**Cover Sheet**

***Clinicaltrials.gov ID NCT03459794***

**Ivermectin and human immunity**

Protocol ID#STUDY00005069

| | | | |
|---|---|---|---|
| PI: | Adrian Wolstenholme | Primary Contact: | Adrian Wolstenholme |
| Submission Type: | Initial Study | | |
| IRB Coordinator: | Brooke Harwell | Parent Protocol: | |
| **Review Category:** | | | |
| **Approved Date:** | 9/27/2017 | | |
| **Expiration Date:** | 7/11/2018 | | |

a component of GeaR OVPR eResearch Portal

Date: Monday, November 26, 2018 12:06:50 PM

Print Close

View: SF: Basic Information UGA v2

# Section 1 - Basic Information

| | | |
|---|---|---|
| 1. | * **Title of Study:**<br>**The effects of ivermectin on the normal human immune system** | If the study is/will be funded, the IRB recommends matching the title in the funding proposal. |
| 2. | * **Short Title:**<br>Ivermectin and human immunity | This can match the long title or be shortened if your project uses an acronym or nickname; however, all system generated lists, searches, and documents (including approval letters) will show the short title. |
| 3. | **Principal Investigator (faculty or senior staff only - see help):**<br>Adrian Wolstenholme | Only UGA faculty and selected staff members (senior staff) are eligible to serve as PI. See the policy for more information: http://research.uga.edu/documents/eligibility |
| 4. | * **Does the Principal Investigator have a financial interest related to this research?** ○ Yes ◉ **No** | See the policy for more information: https://research.uga.edu/docs/policies/compliance/hso/PP_Financial%20Conflicts%20of%20Interests.pdf |
| 5. | * **Are you requesting determination if your project meets the definition of human subjects research?** ○ Yes ◉ **No**<br><br>**Are you requesting determination if your project meets the criteria for developmental review?** ○ Yes ◉ **No**<br><br>**Will an external IRB act as the IRB of record for this study?** ○ Yes ◉ **No** | If you are not sure if your project needs IRB review, choose "Yes" in the first question. A form will open and provide prompts to guide you through an initial assessment to see if your project needs IRB review.<br><br>If you are seeking external funding and the sponsor or the Office for Sponsored Programs requests for IRB approval but you are not ready to create materials for the human subject research activities, choose "Yes" in the second question. A form will open and provide prompts to guide you through an initial assessment to see if you can receive a letter from the IRB without completing a full submission for review.<br><br>If you are collaborating with other institutions and the collaboration model involves review by a central IRB, and UGA is not the lead institution, choose "Yes" on the third question. Be prepared to submit information that the other IRB will review. |

View: UGA SF: Project Funding Details

Project Funding Details

**1.0** ***Mark all that apply:*** **Identify below if the study is/will be supported in whole or in part. If the funding has not been awarded yet, mark pending. Check all that apply. If you have not applied for funding or have no plan to at the time of initial submission, mark "No Funding" and continue to the next page. If you will or have applied for funding, choose Externally Funded or Internally Funded depending on the source (see Help on right.) If the funding has not been awarded yet, mark "Pending." Finally, indicate whether UGA is/will be the prime awardee or a sub-award/contract.**

Funding Status:

- ☐ No Funding
- ☐ Externally Funded
- ☑ **Internally Funded**
- ☐ Pending
- ☐ Primary Awardee is UGA
- ☐ Sub-Award or Sub-Contract to UGA

Internal sources include UGA departments or institutes. External sources may be federal agencies (e.g., NIH, NSF), industry sponsors (e.g., Novartis), or private sponsors (e.g., Bill and Melinda Gates Foundation.)

**2.0** **Identify each funding source. If you have more than one, add each separately. If the sponsor agency is not in the selection list, choose TBD and identify the source in Q5. The Grants Office ID number is required: this is the Grants Portal Project ID (FP000XXXX) or Award ID (AWD000XXXX.)**

| Funding Source | Sponsor's Funding ID | Grants Office ID | Attachments |
|---|---|---|---|
| Clinical & Translational Research Unit | | | CTRU Seed Grant RFP FY18.docx |

The IRB must review any funding proposal, contract, or sub-contract for congruence with the description of human subjects activities described in this submission. The funding proposal or draft contract must be provided.

**3.0** **Name of Project and/or Project PI if different from this IRB submission.**

**4.0** **Describe the scope of this IRB submission compared to the grant proposal (sub-award or statement of work) related to this project.**

Scope of Application:

- ☑ **All human subjects activities in the grant proposal are covered in this IRB Application.**
- ☐ Not all human subjects activities in the grant proposal are covered in this IRB Application; however, these activities will be covered in future UGA IRB Application(s).
- ☐ Not all human subjects activities in the grant proposal are covered in this IRB Application; however, these activities have been covered in another UGA IRB Application. Identify the UGA PI (if different from PI of this IRB Application) and the IRB Project Number below.
- ☐ Not all human subjects activities in the grant proposal are covered in this IRB Application; however, these activities have been or will be reviewed by another institution's IRB. Identify the PI and name of the other institution below.
- ☐ Other, please explain.

**5.0** **Provide any additional information as requested above.**
**This submission is associated with an application to the CTRU Seed Funding Program.**

View: UGA SF: Study Team Members

Study Team Members

**1.0**

**Identify each UGA faculty, staff, or student who will be engaged in the conduct of human research. Do not select the PI again.**

| | Name | Roles | Financial Interest | Involved in Consent | E-mail | Phone | IsStudentProject |
|---|---|---|---|---|---|---|---|
| View | Maisie Anderson-Frost | RESEARCH COORDINATOR | no | yes | Maisie.AndersonFrost@uga.edu | 706-713-2722 | |
| View | ROBERT CAPITANO | RESEARCH COORDINATOR | no | yes | salvator@uga.edu | 706-713-2722 | no |
| View | KRISTIN Capitano | RESEARCH COORDINATOR | no | yes | capitano@uga.edu | 706-713-2722 | no |
| View | STEPHANIE CROYLE | RESEARCH COORDINATOR | no | yes | scroyle@uga.edu | 706-713-2732 | no |
| View | Jennifer Dunlop | RESEARCH COORDINATOR | no | no | jdunlop@uga.edu | 706-713-2722 | |
| View | TEJAL HILL | RESEARCH COORDINATOR | no | yes | tejalh@uga.edu | 706-713-2722 | |
| View | Jonathan Murrow | CO-INVESTIGATOR | no | yes | jmurrow@uga.edu | 706-542-4378 | no |
| View | Barbara Reaves | CO-INVESTIGATOR | no | no | bjreaves@uga.edu | 706-542-6516 | no |
| View | ANGELIA ROGERS | RESEARCH COORDINATOR | no | yes | alorrain@uga.edu | | |
| View | Kimberly Schmitz | RESEARCH COORDINATOR | no | yes | schmitzk@uga.edu | 706-713-2722 | no |

**2.0**

**Identify non-UGA collaborators* who will be engaged in the conduct of human research.**

| Name | Email | Organization |
|---|---|---|
| There are no items to display | | |

**Submit an Individual Investigator Agreement for all study personnel with an institution that does not have an assurance with the Office for Human Research Protections or OHRP (typically, local schools, private doctors, clinics).*

**For study personnel who are affiliated with an institution that has an assurance (has its own IRB), do not submit an Individual Investigator Agreement. Instead indicate that you have an External Site on the Study Scope page.*

If the collaborator has not completed human subjects research training, contact your business department to get a UGA MyID for them. Note: The Individual Investigator Agreement is not required for projects that will be submitted for Exempt determination (see Study Scope page).

View: UGA SF: CITI Training Records

Study Team Members CITI Training Records

**1.0**

**Principal Investigator (PI):** Adrian Wolstenholme

**Job Title:** PROFESSOR

*Please note: The training records update three times daily. Depending on when the course is completed or updated, the record may not be uploaded until 24 hours later.*

**PI CITI Courses:**

| Stage | Group | Date Taken | Expiration Date |
|---|---|---|---|
| 1 - Basic Course | Bio-Medical Research | 6/7/2012 | 6/7/2017 |
| 2 - Refresher Course | Bio-Medical Research | 7/3/2017 | 7/3/2022 |

If a record does not display for someone that has completed training, try removing/deleting that person and adding them again on the Basic Info page (PI) or Study Team Member page.

