Document Coversheet

Study Title: An Open Label Phase 2a Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of (+)-SJ000557733 (SJ733) With or Without Cobicistat in Adult Patients With Acute, Uncomplicated Malaria Over a 42 Day Period

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	11/2/2020
NCT Number:	NCT04709692
IRB Number	53333

PROTOCOL TYPE

Which IRB

◉ Medical ○ NonMedical

Protocol Process Type

○ Exemption
○ Expedited (Must be risk level 1)
◉ Full

IMPORTANT NOTE: Once you have saved your choices under "Which IRB" and "Protocol Process Type", you will not be able to change your selections. If you select the wrong IRB Type and/or your application is deemed eligible for a different Protocol Process Type, it may be necessary to create a new application.

Please see below for guidance on which selections to make, and/or go to ORI's "Getting Started" web page. If you still have questions about which IRB or Protocol Process Type to choose, please contact the Office of Research Integrity (ORI) at 859-257-9428 **prior** to saving your selections.

Which IRB

The **Medical IRB** reviews research emanating from the Colleges of Dentistry; Health Sciences; Medicine; Nursing; Pharmacy and Health Sciences; and Public Health.

The **Nonmedical IRB** reviews research originating from the Colleges of Agriculture; Arts & Sciences; Business & Economics; Communication & Information; Design; Education; Engineering; Fine Arts; Law; and Social Work. The Nonmedical IRB does not review studies that involve administration of drugs, testing safety or effectiveness of medical devices, or studies that involve invasive medical procedures, regardless of from what college the application originates.

Which Protocol Process Type

Under federal regulations, an investigator's application to conduct a research project involving human subjects can be processed by the IRBs in three ways:

- by full review;
- by exemption certification;
- by expedited review.

The preliminary determination that a research project is eligible for exemption certification or expedited review is made by the investigator. For assistance in determining which review process type your IRB application is eligible for, please go to ORI's "Getting Started" web page.

The revised Common Rule expanded exemption certification category 4 for certain secondary research with identifiable information or biospecimens. The regulations no longer require the information or biospecimens to be existing. For more information see the Exemption Categories Tool.

PROJECT INFORMATION

Title of Project: (If applicable, use the exact title listed in the grant/contract application). *** Effective 4/16/2020: If your research involves investigating any aspect of COVID-19, please enter "COVID19" at the start of your Project and Short Titles ***

An Open Label Phase 2a Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of (+)-SJ000557733 (SJ733) with or without Combination with Cobicistat in Adult Patients with Acute, Uncomplicated Plasmodium Falciparum or Vivax Malaria Mono-Infection over a 42 Day Period

Short Title Description

Note: "Short Title" should consist of a couple key words to easily identify your study - these key words (rather than the whole title) will be displayed on the Dashboard in the listing for your study.

SJ733 Phase 2a

Anticipated Ending Date of Research Project: 6/30/2022

Number of human subjects (or records/specimens reviewed): 60

Study is/will be open to new subject enrollment or data/specimen collection: (•) Yes ( ) No

PI CONTACT INFORMATION

The Principal Investigator's (PI) contact information is filled in automatically based on who was logged in when the application was created (with LinkBlue ID). If research is being submitted to or supported by an extramural funding agency such as NIH, a private foundation or a pharmaceutical/manufacturing company, the PI listed on the grant application or the drug protocol must be the same person listed below.

If you are not the Principal Investigator, do NOT add yourself as study personnel. You may change the PI contact information on an application that is in Researcher edit mode by:

- clicking the "Change Principal Investigator" link below;
- searching for the PI's name using the search feature;
- clicking "Select" by the name of the Principal Investigator, then "Save Contact Information".

You will automatically be added as study personnel with edit authorization so you can continue editing the application.

Please fill in any blank fields with the appropriate contact information (gray shaded fields are not editable). Required fields left blank will be highlighted in pink after you click "Save".

To change home and work addresses, go to myUK and update using the Employee Self Service (ESS) portal. If name has changed, the individual with the name change will need to submit a 'Name Change Form' to the Human Resources Benefits Office for entering into SAP. The new name will need to be associated with the individual's Link Blue ID in SAP before the change is reflected in E-IRB. Contact the HR Benefits Office for additional information.

