not be considered to be having an AE when those same findings re-occur, even if

there are intervening normal/absent observations. Any worsening in grade from baseline will be reported as an AE of the appropriate grade per CTCAE v5.

11.2 Recording/Documentation

All AEs occurring from the time the informed consent is signed through the specified study follow-up period (i.e. 12 months) will be documented, recorded, and reported. All events, both expected/unexpected and related/unrelated will be recorded on a source document. Source documents will include progress notes, laboratory reports, consult notes, phone call summaries, survey tools, and data collection tools. Source documents will be reviewed in a timely manner by the research team. All reportable AEs that are identified will be recorded on the appropriate case report form (CRF). The start date, the stop date, the severity of each reportable event, and the PI's judgment of the AE's relationship and expectedness to the study agent/intervention will also be recorded on the appropriate CRF. If a diagnosis is clinically evident (or subsequently determined), the diagnosis rather than the individual signs and symptoms or lab abnormalities will be recorded as the AE. Clinical team members will be entering patient interview, physical exam findings, and vital sign information directly onto tablets with RedCap in the clinic. Laboratory results will be entered by clinical and non-clinical team members from source documents into RedCap from the laboratory location. Adverse events will be logged into RedCap along with these data entry points.

11.3 Causality

Causality (likelihood that the event is caused by the study agent(s)) will be assessed considering the factors listed under the following categories:

Definitely Related

- reasonable temporal relationship
- follows a known response pattern
- clear evidence to suggest a causal relationship
- there is no alternative etiology

Probably Related

- reasonable temporal relationship
- follows a suspected response pattern (based on similar agents)
- no evidence of a more likely alternative etiology

Possibly Related

- reasonable temporal relationship
- little evidence for a more likely alternative etiology

Unlikely Related

- does not have a reasonable temporal relationship

OR

- good evidence for a more likely alternative etiology

Not Related

- does not have a temporal relationship

OR

- definitely due to an alternative etiology

11.4 Reporting Procedures

11.4.1 Expedited Reporting to the NIAID IRB

Unanticipated problems, non-compliance, and other reportable events will be reported to the NIAID IRB according to Policy 801.

11.4.2 Annual Reporting to the NIAID IRB

The following items will be reported to the NIAID and Cameroon IRBs in summary at the time of Continuing Review:

- Serious and non-serious unanticipated problems
- Expected SAEs that are possibly, probably, or definitely related to the research
- SAEs that are not related to the research
- All AEs
- Serious and non-serious protocol deviations
- Serious, continuing, and minor non-compliance
- Any trends or events which in the opinion of the investigator should be reported

11.4.3 Pregnancy

In the rare event that pregnancy does occur on thisthis trial, pregnant subjects will be followed for safety and notifications will be made as required by the DSMB, NIAID IRB, and Ethics Committee in Cameroon. The subject will be advised to notify their health provider of study participation and study agent exposure. The subject's assignment to active study agent or placebo may be unblinded to facilitate care and to potentially reduce uncertainty and stress for a subject who received placebo.

Although pregnancy itself is not an AE, events that meet SAE criteria during pregnancy, delivery, or in the neonate (eg, congenital anomaly/birth defect) are reportable on the CSERF. Of note, women of childbearing age are excluded.

11.5 Type and Duration of the Follow-up of Subjects after Adverse Events

Subjects who suffer from AEs felt to be related to the administration of imatinib will be followed clinically and with laboratory monitoring if needed, until resolution

of the AE, or until 12 months following drug administration, whichever is first. Subjects requiring inpatient treatment as a result of study participation will be provided appropriate hospital care as may be indicated.

11.6 Halting Rules for the Protocol

Halting the study requires immediate discontinuation of study agent administered for all subjects and suspension of enrollment until a decision is made whether or not to continue enrollment and study agent administration.

In the event of any SAE, or an AE equal to or greater than a grade 3 toxicity (CTCAE v5.0) the study will be halted (no new enrollments and no further administration of imatinib) by the investigators until a decision is made whether or not to continue enrollment and drug administration and a report will be submitted to the NIAID IRB, DSMB, and the EC in Cameroon.

The PI will determine if the study should be halted. In addition, the NIAID IRB, the DSMB, or the EC may halt the study at any time following review of any safety concerns.

11.6.1 Reporting a Study Halt

If a halting rule is met, then a description of the AEs or safety issue must be reported by the PI, within one business day, to the NIAID IRB, EC, and the DSMB by fax or email.

11.6.2 Resumption of a Halted Study

The PI, in collaboration with the DSMB, will determine if it is safe to resume the study.

The PI will notify the IRB and the EC of the decision on resumption of the study.