**2.0**

**Study Team Members:**

| Person | Group | Stage | Expiration Date |
|---|---|---|---|
| Maisie Anderson-Frost | Bio-Medical Research | 1 - Basic Course | 10/19/2022 |
| ROBERT CAPITANO | Social & Behavioral Research | 1 - Basic Course | 3/1/2022 |
| | Bio-Medical Research | 1 - Basic Course | 5/12/2021 |
| KRISTIN Capitano | Bio-Medical Research | 1 - Basic Course | 2/18/2021 |
| STEPHANIE CROYLE | Bio-Medical Research | 1 - Basic Course | 6/21/2021 |
| Jennifer Dunlop | Bio-Medical Research | 1 - Basic Course | 12/14/2021 |
| TEJAL HILL | Social & Behavioral Research | 1 - Basic Course | 5/28/2020 |
| | Social & Behavioral Research - Prisoners | 1 - Basic Course | 5/28/2020 |
| | Bio-Medical Research | 1 - Basic Course | 10/24/2022 |
| Jonathan Murrow | Bio-Medical Research | 1 - Basic Course | 4/15/2019 |
| | IRB Members | 1 - Basic Course | 3/5/2023 |

If any study team member including the PI has either not completed training or has not linked previously-completed training to a valid UGAID, the record will show "There are no items to display".
The application will not successfully submit to the IRB if the training requirement is not met. Likewise, if training has expired and a refresher course has not been completed or the training will expire in less than 90 days, the application will not sucessfully submit to the IRB.

| Person | Group | Stage | Expiration Date |
|---|---|---|---|
| Barbara Reaves | Bio-Medical Research | 1 - Basic Course | 7/8/2019 |

| Person | Group | Stage | Expiration Date |
|---|---|---|---|
| ANGELIA ROGERS | Bio-Medical Research | 1 - Basic Course | 1/12/2021 |

| Person | Group | Stage | Expiration Date |
|---|---|---|---|
| Kimberly Schmitz | Social & Behavioral Research | 1 - Basic Course | 11/13/2018 |
| | Bio-Medical Research | 1 - Basic Course | 8/31/2020 |

SF

View: SF: Study Scope

# Study Scope

| | | |
|---|---|---|
| **1.0** | **Will you recruit or conduct the study at a non-UGA agency/institution /facility (i.e., referred to as an External Site) where you do not normally have research privileges?**<br>○ Yes ◉ **No** | Answer "Yes" if you will recruit from a local public or private school, medical practice, community agency/organization, or will conduct your procedures at any of these. |
| **2.0** | **Does the study do any of the following:**<br>▪ **Specify the use of an approved drug or biologic?**<br>▪ **Use an unapproved drug or biologic?**<br>▪ **Use a food or dietary supplement to diagnose, cure, treat, or mitigate a disease or condition?**<br>▪ **Use a food or dietary supplement only to evaluate the dietary supplement's effect on the structure or function of the body?**<br>◉ **Yes** ○ No | |
| **3.0** | **Does the study do any of the following:**<br>▪ **Evaluate the safety or effectiveness of a device?**<br>▪ **Use a humanitarian use device (HUD)?**<br>○ Yes ◉ **No** | |
| **4.0** | **Check all that apply:**<br>☐ Project is Exempt (see Help Text on right)<br>☐ Internet Research<br>☐ Research activities are limited to analysis of data<br>☐ Deception, concealment, or incomplete disclosure<br>☐ HIPAA (Protected Health Information)<br>☑ **Blood Sampling/Collection**<br>☐ Genetic Analysis<br>☐ DXA/X-Ray<br>☐ More than moderate Exercise<br>☐ Electrical Stimulation<br>☑ **Clinical Trial**<br>☐ Data/Tissue Repository | Be sure to mark the first box if the study may meet criteria for exemption. More information about exemption is available in the Policy and Procedure: Exempt Review in the Library or on the website at http://research.uga.edu/hso/irb-guidelines/ |

View: UGA SF: Drugs

Drugs

**1.0** **List all drugs, biologics, foods, and dietary supplements to be used in the study.**

| | Generic Name | Brand Name | Attachment Name |
|---|---|---|---|
| View | Ivermectin | STROMECTOL | stromectol_pi.pdf |

**2.0** **Will the study be conducted under any IND Numbers**

○ Yes ◉ **No**

**If so, identify each IND:**

| IND Number | IND Holder | Other Holder |
|---|---|---|
| There are no items to display | | |

**3.0** **If your study will not be conducted under an IND number, it must meet all of the following six criteria for an IND exemption. Carefully evaluate each criterion and check the box if it applies to your study.**

| |
|---|
| The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)). |
| The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug. |
| The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50). |
| The drug product is lawfully marketed in the United States. |
| The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product). |
| In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug. |

**4.0** **Attach files (such as IND or other information that was not attached for a specific drug).**

| | Document | Category | Date Modified |
|---|---|---|---|
| View | Exemption Criteria.docx(0.01) | Drug Attachment | 8/18/2017 |

View: UGA SF: Blood Sampling/Collection

Blood Sampling/Collection

| | | |
|---|---|---|
| **1.0** | **Choose the method(s) of blood collection.**<br>Venipuncture | |
| **2.0** | **For participants who are healthy, non-pregnant adults weighing at least 110 pounds:**<br>**Will blood be collected more than 2 times per week?**<br>◉ **Yes** ○ No<br>**Will the amount of blood drawn exceed 550 ml in an 8 week period?**<br>○ Yes ◉ **No** | If the answer to either question is "Yes", this project will be reviewed via committee at a convened meeting. |
| **3.0** | **For other adults and children:**<br>**Will blood be collected more than 2 times per week?**<br>○ Yes ◉ **No**<br>**Will the amount of blood drawn exceed the lesser of 50 ml or 3 ml/kg in an 8 week period?**<br>○ Yes ◉ **No** | If the answer to either question is "Yes", this project will be reviewed via committee at a convened meeting. |
| **4.0** | **Indicate the specific volume and frequency (or the schedule) of blood collection.**<br>Blood will be drawn immediately before subjects take an oral dose of ivermectin, then again 4 and 24 hours later. 30 mls of blood will be drawn on each occasion. Only healthy, non-pregnant adults weighing more than 110 pounds and less than 185 pounds will be recruited as donors | |
| **5.0** | **Describe the specific collection procedures, including the use of sterile techniques and adherence to standard laboratory safety practices.**<br>The blood samples will be collected utilizing standard procedures at the CTRU, utilizing all sterile equipment and adhering to standard lab safety practices | |
| **6.0** | **Personnel performing blood draws must have sufficient training and experience in conducting human blood sampling. Describe who will collect the blood and this person's experience/training in the specific blood collection procedures.**<br>Research nurses associated with the CTRU will collect the blood. CTRU nurses have extensive training and experience in phlebotomy. | |
| **7.0** | **If participants will be asked to fast prior to blood collection(s), describe how and when informed consent will be obtained prior to fasting.**<br>It is recommended that Stromectol be administered on an empty stomach, so participants will be asked to fast for two hours prior to the first blood draw. Informed consent will be obtained during the screening interview. | If consent is obtained without requiring the participant to sign a consent form, be sure to request for a waiver of the requirement to document informed consent on the Consent Process page. |
| **8.0** | **Describe why it is important to collect blood for this study, including the specific analysis that will be conducted on the blood samples.**<br>We are studying the effects of Stromectol on the human immune system, so blood is required for analysis of both cytokines and leukocyte gene expression following drug administration. Cytokines and chemokines will be determined using Luminex and a commercial kit. Leukocyte populations will be separated into peripheral blood mononuclear cells (PBMC) and polymorphonuclear cells (PMN) and RNA extracted for RNASeq analysis. We will also test the ability of the PBMC and PMN populations to attach to, and kill, Brugia malayi microfilariae. | The consent document should also describe the type of analyses that will be conducted and should specifically state whether or not the sample will be analyzed for HIV/AIDS. |
| **9.0** | **Describe the plan for disposition of any unused blood, including when and how unused samples will be disposed of.**<br>Unused blood will be disposed of by incineration as soon as practicable after the | If samples will be retained for future analyses, the future |

| | | |
|---|---|---|
| | cells have been isolated. | use must be described in the consent document and the additional/future use can be made optional via a tiered consent statement. |

View: UGA SF: Human Research Participants

Human Research Participants

**1.0** **Click "Add" to provide a general description of the targeted participants. See Help text on the right for definition of human subject.**

| | Targeted Population | Targeted Gender | Age or Age Range | Total Number / Range |
|---|---|---|---|---|
| View | Healthy adults from the General Population | None | 18-65 | 12 |

Human Subject: A living individual about whom an investigator obtains (1) data through intervention or interaction with the individual or (2) identifiable private information. NOTE: if you are not sure if your project involves human subjects, go back to the Basic Information page and request for a determination of human subjects research by answering "Yes" to the first question in Section 5.

Samples of targeted population responses: (e.g., healthy adults from the general population, children enrolled in an after-school program, adolescent females with scoliosis.)

If the target age is adults (in Georgia, it is acceptable to choose "18+" as the target age.

The "Total Number/Range" should include the anticipated number of those who will give consent but may fail screening (if research involves pre-screening participants) and other reasons for attrition (e.g., withdrawals or termination by researchers).