Note: Principal Investigator (PI) role for E-IRB access
The PI is the individual holding primary responsibility on the research project with the following permissions on the E-IRB application:

1. Read;
2. write/edit;
3. receive communications; and
4. submit to the IRB (IR, CR, MR, Other Review*).

Change Principal Investigator:

First Name:	Rodney	Room# & Bldg:	214H Lee T. Todd, Jr. Building, 789 S. Limestone
Last Name:	Guy	Speed Sort#:	0596
Middle Name	K		
Department:	Pharmaceutical Sciences - 7…	Dept Code:	7K300
PI's Employee/Student ID#:	12217189	Rank:	Dean and Professor
PI's Telephone #:	8592577896	Degree:	PhD
PI's e-mail address:	kip.guy@uky.edu	PI's FAX Number:	8592572128
PI is R.N.	○ Yes ◉ No	Trained:	Yes
		Date Trained	8/9/2018

Do you, the PI, have a significant financial interest related to your responsibilities at the University of Kentucky (that requires disclosure per the UK administrative regulation 7:2)?

○ Yes ◉ No

RISK LEVEL

Indicate which of the categories listed below accurately describes this protocol

- ○ (Risk Level 1) Not greater than minimal risk
- ◉ (Risk Level 2) Greater than minimal risk, but presenting the prospect of direct benefit to individual subjects
- ○ (Risk Level 3) Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- ○ (Risk Level 4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of subjects.

*"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests [45 CFR 46.102(i)]

Download UK's guidance document on assessing the research risk for additional information on risk [PDF]

SUBJECT DEMOGRAPHICS

Age level of human subjects: (i.e., 6 mths.; 2yrs., etc..) 18 y to 70 y

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations
(Please note: The IRB will expect this information to be reported at Continuation Review time):

Enter Numbers Only!

Ethnic Origin	#Male	#Female
American Indian/Alaskan Native:		
Asian:		
Black/African American:		
Hispanic/Latino:	40	20
Native Hawaiian/Pacific Islander:		
White/Caucasian:		
Other or Unknown:		

If unknown, please explain why: The trial will be conducted in Iquitos, Peru.

Patients will be recruited from the community, local health-care clinics, and post-secondary educational institutions through word-of-mouth, active recruitment by study staff, and self-referral in response to advertisements. Verbal permission will be sought at private locations where advertisements will be posted, and a signed letter of authorization will be obtained from any performance site where recruitment activities take place. All recruitment materials will be approved by the EC before use. Advertisements will indicate the nature of the study and provide a phone number for further information. Currently, the recruitment sites include 14 villages that have health posts in the districts of Iquitos, San Juan Bautista, and Punchana. Some are located along the road and others at the edges of the rivers. The distance by land or river to the city of Iquitos is less than 1.5 hours, most less than 1 hour. In general, the people who

live in these recruitment areas are representative of the general population that suffers malaria in the Amazon region. They are generally mestizo and do not live in extreme poverty. Their educational level includes completion of primary or high school.

Indicate the categories of subjects and controls to be included in the study. Depending on the subject category applicable to your research you may be required to complete additional forms. [Note, if the study does not involve direct intervention or direct interaction with subjects, (e.g., record-review research, outcomes registries), do not check mark populations which the research does not specifically target. For instance, a large record review of a diverse population may incidentally include a prisoner or an international citizen, but, if the focus or intent of the study has nothing to do with that status, you do not need to check those category(ies).]

Check All That Apply (at least one item must be selected)

- ☐ Children (individuals under age 18)
- ☐ Wards of the State (Children)
- ☐ Emancipated Minors
- ☐ Students
- ☐ College of Medicine Students
- ☐ UK Medical Center Residents or House Officers
- ☐ Impaired Consent Capacity Adults
- ☐ Pregnant Women/Neonates/Fetal Material
- ☐ Prisoners
- ☑ Non-English Speaking
- ☑ International Citizens
- ☐ Normal Volunteers
- ☐ Military Personnel and/or DoD Civilian Employees
- ☑ Patients
- ☐ Appalachian Population

ADDITIONAL INFORMATION:

Please visit the IRB Survival Handbook under the named topic:

- Children/Emancipated Minors
- Students as Subjects
- Prisoners
- Impaired Consent Capacity Adults: Link to required Form

And/Or:

- UKMC Residents or House Officers [see requirement of GME]
- Non-English Speaking [see instructions for recruitment and E-IRB Research Description section on same topic]
- International Citizens [HTML] (DoD SOP may apply [PDF])
- Military Personnel and/or DoD Civilian Employees (DoD SOP may apply [PDF])

The next questions involve assessment of the study relative to potential recruitment of subjects with impaired consent capacity (or likelihood).