11.7 Discontinuation of Study

The study will be discontinued when any SAE felt by the study investigator to be related to imatinib administration and/or microfilarial killing due to imatinib administration is seen in any of the treatment groups. In this case no further drug will be administered, but monitoring and follow up visits, exams, and laboratories will be completed for previously enrolled subjects.

11.8 Withdrawal Criteria for an Individual Subject

An individual subject will be withdrawn for any of the following:

- Non-compliance with study procedures to the extent that it is potentially harmful to the subject or to the integrity of the study data.
- The investigator determines that continued participation in the study would not be in the best interest of the subject.

11.9 Replacement of Withdrawn Subjects or Subjects who Discontinued Study Agent

There will be no replacement of subjects who discontinue study given that this is a single dose study. However, every attempt will be made to follow up subjects who do not present to follow up appointments so that response and side effects may be captured.

11.10 Safety Oversight

The NIAID Intramural DSMB includes independent experts that do not have direct involvement in the conduct of the study and have no significant conflicts of interests as defined by NIAID policy. The DSMB will review the study prior to initiation and twice a year thereafter. The DSMB may convene additional reviews as necessary. The DSMB will review the study data to evaluate the safety, efficacy, study progress, and conduct of the study. All SAEs and all UPs will be reported by the PI to the DSMB at the same time they are submitted to the IRB. The PI will notify the DSMB of any cases of intentional or unintentional unblinding as soon as possible. The PI will notify the DSMB at the time halting criteria are met and obtain a recommendation concerning continuation, modification, or termination of the study. The PI will submit the written DSMB summary reports with recommendations to the IRB.

12 Site Monitoring Plan

As per International Conference on Harmonization (ICH) Good Clinical Practice (GCP) 5.18, clinical protocols are required to be adequately monitored by the study sponsor. Monitors under contract to the Office of Clinical Research Policy and Regulatory Operations (OCRPRO)/NIAID will visit the clinical research site to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents and documentation of the informed consent process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare abstracted information with individual subjects' records and source documents (subjects' charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections-OHRP), and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make study documents (e.g., consent forms) and pertinent hospital or clinical records readily available for inspection by the local IRB, the site monitors, and the NIAID staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the Principal Investigator and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status and regulatory obligations.

13 Statistical Considerations

13. 1 Study Hypotheses

The primary purpose of this study is to learn about the pharmacokinetics of *Loa loa* MF after treatment with different doses of imatinib. Since this drug has not been studied in patients with *Loa loa* microfilariae before (except one patient, see the next section), the data from this study will help to get an idea about how the drug affects the *Loa loa* microfilariae over time. An important issue is how fast the *Loa loa* MF are killed in the blood in the short term, since rapid killing can lead to safety issues when the baseline *Loa loa* MF count is large (much greater than the upper bound of the inclusion criteria of 2500 MF/mL). Another issue is the longer term kinetics, since we want to *Loa loa* MF to be killed slowly.

13.2 Sample Size Justification

This is a pilot study to help in designing a follow-up study. Currently, only one patient with Loa loa parasite infection has gotten imatinib. That patient received a 600mg dose and had no severe adverse events [23]. The MF/ml measurements were 2250 MF/ml (day 0), 719 (day 4), 150 (day 6), and 392 (day 11). In terms of the percent reduction from baseline the values are 68% reduction (day 4), 93% (day 6) and 83% (day 11). In this one patient, the drug showed promise because it reduced the MF/ml values, but they did not reduce as quickly as ivermectin or DEC (70-100% day 1). Because it is only one patient, we have no data on subject-to-subject variability. The sample sizes of 5 on the three dose groups (doses 200mg, 400mg, and 600mg) will allow for estimation of variability across subjects and at different doses. It will also give better estimates on the effect of the dose over time in the population.

In terms of safety, if there is a SAE that occurs in 37% of the population, then we have a 90% probability of seeing one subject with that event in a group of size 5. If the rate of SAEs in the population is 14%, then we have a 90% probability of seeing one subject with that event in a group of size 15 (the total number of subjects that got any dose).

13.3 Final Analysis Plan

<u>Study Endpoints</u>
Primary:
Percent of baseline *Loa loa* microfilariae as determined by concentrated peripheral blood smear. Daily measurements will be taken the first week,

followed by measurements at day 14, day 21, day 28 (month 1), and 3 months (and if needed 6 and 12 months).

Secondary:

1. Tables of AEs by treatment group including grades of AEs, as defined by CTCAE v5.0
2. Percent of baseline *Loa loa* microfilariae over time (up to 12 months).