**2.0** **Identify the inclusion and exclusion criteria. If there are two or more targeted populations, identify eligibility criteria for each.**

**Inclusion Criteria:**
Weight over 110 pounds and under 185 pounds.

**Exclusion Criteria:**
Pregnancy or nursing mothers.
Immunosuppressed individuals.
Hypersensitivity to ivermectin, cellulose, starch, magnesium stearate, butylated hydroxyanisole, or citric acid powder (inert ingredients of Stromectol).
Lactose intolerance (Lactose present in placebo)
Recent (last 3 years) travel to West or Central Africa, or any othet country where onchocerciasis is present
Hepatitis/HIV
Liver or renal dysfunction
Currently taking any of the following medications (potential for drug interaction):
- Blood thinners such as Coumadin (warfarin) or aspirin
- Steroid medications (inhaled, oral or injection)
- Barbiturates
- Benzodiazepines such as Xanax or Klonopin

It is not necessary to list exclusion criteria as the opposite of inclusion criteria. Use these fields to narrow or refine the general description provided in Q1.

| | | |
|---|---|---|
| | - Valproic acid (Lithium)<br>- Calcium channel blockers<br>- Statins (cholesterol medication) | |
| **3.0** | **Describe how potential participants will be initially identified and how eligibility will be determined.**<br>Self-selection by reviewing recruitment materials; potential participants will call the CTRU to be screened to determine eligibility. Verbal consent for screening will be obtained as the first part of the interview. | Possible methods of identification include public record review, private medical or school record review. If individuals will self-select by reviewing the eligiblity criteria listed in the recruitment materials, state this. Or describe the process for screening by phone, in-person or e-mail, or review of records. |
| **4.0** | **If the research will exclude a particular gender or minority group, provide justification.**<br>N/A | When appropriate, provide citations or references to support the justification. |
| **5.0** | **Describe any incentive/compensation for participation.**<br>Participants will receive free parking at the CTRU, where blood will be drawn, and monetary compensation of $25 cash for each time they allow blood to be drawn, plus $25 for taking the drug, for a total of $100 if all parts of the study are completed. A light meal will be provided during the first visit to CTRU to compensate for fasting. | Indicate the form of incentive/compensation (e.g., monetary payment by check, gift card, services without charge, reimbursement for travel cost.) If offering extra class credit, describe the available non-research alternative of comparable time and effort. |

View: UGA SF: Vulnerable and/or Special Populations

Vulnerable and/or Special Populations

| | | |
|---|---|---|
| **1.0** | **Check any/all that apply.**<br>Population:<br>☐ Pregnant women, neonates, or fetuses.<br>☐ Prisoners<br>☐ Minors<br>☐ Mentally-disabled/cognitively-impaired/severe psychological disorders<br>☐ Physically-disabled<br>☐ Terminally ill<br>☐ Economically/educationally disadvantaged<br>☐ A specific group based on religion, race, ethnicity, immigration status, language, or sexual orientation<br>☑ **Students/Employees**<br>☐ Other (please describe) | If you are using a UGA student research pool and pool guidelines require an educational debriefing, please attach the debriefing to the supporting documents page and label it "Educational Debriefing". |
| **2.0** | **Provide justification for including the group(s) checked above in this particular study.**<br>It is possible that some of the participants may be students or employees of the university, possibly within the same department or lab as the investigator. | |
| **3.0** | **Describe the working relationship between any researchers and the participants, as applicable.**<br>It is possible that some of the participants may be graduate students or work in the same department as the investigators. | A working relationship may exist between a researcher and his/her own students or employees. |
| **4.0** | **Describe the safeguards to protect the rights and welfare of these participants and to minimize any possible coercion or undue influence.**<br>Minors or those with cognitive impairments will not be included. The amount of the payment is intended to compensate participants for their time, and not as an undue inducement to take part. We will attempt to recruit participants who do not have a working relationship with the investigators. | For example, assess the amount of payment and how/if it will present undue influence for the financially disadvantaged. For minors or people with cognitive impairment or educational disadvantage, describe how you will ensure participants' understanding of the study (e.g., by using advocatesduring the consent process). To mitigate a working relationship, consider use flyers to recruit participants instead of directly approaching your own staff or students. |

View: UGA SF: Recruitment Methods and Procedures

Recruitment Methods and Materials

| | | |
|---|---|---|
| **1.0** | **Will you recruit (invite) individuals to take part in your study?**<br>◉ **Yes** ○ No | Recruit means to provide information about the study and invite people to take part. Any study that involves interaction with subjects should have a well-defined recruitment process. If you answer "yes", you must submit materials below. |
| **2.0** | **Describe when, where, and how participants will be initially contacted.**<br>Study flyer has been uploaded and will be a main method of recruitment. It will be used in other methods of advertisement include advertising through the CTRU, posting to websites (including the CTRU website), social media, email communication including listservs, newspaper ads. Subjects will be invited to call or email study staff to determine eligibility. | Methods of recruitment could include, but are not limited to: In person, Phone call, flyers, brochures, bulletin boards, letters, social media, media advertisements (e.g., newspaper, radio, TV announcements), research pool project listing systems (e.g., SONA). |
| **3.0** | **Describe any follow-up recruitment (e.g. multiple attempts/contacts for the purpose of inviting someone to participate).**<br>Individuals will only be called more than once for the purpose of inviting them to participate if they have contacted us requesting more information and have not been successful at reaching us. Additional attempts to call them may be made if the first attempt was not successful and the required number of participants has not been reached. | |
| **4.0** | **Recruitment Materials: (add all to be seen or heard by subjects)** | Add all materials to be seen or heard by subjects. All file types are supported. |

| | Document | Category | Date Modified |
|---|---|---|---|
| View | Study ad edit.docx(0.04) | Recruitment Materials | 8/22/2017 |
| View | Screening Consent and phone script(5) | Recruitment Materials | 1/26/2018 |

View: UGA SF: Consent Process and Materials

Consent Process and Materials

**1.0 Select the applicable option(s) below to describe the consent process/es for this study.**

| | | |
|---|---|---|
| ☑ | **Informed consent will be obtained and documented** | **The consent process includes all elements of consent and participants will sign a consent document.** |
| ☑ | **Signatures will not be obtained on consent documents** | **Participants will not physically sign a document as part of the consent process.** |
| ☐ | Informed consent will not be obtained or some or all elements will be waived or altered | There will not be a consent process or the consent process will not include all elements of informed consent. |

If there are multiple consent processes (for different subject groups or for separate phases of data collection), you may mark more than one, as applicable. If the study involves deception or incomplete disclosure, indicate that consent will be waived or altered. For data collection via the Internet, indicate that participants will not sign consent documents.

**2.0 Describe how, where and when informed consent will be obtained from research participants.**

Consent will be obtained for fasting during the screening interview. Signed informed consent for other aspects of the study will be obtained at the time of the participant's first visit to CTRU.

Where one or more processes will be used (e.g., no signature for an online consent but signed forms for interviews of some survey participants), describe each process separately. If there are discrete subject groups (e.g., minors and adults), describe each process (e.g., parental permission, minor assent, adult consent) separately. See Policy and Procedure: Informed Consent Process for Research in the Library for additional guidance.

**3.0**

**Consent Forms:**

**Important Note:** The IRB strongly recommends the use of consent templates that are available on the consent materials page to ensure that all the elements of informed consent are included (per 45 CFR 116). If more than one consent document will be used, please name each accordingly.

**Refer to the following templates:**

Consent Template - Parental Permission Form
Policy and Procedure: Informed Consent Process for Research
Consent Template - Minor Assent
Consent Template - Consent Form (with signature)
Consent Template - Telephone Eligibility Screening Consent Script
Consent Template - Consent Cover Letter (no signature)
Consent Template - Consent Form for Use of Data Already Collected (Artifacts)

**Attach consent forms below:**

| | Document | Category | Date Modified |
|---|---|---|---|
| View | Consent form(7) | Consent Form | 2/6/2018 |

Guidance and policies and procedures for informed consent can be found in the IRB Library. _

View: UGA SF: Waiver of Requirements to Document Informed Consent

Waiver of Requirements to Document Informed Consent

| | | |
|---|---|---|
| **1.0** | **The IRB may waive the requirement to obtain a signed consent document for some or all subjects if it finds that the project meets one of the criteria below. Please choose the appropriate criterion.**<br>Criteria 2 | |
| **2.0** | **Provide supporting justification for requesting a waiver to document informed consent.**<br>We are simply asking participants to avoid eating solid food for two hours prior to the first visit, to ensure reproducible effects of the drug - which is recommended be given on an empty stomach. This is much less than the fasting required prior to annual medical exams for example and presents minimal risk. | |

View: UGA SF: Research Design, Methods and Procedures

Research Design, Methods and Procedures

| | | |
|---|---|---|
| **1.0** | **Brief Description (see Help)**<br>We hypothesize that ivermectin interacts with the human innate immune system and that this contributes to its anti-parasitic effects. Participants will donate blood before and after being administered the normal human dose of the drug. We compare the CBC and cytokine profile of the two samples, and measure any changes in gene expression in leukocyte populations 4 and 24hrs after the drug is taken. | Summarize the overall research question and the primary objectives.<br><br>If the project does not involve a systematic investigation (e.g., biography) or is not designed to contribute to generalizable knowledge (e.g., oral history, quality assurance), request for a determination of human subject research by answering "Yes" to the first question in Section 5 on the Basic Information page (first page of the submission). |
| **2.0** | **Research Design and Methods**<br>**Describe the overall research design and method(s) of data collection. Also, identify specific factors or variables and, if applicable, treatment and control conditions or groups.**<br>Subjects will visit the CTRU twice on consecutive days and blood will be drawn from them. On the first occasion they will be weighed and will complete the consent process. They will have been randomly assigned to the test (Stromectol) or control (placebo) group, with 8 participants in the test group and 4 participants in the control group. Stromectol will be obtained from a medical supply distributor and a placebo will be obtained through the UGA School of Pharmacy. Drugs will be prescribed by Jonathan Murrow MD. They will be stored in their original packaging at room temperature in a drug locker in the lab at CTRU. Participants will be identified by number and allocated to groups using a block randomization protocol. Randomization and drug dispensation will be done by CTRU. 18ml of blood will drawn in a fasting state and they will be administered 150 mcg/kg Stromectol or the equivalent number of placebo tablets immediately after blood is drawn. Participants will remain at CTRU for four hours after they take the drug, then another 15ml of blood will be drawn. On the second day they will attend CTRU at the same time and the third blood sample (18ml) will be drawn 24 hrs after administration of the drug. On each occasion the drawn blood will be coded by CTRU staff prior to being collected by a member of the Department of Infectious Diseases and taken to the laboratory (Wildlife Health G0007) for the isolation of leukocyte populations (peripheral monocytes, lymphocytes and polymorphonuclear cells (PMNs)) and for the preparation of serum. Complete blood counts will also be carried out. Sera will be analyzed on the Luminex for cytokine/chemokine content. RNA will be isolated from the cell populations for RNASeq analysis. | If groups or conditions will be assigned, specify the number of research participants that will be assigned to each condition or group. |
| **3.0** | **Duration of Participation and Study Timeline**<br>**Describe the time commitment per activity per individual subject and provide the estimated total duration of participation. If known, also describe the anticipated duration to enroll all study subjects and the estimated time until completion of primary analyses.**<br>Subjects will visit the CTRU twice in two days. On the first visit, they will have fasted for at least two hours. They will be asked to sign the consent form and will be weighed. They will donate blood, then take Stromectol at a dose of 150mcg/kg, or the placebo. After taking the drug, they will remain at the CTRU for four hours, then another blood sample will be drawn. On the second day they will attend CTRU at the same time (24 hrs after the first visit), when they will again donate blood. The first visit should last about 5 hrs and the second visit less than 1 hr. | |
| **4.0** | **Procedures**<br>**Describe in detail, and in sequence, all study procedures from the** | Practice is the exercise of an |