☐ Check this box if your study does not involve direct intervention or direct interaction with subjects (e.g., record-review research, secondary data analysis). (you will not need to answer the impaired consent capacity questions)

Does this study focus on adult subjects with any of the clinical conditions listed below that present a high *likelihood* of impaired consent capacity or *fluctuations* in consent capacity? (see examples below)

○ Yes ◉ No

If Yes, go to the following link and complete and attach the indicated form unless you are filing for an exemption certification: https://ris.uky.edu/ori/oriforms/formt/Scale.asp

Examples of such conditions include:

- Traumatic brain injury or acquired brain injury
- Severe depressive disorders or Bipolar disorders
- Schizophrenia or other mental disorders that involve serious cognitive disturbances
- Stroke
- Developmental disabilities
- Degenerative dementias
- CNS cancers and other cancers with possible CNS involvement
- Late stage Parkinson's Disease
- Late stage persistent substance dependence
- Ischemic heart disease
- HIV/AIDS
- COPD
- Renal insufficiency
- Diabetes
- Autoimmune or inflammatory disorders
- Chronic non-malignant pain disorders
- Drug effects
- Other acute medical crises

Attachments

INFORMED CONSENT/ASSENT PROCESS/WAIVER

For your informed consent attachment(s), please download the most up-to-date version listed in "All Templates" under the APPLICATION LINKS menu on the left, and revise to be in accord with your research project.

Additional Resources:

- Sample Repository/Registry/Bank Consent (Word)
- Instructions for Proposed Informed Consent Document
- Instructions for Proposed Assent Form

Consent/Assent Tips:

- **If you have multiple consent documents, be sure to upload each individually (not all in a combined file).**
- **Changes to consent documents (e.g., informed consent form, assent form, cover letter, etc...) should be reflected in a 'tracked changes' version and uploaded separately with the Document Type "Highlighted Changes".**
- **It is very important that only the documents you wish to have approved by the IRB are attached; DELETE OUTDATED FILES -- previously *approved* versions will still be available in Protocol History.**
- **Attachments that are assigned a Document Type to which an IRB approval stamp applies will be considered the version(s) to be used for enrolling subjects once IRB approval has been issued.**
  Document Types that do NOT get an IRB approval stamp are:
  - **"Highlighted Changes",**
  - **"Phone Script", and**
  - **"Sponsor's Sample Consent Form".**

How to Get the Informed Consent Section Check Mark

1. **You must check the box for at least one of the consent items and/or check mark one of the waivers, then if applicable attach the corresponding document(s) as a PDF (if open to enrollment).**
2. **If you no longer need a consent document approved (e.g., closed to enrollment), or, the consent document submitted does not need a stamp for enrolling subjects (e.g., umbrella study, or sub-study), only check mark the "Stamped Consent Doc(s) Not Needed".**
3. **After making your selection(s) be sure to scroll to the bottom of this section and SAVE your work!**

Check All That Apply

- ☐ Informed Consent Form (and/or Parental Permission Form)
- ☐ Assent Form
- ☐ Cover Letter (for survey/questionnaire research)
- ☐ Phone Script
- ☑ Informed Consent/HIPAA Combined Form
- ☐ Debriefing and/or Permission to Use Data Form
- ☐ Sponsor's sample consent form for Dept. of Health and Human Services (DHHS)-approved protocol
- ☐ Stamped Consent Doc(s) Not Needed

Attachments

Attach Type	File Name
Informed ConsentHIPAA Combined Form	Phase2a_Main_Consent_Cert_of_Translation.pdf
Informed ConsentHIPAA Combined Form	Phase2a_PK_Consent_Cert_of_Translation.pdf
Informed ConsentHIPAA Combined Form	SJ733_Phase2a_PK_Consent_v1.0_en.pdf
Informed ConsentHIPAA Combined Form	SJ733_Phase2a_PK_Consent_v1.0_es.pdf
Informed ConsentHIPAA Combined Form	SJ733_Phase2a_Main_Consent_v1.0_en.pdf
Informed ConsentHIPAA Combined Form	SJ733_Phase2a_Main_Consent_v1.0_es.pdf

☐ Request for Waiver of Informed Consent Process

If you are requesting IRB approval for waiver of the requirement for the informed consent process, or alteration of some or all of the elements of informed consent (i.e. medical record review, deception research, or collection of biological specimens), complete Section 1 and Section 2 below.