One of the primary pre-specificed safety concerns with treatment of *Loa loa* is rapid killing of the *Loa loa* MF in patients with high baseline *Loa loa* MF. We begin with a linear model on a log transformation of the primary endpoint, with different effects over time for the different dose groups. We include a baseline subject effect for each subject, so that we are primarily modeling the percent reduction from baseline. A sandwich estimator of variance will be used to account for the within subject correlation. The longer term effects of the drug are also of interest. Since imatinib has not been given in *Loa loa* patients before we will allow flexibility in model building. We will likely start with a linear model on the log10(percent of baseline *Loa loa* MF) with time as a linear factor and effects for dose. We may explore other linear models on the same response using segmented line regression with possible dose by time interactions. These models will help inform any further studies of imatinib in the treatment of *Loa loa*.

Exploratory Analyses:

The exploratory objective for this study is to assess laboratory abnormalities associated with potential killing of *Loa loa* microfilariae. We may build some generalized linear models at different points in time to see if the log of the proportion of baseline *Loa loa* MF (or some other transformation of those MF levels) are predictive of different laboratory values. Care will be taken so that the final model does not overfit the data, or that the variability of the final results properly account for the model building process. As an example of the latter, we could run a boostrap procedure that repeats the model selection process and gives a proportion of the bootstrap data sets that predict certain effects.

Handling of Missing and Spurious Data:

For the AE analyses, every effort will be made to prevent missing data. Because the treatment is only one dose, if a subject drops out after getting treatment, the subject will be encouraged to continue to report AEs for the duration of time that they would have remained in the study.

For the percent change of MF analyses, if some responses are missing, then there are two approaches. (1) If the cause of the missingness is likely to be unrelated to the response, the we will simply remove that subject from the analysis. (2) If the cause of the missingness is probably related to the response, and there are a substantial number of missing values, then we will run some sensitivity analyses, where the missing response is replaced by either (i) the best response (in terms of making the treatment look efficacious), or (ii) the worst response, or (iii) some intermediary predicted response. These sensitivity

analyses will give a range of possible values for what the result would have been if there had been no missingness.

13.4 Planned Interim Analyses

The purpose of the interim analysis is to determine if, after all subjects have had treatment and their 3-month visit, it is likely that any future 6- and 12-month visits will give us information that is useful enough to be worth the effort of collecting that data.

Such long-term follow-up will be useful if, in a substantial portion of subjects, the effects of imatinib continue to be active after 3 months. A suspected trajectory of the effect of a single dose of imatinib is that the MF counts will decrease to a nadir, and then climb up again, indicating that the imatinib is no longer active. We will assume it is useful to continue following subjects if by the 3-month visit more than 2 subjects who received imatinib (out of the total of 15) have not apparently reached their nadir yet.

A subject will be said to have reached their nadir by 3 months if the following occurs:

- a reduction of MF to less than 20% of pre-treatment levels is subsequently followed by a MF rise to or above 40% of pretreatment levels;
- however, if after the MF dropping to 20% of pretreatment levels, then rising to 40% there is at least 1 MF count below 40% of pre-treatment levels and the trend appears decreasing, then the subject will be considered to not have reached their nadir. A decreasing trend is defined as a slope of less than 0 of the least squares fit line predicting MF count over time, based only on the MF counts from the first MF count at or above 40% of pre-treatment levels until the MF count at the 3-month visit.

The interim analysis will occur after the last enrolled subject has had his or her 3-month visit, but before that subject had his or her 6-month visit. Because the biostatistician and the pharmacist are the only 2 unblinded members of the research team, they will be the only 2 members able to help with the performance of these interim analyses. All other study members will remain blinded until the study end.

13.5 Safety Analysis

The safety analysis will be primarily descriptive, listing tables of AEs. Of particular concern are safety events possbibly related to imatinib or reactions to microfilarial death.

14 Ethics/Protection of Human Subjects

14.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an on-going conversation between the human research subject and the researchers which begins before consent is given and continues until the end of the subject's involvement in the research. Discussions about the research will provide essential information about the study and include: purpose, duration, experimental procedures, alternatives, risks and benefits. Subjects will be given the opportunity to ask questions and have them answered.

Consent will be administered in French and explained in the subject's local dialect. The subjects will sign two copies of the informed consent document prior to undergoing any research procedures, one which they will retain and the other will be kept with the study. The researcher will document the signing of the consent form in the subject's medical record. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The subjects may withdraw consent at any time throughout the course of the trial.

14.2 Subject Confidentiality

All records will be kept confidential to the extent provided by federal, state and local law. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. Records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, [the FDA], the NIAID, the OHRP, or the sponsor's designee.

15 Data Handling and Record Keeping

15.1Data Capture and Management

Study data will be maintained in CRFs and collected directly from subjects during study visits and telephone calls, or will be abstracted from subjects' medical records. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary to confirm the data abstracted for this study. Data entry into RedCap/DataFax electronic database will be performed by authorized individuals. The Investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner.