| | | |
|---|---|---|
| | **perspective of the participant. Begin with any procedure that involves interaction or collection of data to determine eligibility, if applicable. Separate any procedures that are part of regular practice from procedures that are specific to this research study. If procedures are long and complicated, use a table, flowchart or diagram to outline the study procedures.**<br>Participants will respond to an invitation to take part, either by phone or by responding to a posted flyer. After the screening interview, they will visit the CTRU two times within a 1-week period. They will receive a reminder with fasting instructions prior to their first visit. On the first visit, they will complete and sign the consent form and be weighed. They will then undergo a blood draw and then will take 3 or 4 tablets of Stromectol (ivermectin), depending on their weight. They will stay at the CTRU for the next four hours, and then another blood draw will be performed. On the second visit the following day, another blood draw will be performed. After this, or after they voluntarily withdraw from the study, they will receive $25 in cash for each blood sample they have donated, and $25 cash for taking the drug. | occupation or a profession; activities that are part of "practice" are conducted with all members of a population whether or not they consent to participate in research.<br><br>Research activities are voluntary, must follow a documented protocol, and are conducted under specific conditions in order to draw generalizable conclusions.<br><br>A project may use a combination of practice and research in order to reach desired objectives. |
| **5.0** | **Data Analysis**<br>**Describe the data analysis plan, including any statistical procedures. For qualitative studies, specify the proposed analytic approaches.**<br>Differences between the samples taken from individual participants will be assessed via ANOVA. Data will be stored on the principal investigator's computer, anonymously. RNASeq data will be deposited in a relevant database, as required by most journals and funding agencies; this will not be able to be linked to any study participant. RNASeq data will be analyzed using DESEQ2 or similar method to identify transcripts that are significantly altered in participants receiving the drug but not the placebo. | If data or specimens will be banked for future use, describe where/how these will be stored and accessed and how they may be used/analyzed. If analysis will be conducted by investigators outside UGA, be sure to include these sites and investigators in the corresponding submission forms. |

View: UGA SF: Data Collection Instruments and Measures

Data Collection Materials

**1.0**

**Click "Add" to list, describe, and attach all the materials that will be used to collect and record data/information for this study.**

| | Instrument Name | Instrument Description | Participant Groups who will Complete | Attachment |
|---|---|---|---|---|
| View | Data Spreadsheet | Record of CBC, Luminex and parasite killing data | Drs Reaves & Wolstenholme | data to be recorded.xlsx(0.01) |

Data Collection Materials may include, but are not limited to: surveys, interview guides/questions, questionnaires, focus group guides/questions, observation guides, bio-metric measure recording sheets. Do not list equipment such as audio/video-recording devices, EKG, Ultrasound.

View: UGA SF: Risks and Benefits

Risks and Benefits

| | | |
|---|---|---|
| **1.0** | **If there is collection of information that could place a participant at risk of criminal or civil liability or damage a participant's financial standing, employability, or reputation, mark any box(es) that apply below. If information to be collected is not sensitive, do not mark any. The list below is not exhaustive but represents common elements or procedures in research where the primary risk is potential harm associated with breach of confidentiality.**<br>There are no items to display | If the study includes collection of identifiable sensitive information (e.g., mental or physical health, drug/alcohol use, sexual identity or behaviors, religious beliefs or practices), then a breach of confidentiality may be the primary risk for participants. |
| **2.0** | **Describe in detail the nature and degree of risk and discomfort associated with participation. Address any items marked above in detail. Include any foreseeable physical risks, psychological harm, and/or privacy concerns that are associated with the procedures/interventions (See HELP on right.).**<br>The risks of drawing blood from the arm include the possibilities of a small bruise, infection, bleeding or lightheadedness/fainting.<br><br>In controlled clinical trials, the following laboratory adverse experiences were reported as possibly, probably, or definitely related to ivermectin in ≥1% of the patients: eosinophilia (3%) and hemoglobin increase (1%). The following adverse reactions have been reported since ivermectin was registered overseas: Hypotension (mainly orthostatic hypotension), worsening of bronchial asthma, toxic epidermal necrolysis, Stevens-Johnson syndrome, seizures, hepatitis, elevation of liver enzymes, and elevation of bilirubin.<br><br>The Mazzotti-type and ophthalmologic reactions associated with the treatment of onchocerciasis or the disease itself would not be expected to occur in uninfected people; this disease is not endemic to the USA. | Assess risk and discomfort associated with all study procedures including access to and use of identifiable information or specimens. Consider the procedures described on the Research Design, Methods and Procedures page, the recruitment process, and the study consent process when assessing privacy concerns. |
| **3.0** | **Describe the measures that will be taken to minimize each of the potential risks and discomforts identified in questions 1 and 2.**<br>Nurses at the CTRU are well trained in sterile venipuncture procedure and care is taken to minimize bruising, fainting and other adverse incidents related to venipuncture. Participants will remain at the CTRU for four hours after taking the drug, which will allow monitoring of any unforeseen adverse events. | Measures to mitigate risk associated with breach of confidentiality (if any are identified in Q1) include limiting collection and/or retention of identifers provided with data, or using coding procedures to replace direct identifiers with codes/pseudonyms. Lab safety protocols, appropriate eligibility criteria, and monitoring for safety may be measures to mitigate physical and psychological risk. Privacy concerns can be addressed by allowing people to control the nature of information they give, the time and place where study procedures take place, the things they are required to do, and who has access to their identifiable inforamation. For |

| | | |
|---|---|---|
| | | example, people may want to be weighed in a private location. |
| **4.0** | **Describe any anticipated direct benefits to participants. If there are none, please state so.**<br>None | |
| **5.0** | **Describe any anticipated benefits to others (e.g., societal) that may result from the research. Describe the generalizable or transferable knowledge that may result.**<br>Ivermectin is a crucially important drug in programs to globally eliminate human filarial diseases. A better understanding of how it interacts with the human innate immune system may aid in the design and implementation of those programs, or lead to novel approaches to the development of new treatments to improve their efficacy. | The IRB must determine that benefits outweigh risks in order to approve research. If there is no or little risk, there can be fewer anticipated benefits.This response must match the study consent document, if applicable. |

View: UGA SF: Confidentiality and Privacy

Confidentiality and Privacy

| | | |
|---|---|---|
| **1.0** | **Will the researchers collect or record any direct identifiers with the data (e.g., names, addresses, telephone numbers)?**<br>○ No. Skip to Q5<br>◉ **Yes. Complete Q2-4** | If the research activities are limited to analysis of de-identified datasets or specimens, request for a determination of human subject research by answering "Yes" to the first question in Section 5 on the Basic Information Page (the first page of the submission.)<br><br>For no risk studies or studies where sensitive information are not obtained, it is acceptable to use direct identifiers. However, if there is potential risk associated with a breach of confidentiality, consider utilizing a coding procedure to replace direct identifiers with codes or unique study IDs. |
| **2.0** | **Indicate which of the direct identifiers below will be collected or included with the data:**<br>☐ Audio-Recordings of Participants<br>☐ Postal Address<br>☑ **Email Addresses**<br>☐ Videos of Participants<br>☑ **Telephone Numbers**<br>☐ Photographs of participant in which he/she is identifiable<br>☐ Full Names | |
| **3.0** | **Will the researchers retain direct identifiers after data collection is complete?**<br>○ Yes ◉ **No** | |
| **4.0** | **If the answer to Q3 is yes, why is it necessary to retain direct identifiers after completion of data collection?** | |
| **5.0** | **Will the researchers use a coding system and/or will the data be collected via the Internet?**<br>◉ **Yes** ○ No | Data collection methods via the Internet include, but are not limited to: online data collection host/tool such as Qualtrics or SurveyMonkey, social media. websites. |
| **6.0** | **Describe the coding system that will be used to link the code (pseudonym or study ID) to the participant (e.g., code key or master list). If data are collected via the Internet, describe what indirect identifiers may be collected (e.g., IP addresses).**<br>A random code will be allocated to each participant by the CTRU, but this system will not be divulged to the investigators. Each sample will have a randomly generated numerical code. At the end of the study, the sample numbers corresponding to each participant, but not the participants' identity, | Many Internet hosts/tools offer a way for investigators to have IP addresses stripped before data are downloaded by the researcher. If this is |