Note: The IRB does not approve waiver or alteration of the consent process for greater than minimal risk research, except for planned emergency/acute care research as provided under FDA regulations. Contact ORI for regulations that apply to single emergency use waiver or acute care research waiver (859-257-9428).

SECTION 1.

Check the appropriate item:

☐ I am requesting waiver of the requirement for the informed consent process.

☐ I am requesting alteration of the informed consent process.

If you checked the box for this item, describe which elements of consent will be altered, and/or omitted, and justify the alteration.

SECTION 2.

The IRB may consider your request provided that **all** of the following conditions apply to your research and are appropriately justified. Explain in the space provided for each condition how it applies to your research.

a) The research involves no more than minimal risk to the subject.

b) The rights and welfare of subjects will not be adversely affected.

c) The research could not practicably be carried out without the requested waiver or alteration.

d) Whenever possible, the subjects or legally authorized representatives will be provided with additional pertinent information after they have participated in the study.

e) If the research involves using or accessing identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

- Private information/specimens are “identifiable” if the investigator may ascertain the identity of the subject or if identifiers are associated with the information (e.g., medical records). This could be any of the 18 HIPAA identifiers including dates of service.
- If not using identifiable private information or identifiable biospecimens, insert N/A below.

Request for Waiver of Documentation of Informed Consent Process

If you are requesting IRB approval for waiver of the requirement for documentation of informed consent (i.e. telephone survey or mailed survey, internet research, or certain international research), **your research activities must fit into one of three regulatory options**:

1. The only record linking the participant and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves participants who use illegal drugs).
2. The research presents no more than minimal risk to the participant and involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script).
3. The participant (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm, and the research presents no more than minimal risk to the subject and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Select the option below that best fits your study, and explain in the space provided how your study meets the criteria for the selected regulatory option.

Note: The IRB cannot waive the requirement for documentation or alter the consent form for FDA-regulated research unless it meets Option #2 below. FDA does not accept Option #1.

Note: Even if a waiver of the requirement for documentation is approved by the IRB, participants must still be provided oral or written (e.g., cover letter) information including all required and appropriate elements of consent so they have the knowledge and opportunity to consider whether or not to participate. To help ensure required elements are included in your consent document, please use the **Cover Letter Template** as a guide: *English*- [WORD], Spanish- [WORD] The cover letter template was developed specifically for survey/questionnaire research; however, it may be useful as a guide for developing a consent document for other types of research as well.

Option 1

a) The only record linking the participant and the research would be the consent document:

b) The principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves subjects who use illegal drugs).

Under this option, each participant (or legally authorized representative) must be asked whether (s)he wants to sign a consent document; if the participant agrees to sign a consent document, only an IRB approved version should be used.

Option 2

a) The research presents no more than minimal risk to the participant:

b) Involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script):

Option 3

a) The subject (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm.

b) The research presents no more than minimal risk to the subject.

c) There is an appropriate alternative mechanism for documenting that informed consent was obtained.

STUDY PERSONNEL

Do you have study personnel who will be assisting with the research?
After selecting 'Yes' or 'No' you must save by hitting the 'Save Study Personnel Information' button.

(•) Yes ( ) No

Manage Study Personnel

Identify other study personnel assisting in research project:

- The individual listed as PI in the 'PI Contact Information' section should NOT be added to this section.
- If the research is being completed to meet the requirements of a University of Kentucky academic program, the faculty advisor is also considered study personnel and should be listed as such below. ***Residents and students who are PI's are encouraged to designate at least one other individual (e.g., faculty advisor) as a contact with an editor role (DP).***
- Role: DP = Editor (individual can view, navigate, and edit the application for any review phase (IR, CR/FR, MR) or 'Other Review", and submit Other Reviews on behalf of the PI.)
- Role: SP = Reader (individual can view and navigate through the currently approved application only.)

To add an individual via the below feature, search for applicable personnel first, then click "select" by the listing for the person you want to add as study personnel to your protocol. For each individual selected, be sure to specify responsibility in the project, whether authorized by the principal investigator to obtain informed consent, AND denote who should regularly receive E-IRB notifications.