15.2 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH GCP Guideline. Study records will be maintained by the PI in accordance with CFR 312.62 and in compliance with institutional, IRB, state, and federal medical records retention requirements, whichever is longest. All stored records will be kept confidential to the extent required by federal, state, and local law.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator will provide written notification of such intent to OCRPRO/NIAID with the name of the person who will accept responsibility for the transferred records and/or their new location. Destruction or relocation of research records will not proceed without written permission from OCRPRO/NIAID.

The consent will be administered in French by a local team member. Participant will sign or mark with an "X" on 2 copies, and will retain one for themselves and one will be kept on permanent record.

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Appendix A: Schedule of Evaluations

Evaluation	Screening (-14 to -1 days)	Baseline (Day 0)	D1	D2	D3	D4	D5	D6	D7	D14	D21	D28	3 Mo (D84-98)	6 Mo	12 Mo
Medical/Medication History	X	X	X												
Clinical Assessment (including symptom assessment)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Targeted Physical Exam	X	X	X	X	X	X	X	X	X	X	X[a]	X[a]	X[a]	X[a]	X[a]
Informed Consent	X														
CBC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
WBC differential		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatic panel (ALT, AST, Alk phos, bilirubin)	X	X	X			X			X						
Chemistry (Sodium, potassium, creatinine)	X	X	X			X			X						
Urinalysis		X	X	X	X	X	X	X	X						
Concentrated blood smear for MF and/or calibrated thick smear	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Imatinib drug level		X[c]	X[d]												
Ov16/WB123 IgG4 serology (for *O. volvulus/W.bancrofti*)	X														
Blood spot	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection[b]		X											X	X	X
Stool collection[b]		X											X	X	X
Serum collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Alk phos = alkaline phosphatase; ALT = alanine transaminase; AST =aspartate transaminase; CBC = complete blood count;; D = day; Mo = month; MF = microfilariae; PCR = polymerase chain reaction; WBC = white blood cell; X = to be performed.

a Only performed if the subject indicates symptoms.
b Optional (subjects not required to give these samples to remain in study).
c 2-4 hours post imatinib/placebo dose.
d 24 hours postdose.

Appendix B: Blood Volumes for Specimen Collection

Evaluations	**Study Schedule**														
Visit	**Screening**	**Baseline 01**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12 3 Month Follow up[1]**	**13 6 Month Follow-up[5]**	**14 12 Month Follo w-up[5]**
Week of Study	-2 to -1	Wk 0	W1	W1	W1	W1	W1	W1	W1	W2	W3	W4	W13 (12-14)	W26	W52
Day of Study	-14 to -1	[4]D 0	D1	D2	D3	D4	D5	D6	D7	D14	D21	D28	91 (84-98)	~D178	D 365
Clinical															
CBC	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Chemistry/LF	4	4	4			4			4						
MF smear	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Ov16/Wb123	<1														
Research															
Blood spot		1	1	1	1	1	1	1	1	1	1	1	1	1	1
Serum storage	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Imatinib blood level	0	2	2												
[2]**Daily Volume (mL)**	10	13	13	7	7	11	7	7	7	7	7	7	7	7	7
[3]**Cumulative Volume (mL)**	10	23	36	43	50	61	68	75	86	93	100	107	114	121	128

[1] 3 months (+/- 1 week) following imatinib administration
[2]Per NIH MEC Policy M95-9, maximum blood volumes drawn for *research purposes* for *pediatric* subjects: no more than 5 mL/kg in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period. Exceptions to this policy shall be approved by the IRB.
[3]Per NIH MEC Policy M95-9, maximum blood volumes drawn for *research purposes* for an *adult* subject (aged 18 years or older) may not exceed: 10.5 mL/kg or 550 mL, whichever is smaller, over any eight week period. Exceptions to this policy shall be approved by the IRB.
[4] Day 0 evaluations are the baseline for subsequent safety assessments.
[5] Follow up visit can be conducted any day of that month following enrollment.

Appendix C: Symptom/signs assessment

Symptom	Yes/No		Date started	Date ended	Description
Nausea	Y	N			
Vomiting	Y	N			
Headache	Y	N			
Fatigue	Y	N			
Joint Pain	Y	N			
Muscle Pain	Y	N			
Muscle Cramps	Y	N			
Edema, facial	Y	N			
Edema, extremity	Y	N			
Rash or Hyperpigmentation	Y	N			
Mouth ulcers	Y	N			
Decreased appetite	Y	N			
Fever	Y	N			
Rhinorrhea	Y	N			
Pruritus	Y	N			
Difficulty breathing	Y	N			
Dizziness	Y	N			
Fecal incontinence	Y	N			
Urine incontinence	Y	N			
Confusion	Y	N			