| | | |
|---|---|---|
| | will be revealed to the investigators. | available, the IRB suggests using such tools. If this is not available, or not utlized, be sure to acknowledge that IP addresses may be included in the data and provide resonses to Q7-9. |
| **7.0** | **If a coding system is used or data are collected via the Internet, will the link/indirect identifier be retained after data collection is complete?**<br>○ Yes ◉ **No** | |
| **8.0** | **If the answer ty Q7 is yes, why is it necessary to retain the link/indirect identifier?** | Common reasons to retain a link include but are not limited to: multiple data sources, data collected over multiple timepoints. |
| **9.0** | **Describe how long the direct/indirect identifiers or the link will be retained, where and how this information will be stored, and what security provisions will be taken to protect the data. If information that associates a person with his/her data will be retained after data collection is complete, all potential uses of this information must be described here and in the consent documents.**<br>No direct identifiers will be collected with the data, only to generate study IDs and send reminders. The link between identifiable information and study IDs will be retained only long enough for data collection. This link will be kept password-protected on secure servers, only accessible by CTRU staff. | If there is risk associated with a breach of confidentiality, the IRB recommends that direct identifiers or links between the participant and his/her data be destroyed at the earliest point possible congruent with the research design and plans for analysis. Note: For non-Exempt research, if the study involves minors and identifiable data will continue to be used/analyzed after the minor becomes an adult (18 in Georgia), consent must be obtained from the now-adult participant even if parental permission and assent were previously obtained. |
| **10.0** | **Is it reasonable foreseeable that the study will collect or be privy to information that State or Federal law requires to be reported to other officials (e.g., child or elder abuse) or ethically might require action by the research (e.g., suicidal ideation, intent to hurt self or others)? If "Yes", this must be described in the the consent documents.**<br>○ Yes ◉ **No** | If the investigator does not have a mandate to report such information, but the investigator will voluntarily breach confidentiality to report such matters, this must be declared here and in the study consent documents. |

View: UGA SF: Supporting Documents

Supporting Documents

**1.0 Attach supporting documents and any other study-related materials not specifically requested on previous sections.**

| | Document | Category | Date Modified |
|---|---|---|---|
| View | Fasting Instructions for Participants.docx(1) | Other | 9/14/2017 |

View: SF: Final Page

# Final Page

You have reached the end of the IRB submission form. When you are ready to submit to the IRB, follow the next steps carefully:

1. Click **Hide/Show Errors** to check for missing information. Address any errors.

2. Click **Finish** to exit the form.

3. **Important!** If you are the PI, click **Submit** on the next page. If you are not the PI, click **Notify PI to Submit** to send an e-mail to the PI indicating that the submission is ready to send to the IRB.

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

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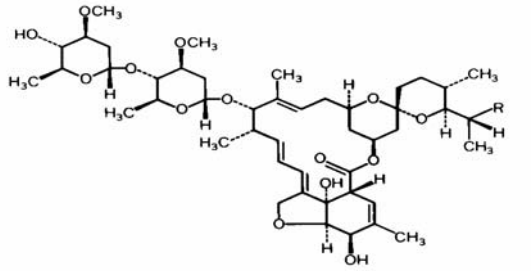
TABLETS

# STROMECTOL®

## (IVERMECTIN)

### DESCRIPTION

STROMECTOL* (Ivermectin) is a semisynthetic, anthelmintic agent for oral administration. Ivermectin is derived from the avermectins, a class of highly active broad-spectrum, anti-parasitic agents isolated from the fermentation products of *Streptomyces avermitilis.* Ivermectin is a mixture containing at least 90% 5-*O*-demethyl-22,23-dihydroavermectin $A_{1a}$ and less than 10% 5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)avermectin $A_{1a}$, generally referred to as 22,23-dihydroavermectin $B_{1a}$ and $B_{1b}$, or $H_2B_{1a}$ and $H_2B_{1b}$, respectively. The respective empirical formulas are $C_{48}H_{74}O_{14}$ and $C_{47}H_{72}O_{14}$, with molecular weights of 875.10 and 861.07, respectively. The structural formulas are:



Component $B_{1a}$, R = $C_2H_5$ Component $B_{1b}$, R = $CH_3$

Ivermectin is a white to yellowish-white, nonhygroscopic, crystalline powder with a melting point of about 155°C. It is insoluble in water but is freely soluble in methanol and soluble in 95% ethanol.

STROMECTOL is available in 3-mg tablets containing the following inactive ingredients: microcrystalline cellulose, pregelatinized starch, magnesium stearate, butylated hydroxyanisole, and citric acid powder (anhydrous).

### CLINICAL PHARMACOLOGY

*Pharmacokinetics*

Following oral administration of ivermectin, plasma concentrations are approximately proportional to the dose. In two studies, after single 12-mg doses of STROMECTOL in fasting healthy volunteers (representing a mean dose of 165 mcg/kg), the mean peak plasma concentrations of the major component ($H_2B_{1a}$) were 46.6 (±21.9) (range: 16.4-101.1) and 30.6 (±15.6) (range: 13.9-68.4) ng/mL, respectively, at approximately 4 hours after dosing. Ivermectin is metabolized in the liver, and ivermectin and/or its metabolites are excreted almost exclusively in the feces over an estimated 12 days, with less than 1% of the administered dose excreted in the urine. The plasma half-life of ivermectin in man is approximately 18 hours following oral administration.

The safety and pharmacokinetic properties of ivermectin were further assessed in a multiple-dose clinical pharmacokinetic study involving healthy volunteers. Subjects received oral doses of 30 to 120 mg (333 to 2000 mcg/kg) ivermectin in a fasted state or 30 mg (333 to 600 mcg/kg) ivermectin following a standard high-fat (48.6 g of fat) meal. Administration of 30 mg ivermectin following a high-fat meal resulted in an approximate 2.5-fold increase in bioavailability relative to administration of 30 mg ivermectin in the fasted state.

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* Registered trademark of Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.**

*In vitro* studies using human liver microsomes and recombinant CYP450 enzymes have shown that ivermectin is primarily metabolized by CYP3A4. Depending on the *in vitro* method used, CYP2D6 and CYP2E1 were also shown to be involved in the metabolism of ivermectin but to a significantly lower extent compared to CYP3A4. The findings of *in vitro* studies using human liver microsomes suggest that clinically relevant concentrations of ivermectin do not significantly inhibit the metabolizing activities of CYP3A4, CYP2D6, CYP2C9, CYP1A2, and CYP2E1.

*Microbiology*

Ivermectin is a member of the avermectin class of broad-spectrum antiparasitic agents which have a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

The selective activity of compounds of this class is attributable to the facts that some mammals do not have glutamate-gated chloride channels and that the avermectins have a low affinity for mammalian ligand-gated chloride channels. In addition, ivermectin does not readily cross the blood-brain barrier in humans.

Ivermectin is active against various life-cycle stages of many but not all nematodes. It is active against the tissue microfilariae of *Onchocerca volvulus* but not against the adult form. Its activity against *Strongyloides stercoralis* is limited to the intestinal stages.

*Clinical Studies*

*Strongyloidiasis*

Two controlled clinical studies using albendazole as the comparative agent were carried out in international sites where albendazole is approved for the treatment of strongyloidiasis of the gastrointestinal tract, and three controlled studies were carried out in the U.S. and internationally using thiabendazole as the comparative agent. Efficacy, as measured by cure rate, was defined as the absence of larvae in at least two follow-up stool examinations 3 to 4 weeks post-therapy. Based on this criterion, efficacy was significantly greater for STROMECTOL (a single dose of 170 to 200 mcg/kg) than for albendazole (200 mg b.i.d. for 3 days). STROMECTOL administered as a single dose of 200 mcg/kg for 1 day was as efficacious as thiabendazole administered at 25 mg/kg b.i.d. for 3 days.

Summary of Cure Rates for Ivermectin Versus Comparative Agents in the Treatment of Strongyloidiasis

| | Cure Rate* (%) | |
|---|---|---|
| | Ivermectin** | Comparative Agent |
| Albendazole*** Comparative | | |
| International Study | 24/26 (92) | 12/22 (55) |
| WHO Study | 126/152 (83) | 67/149 (45) |
| Thiabendazole† Comparative | | |
| International Study | 9/14 (64) | 13/15 (87) |
| US Studies | 14/14 (100) | 16/17 (94) |

* Number and % of evaluable patients
** 170-200 mcg/kg
*** 200 mg b.i.d. for 3 days
† 25 mg/kg b.i.d. for 3 days

In one study conducted in France, a non-endemic area where there was no possibility of reinfection, several patients were observed to have recrudescence of *Strongyloides* larvae in their stool as long as 106 days following ivermectin therapy. Therefore, at least three stool examinations should be conducted over the three months following treatment to ensure eradication. If recrudescence of larvae is observed, retreatment with ivermectin is indicated. Concentration techniques (such as using a Baermann apparatus) should be employed when performing these stool examinations, as the number of *Strongyloides* larvae per gram of feces may be very low.

*Onchocerciasis*

The evaluation of STROMECTOL in the treatment of onchocerciasis is based on the results of clinical studies involving 1278 patients. In a double-blind, placebo-controlled study involving adult patients with moderate to severe onchocercal infection, patients who received a single dose of 150 mcg/kg STROMECTOL experienced an 83.2% and 99.5% decrease in skin microfilariae count (geometric mean) 3 days and 3 months after the dose, respectively. A marked reduction of >90% was maintained for up to 12 months after the single dose. As with other microfilaricidal drugs, there was an increase in the microfilariae count in the anterior chamber of the eye at day 3 after treatment in some patients. However, at 3 and 6 months after the dose, a significantly greater percentage of patients treated with STROMECTOL had decreases in microfilariae count in the anterior chamber than patients treated with placebo.

In a separate open study involving pediatric patients ages 6 to 13 (n=103; weight range: 17-41 kg), similar decreases in skin microfilariae counts were observed for up to 12 months after dosing.

## INDICATIONS AND USAGE

STROMECTOL is indicated for the treatment of the following infections:

**Strongyloidiasis of the intestinal tract.** STROMECTOL is indicated for the treatment of intestinal (i.e., nondisseminated) strongyloidiasis due to the nematode parasite *Strongyloides stercoralis*.

This indication is based on clinical studies of both comparative and open-label designs, in which 64-100% of infected patients were cured following a single 200-mcg/kg dose of ivermectin. (See CLINICAL PHARMACOLOGY, *Clinical Studies*.)

**Onchocerciasis.** STROMECTOL is indicated for the treatment of onchocerciasis due to the nematode parasite *Onchocerca volvulus*.

This indication is based on randomized, double-blind, placebo-controlled and comparative studies conducted in 1427 patients in onchocerciasis-endemic areas of West Africa. The comparative studies used diethylcarbamazine citrate (DEC-C).

NOTE: STROMECTOL has no activity against adult *Onchocerca volvulus* parasites. The adult parasites reside in subcutaneous nodules which are infrequently palpable. Surgical excision of these nodules (nodulectomy) may be considered in the management of patients with onchocerciasis, since this procedure will eliminate the microfilariae-producing adult parasites.

## CONTRAINDICATIONS

STROMECTOL is contraindicated in patients who are hypersensitive to any component of this product.

## WARNINGS

Historical data have shown that microfilaricidal drugs, such as diethylcarbamazine citrate (DEC-C), might cause cutaneous and/or systemic reactions of varying severity (the Mazzotti reaction) and ophthalmological reactions in patients with onchocerciasis. These reactions are probably due to allergic and inflammatory responses to the death of microfilariae. Patients treated with STROMECTOL for onchocerciasis may experience these reactions in addition to clinical adverse reactions possibly, probably, or definitely related to the drug itself. (See ADVERSE REACTIONS, *Onchocerciasis*.)

The treatment of severe Mazzotti reactions has not been subjected to controlled clinical trials. Oral hydration, recumbency, intravenous normal saline, and/or parenteral corticosteroids have been used to treat postural hypotension. Antihistamines and/or aspirin have been used for most mild to moderate cases.

## PRECAUTIONS

*General*

After treatment with microfilaricidal drugs, patients with hyperreactive onchodermatitis (sowda) may be more likely than others to experience severe adverse reactions, especially edema and aggravation of onchodermatitis.

Rarely, patients with onchocerciasis who are also heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy either spontaneously or following treatment with an effective microfilaricide. In these patients, the following adverse experiences have also been reported: pain (including neck and back pain), red eye, conjunctival hemorrhage, dyspnea, urinary and/or fecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma. This syndrome has been seen very rarely following the use of ivermectin. In individuals who warrant treatment with ivermectin for any reason and have had significant exposure to *Loa loa*-endemic areas of West or Central Africa, pretreatment assessment for loiasis and careful post-treatment follow-up should be implemented.

*Information for Patients*

STROMECTOL should be taken on an empty stomach with water. (See CLINICAL PHARMACOLOGY, *Pharmacokinetics*.)

*Strongyloidiasis:* The patient should be reminded of the need for repeated stool examinations to document clearance of infection with *Strongyloides stercoralis*.

*Onchocerciasis:* The patient should be reminded that treatment with STROMECTOL does not kill the adult *Onchocerca* parasites, and therefore repeated follow-up and retreatment is usually required.

*Drug Interactions*

Post-marketing reports of increased INR (International Normalized Ratio) have been rarely reported when ivermectin was co-administered with warfarin.

*Carcinogenesis, Mutagenesis, Impairment of Fertility*

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of ivermectin.

Ivermectin was not genotoxic *in vitro* in the Ames microbial mutagenicity assay of *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 with and without rat liver enzyme activation, the Mouse Lymphoma Cell Line L5178Y (cytotoxicity and mutagenicity) assays, or the unscheduled DNA synthesis assay in human fibroblasts.

Ivermectin had no adverse effects on the fertility in rats in studies at repeated doses of up to 3 times the maximum recommended human dose of 200 mcg/kg (on a mg/m$^2$/day basis).

*Pregnancy, Teratogenic Effects*

*Pregnancy Category C*

Ivermectin has been shown to be teratogenic in mice, rats, and rabbits when given in repeated doses of 0.2, 8.1, and 4.5 times the maximum recommended human dose, respectively (on a mg/m$^2$/day basis). Teratogenicity was characterized in the three species tested by cleft palate; clubbed forepaws were additionally observed in rabbits. These developmental effects were found only at or near doses that were maternotoxic to the pregnant female. Therefore, ivermectin does not appear to be selectively fetotoxic to the developing fetus. There are, however, no adequate and well-controlled studies in pregnant women. Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.

*Nursing Mothers*

STROMECTOL is excreted in human milk in low concentrations. Treatment of mothers who intend to breast-feed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the newborn.

*Pediatric Use*

Safety and effectiveness in pediatric patients weighing less than 15 kg have not been established.

*Geriatric Use*

Clinical studies of STROMECTOL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, treatment of an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

*Strongyloidiasis in Immunocompromised Hosts*

In immunocompromised (including HIV-infected) patients being treated for intestinal strongyloidiasis, repeated courses of therapy may be required. Adequate and well-controlled clinical studies have not been conducted in such patients to determine the optimal dosing regimen. Several treatments, i.e., at 2-week intervals, may be required, and cure may not be achievable. Control of extra-intestinal strongyloidiasis in these patients is difficult, and suppressive therapy, i.e., once per month, may be helpful.

## ADVERSE REACTIONS

*Strongyloidiasis*

In four clinical studies involving a total of 109 patients given either one or two doses of 170 to 200 mcg/kg of STROMECTOL, the following adverse reactions were reported as possibly, probably, or definitely related to STROMECTOL:

*Body as a Whole:* asthenia/fatigue (0.9%), abdominal pain (0.9%)

*Gastrointestinal:* anorexia (0.9%), constipation (0.9%), diarrhea (1.8%), nausea (1.8%), vomiting (0.9%)

*Nervous System/Psychiatric:* dizziness (2.8%), somnolence (0.9%), vertigo (0.9%), tremor (0.9%)

*Skin:* pruritus (2.8%), rash (0.9%), and urticaria (0.9%).

In comparative trials, patients treated with STROMECTOL experienced more abdominal distention and chest discomfort than patients treated with albendazole. However, STROMECTOL was better tolerated than thiabendazole in comparative studies involving 37 patients treated with thiabendazole.

The Mazzotti-type and ophthalmologic reactions associated with the treatment of onchocerciasis or the disease itself would not be expected to occur in strongyloidiasis patients treated with STROMECTOL. (See ADVERSE REACTIONS, *Onchocerciasis*.)

*Laboratory Test Findings*

In clinical trials involving 109 patients given either one or two doses of 170 to 200 mcg/kg STROMECTOL, the following laboratory abnormalities were seen regardless of drug relationship: elevation in ALT and/or AST (2%), decrease in leukocyte count (3%). Leukopenia and anemia were seen in one patient.

*Onchocerciasis*

In clinical trials involving 963 adult patients treated with 100 to 200 mcg/kg STROMECTOL, worsening of the following Mazzotti reactions during the first 4 days post-treatment were reported: arthralgia/synovitis (9.3%), axillary lymph node enlargement and tenderness (11.0% and 4.4%, respectively), cervical lymph node enlargement and tenderness (5.3% and 1.2%, respectively), inguinal lymph node enlargement and tenderness (12.6% and 13.9%, respectively), other lymph node enlargement and tenderness (3.0% and 1.9%, respectively), pruritus (27.5%), skin involvement including edema, papular and pustular or frank urticarial rash (22.7%), and fever (22.6%). (See WARNINGS.)

In clinical trials, ophthalmological conditions were examined in 963 adult patients before treatment, at day 3, and months 3 and 6 after treatment with 100 to 200 mcg/kg STROMECTOL. Changes observed were primarily deterioration from baseline 3 days post-treatment. Most changes either returned to baseline condition or improved over baseline severity at the month 3 and 6 visits. The percentages of patients with worsening of the following conditions at day 3, month 3 and 6, respectively, were: limbitis: 5.5%, 4.8%, and 3.5% and punctate opacity: 1.8%, 1.8%, and 1.4%. The corresponding percentages for patients treated with placebo were: limbitis: 6.2%, 9.9%, and 9.4% and punctate opacity: 2.0%, 6.4%, and 7.2%. (See WARNINGS.)

In clinical trials involving 963 adult patients who received 100 to 200 mcg/kg STROMECTOL, the following clinical adverse reactions were reported as possibly, probably, or definitely related to the drug in ≥1% of the patients: facial edema (1.2%), peripheral edema (3.2%), orthostatic hypotension (1.1%), and tachycardia (3.5%). Drug-related headache and myalgia occurred in <1% of patients (0.2% and 0.4%, respectively). However, these were the most common adverse experiences reported overall during these trials regardless of causality (22.3% and 19.7%, respectively).

A similar safety profile was observed in an open study in pediatric patients ages 6 to 13.

The following ophthalmological side effects do occur due to the disease itself but have also been reported after treatment with STROMECTOL: abnormal sensation in the eyes, eyelid edema, anterior uveitis, conjunctivitis, limbitis, keratitis, and chorioretinitis or choroiditis. These have rarely been severe or associated with loss of vision and have generally resolved without corticosteroid treatment.

*Laboratory Test Findings*

In controlled clinical trials, the following laboratory adverse experiences were reported as possibly, probably, or definitely related to the drug in ≥1% of the patients: eosinophilia (3%) and hemoglobin increase (1%).

*Post-Marketing Experience*

The following adverse reactions have been reported since the drug was registered overseas:

*Onchocerciasis*

Conjunctival hemorrhage

*All Indications*

Hypotension (mainly orthostatic hypotension), worsening of bronchial asthma, toxic epidermal necrolysis, Stevens-Johnson syndrome, seizures, hepatitis, elevation of liver enzymes, and elevation of bilirubin.

## OVERDOSAGE

Significant lethality was observed in mice and rats after single oral doses of 25 to 50 mg/kg and 40 to 50 mg/kg, respectively. No significant lethality was observed in dogs after single oral doses of up to 10 mg/kg. At these doses, the treatment-related signs that were observed in these animals include ataxia, bradypnea, tremors, ptosis, decreased activity, emesis, and mydriasis.

In accidental intoxication with, or significant exposure to, unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, inhalation, injection, or exposure to body surfaces, the following adverse effects have been reported most frequently: rash, edema, headache, dizziness, asthenia, nausea, vomiting, and diarrhea. Other adverse effects that have been reported include: seizure, ataxia, dyspnea, abdominal pain, paresthesia, urticaria, and contact dermatitis.

In case of accidental poisoning, supportive therapy, if indicated, should include parenteral fluids and electrolytes, respiratory support (oxygen and mechanical ventilation if necessary) and pressor agents if clinically significant hypotension is present. Induction of emesis and/or gastric lavage as soon as possible, followed by purgatives and other routine anti-poison measures, may be indicated if needed to prevent absorption of ingested material.

## DOSAGE AND ADMINISTRATION

*Strongyloidiasis*

The recommended dosage of STROMECTOL for the treatment of strongyloidiasis is a single oral dose designed to provide approximately 200 mcg of ivermectin per kg of body weight. See Table 1 for dosage guidelines. Patients should take tablets on an empty stomach with water. (See CLINICAL PHARMACOLOGY, *Pharmacokinetics*.) In general, additional doses are not necessary. However, follow-up stool examinations should be performed to verify eradication of infection. (See CLINICAL PHARMACOLOGY, *Clinical Studies.*)

Table 1
Dosage Guidelines for STROMECTOL for Strongyloidiasis

| Body Weight (kg) | Single Oral Dose Number of 3-mg Tablets |
|---|---|
| 15-24 | 1 tablet |
| 25-35 | 2 tablets |
| 36-50 | 3 tablets |
| 51-65 | 4 tablets |
| 66-79 | 5 tablets |
| ≥80 | 200 mcg/kg |

*Onchocerciasis*

The recommended dosage of STROMECTOL for the treatment of onchocerciasis is a single oral dose designed to provide approximately 150 mcg of ivermectin per kg of body weight. See Table 2 for dosage guidelines. Patients should take tablets on an empty stomach with water. (See CLINICAL PHARMACOLOGY, *Pharmacokinetics*.) In mass distribution campaigns in international treatment programs, the most commonly used dose interval is 12 months. For the treatment of individual patients, retreatment may be considered at intervals as short as 3 months.

Table 2
Dosage Guidelines for STROMECTOL for Onchocerciasis

| Body Weight (kg) | Single Oral Dose Number of 3-mg Tablets |
|---|---|
| 15-25 | 1 tablet |
| 26-44 | 2 tablets |
| 45-64 | 3 tablets |
| 65-84 | 4 tablets |
| ≥85 | 150 mcg/kg |

**HOW SUPPLIED**

No. 8495 — Tablets STROMECTOL 3 mg are white, round, flat, bevel-edged tablets coded MSD on one side and 32 on the other side. They are supplied as follows:

**NDC** 0006-0032-20 unit dose packages of 20.

*Storage*

Store at temperatures below 30°C (86°F).


Manufactured by:
Merck Sharp & Dohme BV
Waarderweg 39
2031 BN Haarlem
Netherlands

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# Research Participants Needed!

Researchers at the University of Georgia are conducting a study on how an important drug, ivermectin, might interact with the human immune system. The drug is used to treat infections with parasitic nematodes (roundworms)

Participants should:

- Be between the ages of 18-65 years old;
- Be healthy and weigh more than 110 lbs, but less than 186 lbs.
- Not be pregnant or breastfeeding
- Not have travelled to West or Central Africa in the past 3 years
- Not be immunosuppressed
- Live in the Athens area or surrounding communities.

Eligible subjects will be asked to take a single dose of ivermectin (3-4 tablets depending on weight) and undergo three blood draws over the course of two days. They will be asked to remain at the CTRU for four hours after taking the drug. Subjects will receive $100 for completing the study.

The study will be conducted at the Clinical and Translational Research Unit on the UGA Health Sciences Campus. The Principal Investigator is Dr. Adrian Wolstenholme.

**For more information, call: 706-713-2721 or email ctru@uga.edu**

**Telephone Eligibility Screening Consent Script**

**Study: Ivermectin and human immunity**

Thank you for calling the Clinical and Translational Research Unit to find out more about the research study entitled, Ivermectin and Human Immunity. My name is _____[study team member doing screening]. I am one of the researchers helping with this study at the University of Georgia.

The purpose of this research study is to look at how a drug called ivermectin affects healthy people, in particular, whether it has an effect on the immune system. Ivermectin is used to treat infections with parasitic worms and we hope that this study will help us understand how the drug works. Do you think you might be interested in participating in this study?

**{If No}:** Thank you very much for your time.

**{If Yes}:** Before enrolling people in this study, we need to ask you some questions to determine if you are eligible for this study. What I would now like to do is to ask you some questions about yourself. This should only take about 5 minutes of your time.

There is a possibility that some of these questions may make you uncomfortable or distressed; if so, please let me know. You don't have to answer those questions if you don't want to.

All information that I receive from you during this phone interview, including your name and any other information that can possibly identify you, will be strictly confidential and will be kept under lock and key. Remember, your participation is voluntary; you can refuse to answer any questions, or stop this phone interview at any time without penalty or loss of benefits to which you are otherwise entitled.

Do I have your permission to ask you these questions?

**{If No}:** Thank you very much for your time.

**{If Yes}:** Are you:

1. Within the ages of 18-65 years old, inclusive;

2. Healthy and have a weight over 110 lbs, and under 185 lbs;

3. Willing and able to undergo multiple blood draws;

4. A stable resident of the Athens area?

**{If No to any questions}:** Unfortunately you are not eligible for this study. All the information you gave me will be immediately destroyed. Thank you very much for your time.

**[If yes to all, proceed to next questions]**

**(Exclusion Criteria):**

1. Are you pregnant or breastfeeding;

2. Have you ever been told that you are immunosuppressed or have a problem with your immune system;

4. Have you travelled to West or Central Africa in the past three years, or any other country where river blindness is present? (If asked, the specific countries of concern are Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Republic of Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Gabon, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Malawi, Mali, Mozambique, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, South Sudan, Sudan, Togo, Uganda, United Republic of Tanzania, Yemen, plus a very isolated region on the Brazil/Venezuela border. The rest of Brazil is safe.)

5. Do you have any known allergies? (Those that would cause ineligibility are: ivermectin/Stromectol, cellulose, pregelatinized starch, magnesium stearate, butylated hydroxyanisole, citric acid or cornstarch).

6. Do you have hepatitis?

7. Are you currently taking warfarin?

**{If Yes to any of these questions}:** Unfortunately you are not eligible for this study. All the information you gave me will be immediately destroyed. Thank you very much for your time.

**[If No to all of these questions]:** You are eligible to participate in the study and I would like to extend you an invitation to participate in this research. If you decide to participate in the study, there will be two study visits on consecutive days. Before the first visit we ask that you not eat anything solid for two hours before visiting CTRU, as the tablets we are using work better on an empty stomach. Normal drinks such as water, coffee and juice are fine. The first visit will last about 5 hours, and we will provide a light meal during this time. Is that acceptable?

**[If No to this question]:** Unfortunately you are not eligible for this study. All the information you gave me will be immediately destroyed. Thank you very much for your time.

**[If Yes to this question]:** Thank you**.** The second visit will last less than 1 hour and will be 24 hrs after the start of the first visit. Compensation of $100 is available for completing the study. The first study visit will involve going through the consent process, being weighed and providing a blood sample. We will not take any permanent record of your weight, this is only so that can give you the correct number of tablets. You will then be given some tablets; these tablets may be ivermectin, the drug we are studying, or a placebo. The number of tablets you will be given depends on your weight. We will ask you to wait with us for four hours, at which time another blood sample will be taken. On the second visit, we will take a third blood sample. To participate, we ask that you come to the Clinical and Translational Research Unit located on the Health Sciences Campus of the University of Georgia. At the first visit, the purpose of the research along with all of the procedures that you will be asked to complete as part of the research study will be explained in detail. We will give you an opportunity to have all of your questions about the research answered before you decide to enroll in the study. You can refuse to participate or stop taking part in the study at any time without giving any reason, and without penalty or loss of benefits to which you are otherwise entitled.

Are you still interested in participating in the study?

**{If No}:** Thank you very much for your time.

**{If Yes}:** We can schedule a convenient time for you to come to the CTRU.

**[Schedule time to come to CTRU. Record name, phone number and email address for reminder notifications.]**

**Fasting Instructions for Participants**

This study uses a drug named Stromectol, which is absorbed better into the body if it is taken on an empty stomach. For this reason, we request that you do not eat anything solid for two hours prior to your first visit to the CTRU. Drinks such as water, coffee and juice are fine, but not energy drinks or smoothies. We will provide a light meal during this first visit after you have taken the tablets.

Thank you for volunteering for the study and for your cooperation with this request.

**UNIVERSITY OF GEORGIA**
**CONSENT FORM**
**Ivermectin and Human Immunity**

**Researcher's Statement**
We are asking you to take part in a research study. Before you decide to participate in this study, it is important that you understand why the research is being done and what it will involve. This form is designed to give you the information about the study so you can decide whether to be in the study or not. Please take the time to read the following information carefully. Please ask the researcher if there is anything that is not clear or if you need more information. When all your questions have been answered, you can decide if you want to be in the study or not. This process is called "informed consent." A copy of this form will be given to you.

**Principal Investigator:** Dr. Adrian Wolstenholme
Department of Infectious Diseases
706-542-2404
adrianw@uga.edu

**Purpose of the Study**
Ivermectin is an FDA-approved drug used for the treatment of infections with parasitic nematodes (roundworms) in people. Every year it is given to hundreds of millions of people worldwide as part of international efforts to eliminate serious tropical diseases, river blindness and lymphatic filariasis (elephantiasis). Despite this, we really do not understand how the drug works against the parasites that cause these diseases, so the purpose of this study is to test the idea that the drug works together with the human immune system to remove the parasites.

**Study Procedures**
If you agree to participate, you will be asked to visit the Clinical and Translational Research Unit (CTRU) Building twice on consecutive days. You will be asked to remain at the CRRU for 5 hours on the first day to complete the procedures which will include providing information about your race, ethnicity, age and gender. In addition, additional screening criteria will identify anyone who may not be eligible for the study. You will review and sign a copy of this consent form with CTRU staff to give your permission to enter the study. A trained research nurse will draw 18ml (a little more than one tablespoon) of blood from you using standard phlebotomy techniques, and you will be weighed. We will not keep any permanent record of your weight, this is only so that give you the correct number of tablets. You will then be given three to four tablets (depending on your weight) to take. These will either be ivermectin (marketed as Stromectol in the USA), or a placebo. Which kind of tablet you will get will be determined completely by chance. You will not know which you have been given. You will be asked to wait in the CTRU for an additional four hours, after which a second sample of blood (15ml) will be taken. You will then be free to leave. We will provide a light meal after you have taken the tablets, which are best taken on an empty stomach. On the second day, the visit should last less than 1 hour. A third blood sample (18ml) will be drawn, approximately 24 hours after you took the tablets. We will then analyze the blood samples to determine if the drugs increase the ability of the blood cells to kill the parasites.

**Risks and Discomforts**

The risks and discomforts associated with your participation are related to the blood draws and possible side effects of the ivermectin. Ivermectin is generally considered to be very safe, but has not been extensively tested in pregnant women or immunosuppressed people. In clinical trials, the following clinical adverse reactions were reported as possibly, probably, or definitely related to the drug in 1-4% of the patients: nausea, diarrhea, changes in white blood cell count, abnormalities in liver function, swelling of the face, swelling of the arms/legs, blood pressure drop when standing up quickly, fast heart rate and muscle pain. Drug-related headache occurred in <1% of patients (0.2%). If you are infected with a parasitic worm called *Loa loa* (the eyeworm) or *Onchocerca volvulus* (the parasite that causes river blindness), ivermectin may cause a severe reaction to dying worms. In order to avoid this, please do not take part in the study if you have travelled in the past 3 years to West or Central Africa (as this is the region of the world where it is possible to become infected with *Loa loa*) or other countries in which Onchocerciasis may be contracted. In addition, if you are currently taking Warfarin or have hepatitis you are not eligible to take part in the study. You will be required to stay at the CTRU for four hours after taking the dose of ivermectin in order for nursing staff to monitor you for any possible adverse effects, and will give prompt medical attention in case of any adverse effects. Risks associated with drawing blood include redness, swelling, pain or discomfort, and bruising at the site of the needle stick. Although rare, infection may also occur. Some people may experience dizziness, lightheadedness, and/or fainting. The CTRU nurses are very experienced in blood draws and will try to minimize any discomfort or bruising.

**Benefits**

This study will not directly benefit you. However, it will benefit society. A better understanding of individual people's response to the parasite may help in the ongoing effort towards global elimination of river blindness and lymphatic filariasis.

**Incentives for participation**

If you choose to volunteer, we will ask you to sign this consent form. We will provide you with $100 as compensation for completing the study, however, if you do not complete the study, you will be compensated $25 for each blood draw that you do complete, plus $25 for taking the ivermectin or placebo. This will be paid in cash after your second and final visit to the CTRU. You will be asked to sign a form verifying that you received this compensation.

**Privacy/Confidentiality**

To ensure confidentiality, you will be assigned a code and your samples will be assigned a random number and we will not attach any personal tracking information to any of the samples collected from you. We do ask you to consider providing the following information for us on a separate questionnaire form: race, ethnicity, age, and gender. This information will be linked to your blood sample, to experimental results obtained using the blood sample and will be reported to the National Institutes of Health, the main funder of medical research in the United States. Providing this information is entirely optional. If you decide to provide this information, please complete the questionnaire before the first blood donation. Researchers will not release identifiable results of the study to anyone other than individuals working on the project without your written

consent unless required by law. The project's research records may be reviewed by Food and Drug Administration and by departments at the University of Georgia responsible for regulatory and research oversight.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. You can search this Web site at any time.

**Taking part is voluntary**

Your involvement in the study is voluntary, and you may choose not to participate or to stop at any time without penalty or loss of benefits to which you are otherwise entitled. If you decide to withdraw from the study, the information that can be identified as yours will be kept as part of the study and may continue to be analyzed, unless you make a written request to remove, return, or destroy the information.

**If you are injured by this research**

The researchers will exercise all reasonable care to protect you from harm as a result of your participation. In the event that any research-related activities result in an injury, the sole responsibility of the researchers will be to arrange for your transportation to an appropriate health care facility. If you think that you have suffered a research-related injury, you should seek immediate medical attention and then contact Dr. Adrian Wolstenholme right away at 706-542-2404. In the event that you suffer a research-related injury, your medical expenses will be your responsibility or that of your third-party payer, although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

**If you have questions**

The main researcher conducting this study is Dr. Adrian Wolstenholme, a Professor at the University of Georgia, who is assisted by Dr. Barbara Reaves, a Senior Research Scientist. Please ask any questions you have now. If you have questions later, you may contact Dr Wolstenholme at adrianw@uga.edu or at 706-542-2404. If you have any questions or concerns regarding your rights as a research participant in this study, you may contact the Institutional Review Board (IRB) Chairperson at 706.542.3199 or irb@uga.edu.

**Research Subject's Consent to Participate in Research:**

To voluntarily agree to take part in this study, you must sign on the line below. Your signature below indicates that you have read or had read to you this entire consent form, and have had all of your questions answered.

| _____ | _____ | _____ |
|---|---|---|
| Name of Researcher | Signature | Date |

| _____ | _____ | _____ |
| --- | --- | --- |
| Name of Participant | Signature | Date |

Please sign both copies, keep one and return one to the researcher.

## Statistical Analysis Plan

### *Changes in Cytokine Levels*

Cytokine levels were obtained from the Luminex data. The mean level plus or minus standard error of each analyte were calculated for each arm at each time point (0, 4 , 24 hrs post-treatment). For the control and ivermectin arms, levels at 4 hrs and 24 hrs post-treatment were compared to the levels pre-treatment using simple t-tests to determine if any individual results required further investigation, taking $p = <0.05$ as the level of significance. Since none of the individual analyte results met this criterion, no further analysis was carried out.

### *Changes in Gene Expression*

The Nanostring data were analysed on their proprietary software, nSolver™ (Nanostring Technologies Inc, Seattle). The data passed quality control criteria. The software calculated the $\log_2$ geometric mean levels of each mRNA measured and used t tests to determine statistically significant changes in expression between 4 and 24 hrs post-treatment for the control and ivermectin arms. The Benjamini-Yekutieli False Discovery Rate method was used to account for the expectation that significant changes in genes may be correlated with or dependent on each other, and the subsequent resulting FDR adjusted p-value of $<0.05$ used to determine those changes that were deemed to be statistically significant.

### *Complete Blood Counts*

The mean numbers of each cell type were calculated for each arm at 24 hrs post-treatment and compared to those pre-treatment using a simple t-test, with $p = <0.05$ as the level of significance. Since none of the measurements passed this test, no further analysis was performed.