NOTE: Study personnel are required to receive human research protection (HSP) training before implementing any research procedures (e.g., CITI). For information about mandatory training requirements for study personnel, visit UK's FAQ's on Mandatory Training web page, or contact ORI at 859-257-9428. If you have documentation of current HSP training other than that acquired through UK CITI, you may submit it to ORI (Jen.Hill@uky.edu) for credit.

Study personnel assisting in research project:

Last Name	First Name	Responsibility In Project	Role	AC	Contact	Degree	StatusFlag	(HSP)	(HSP)Date	Removed?	Last Updated	SFI
Ashe	Laura	Study Coordinator	DP	N	N	CCRC	P	Y	06/23/2020	N	10/22/2019	N
Hammill	Jared	Project Assistance/Support	DP	N	Y	PhD	P	Y	08/01/2019	N	08/06/2019	N
Orozco	Blanca	Project Assistance/Support	DP	N	N		P	Y	06/09/2020	N	04/21/2020	N
Lambert	Kasandra	Project Assistance/Support	SP	N	N		P	Y	09/23/2020	Y	06/01/2020	N

RESEARCH DESCRIPTION

****!!!PLEASE READ!!!** Known Issue: The below text boxes do not allow symbols, web addresses, or special characters (characters on a standard keyboard should be ok). If something is entered that the text boxes don't allow, user will lose unsaved information.**

Workaround(s):

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section, or under the Additional Information section to include the information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

Background: Provide an introduction and background information. Describe past experimental and/or clinical findings leading to the formulation of your study. For research involving investigational drugs, describe the previously conducted animal and human studies. You may reference grant application/sponsor's relevant protocol pages and attach as an appendix in the E-IRB "Additional Information" section, however, a summary paragraph must be provided in the text box below. For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol. Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference in the applicable E-IRB "Study Drug" or "Study Device" section.

SJ733 is a new antimalarial drug candidate that has undergone single ascending dose, pharmacoboosted single ascending dose (pharmacoenhancement with cobicistat), food effect single dose, and multiple ascending dose Phase 1 studies in healthy volunteers to demonstrate safety, tolerability, and its pharmacokinetic profile. SJ733 has also been tested in a two-cohort single dose, Phase 1b, human Induced Blood Stage Malaria (IBSM) challenge study. Overall, SJ733's excellent tolerability and safety profile, combined with its rapid antiparasitic effect, support its candidacy as an antimalarial therapy. The Phase 1 clinical data and PK/PD models suggest that SJ733 is most likely to be curative as a 3-daily-dose pharmacoenhanced therapy, due to its moderately rapid clearance.

The present proof-of-concept Phase 2a trial will be an adaptive, open label study to examine the antimalarial efficacy, safety, and tolerability of SJ733 in adult patients with uncomplicated P. vivax or P. falciparum blood-stage malaria monoinfection. SJ733 will be administered orally once every day for three consecutive days, with or without a fixed dose of the pharmacoenhancer cobicistat, to determine if pharmacoenhancement is required, and if significant improvements in drug efficacy are seen at higher total exposures of SJ733. Success will be defined independently for each treatment arm at Day 14 as: 1) the absence of any repeated drug-related serious adverse event; and 2) crude ACPR = 80% (equivalent to = 20% recurrence). Crude ACPR is defined as the absence of microscopically determined parasitemia (thick smear), irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure, or late parasitological failure. Additional aims are to characterize the antiparasitic activity, safety, tolerability, and pharmacokinetics of SJ733 over the period of 42 days. The results of this trial will help identify effective, well-tolerated doses for investigation in combination with a partner drug within a Phase 2b clinical study.

Objectives: List your research objectives. You may reference grant application/sponsor's relevant protocol pages and attach as an appendix in the E-IRB "Additional Information" section, however, a summary paragraph must be provided in the text box below.

Primary Objectives:
1) To determine the efficacy of SJ733 with or without combination with the pharmacoenhancer cobicistat, given once per day for three-consecutive days by examining parasitemia 14-days after initiation of therapy for the treatment of uncomplicated P. vivax or P. falciparum malaria monoinfection.
2) To evaluate the safety and tolerability of SJ733, with or without combination with the pharmacoenhancer cobicistat, given once per day for three-consecutive days in patients with P. falciparum and P. vivax malaria infection.

Secondary Objectives:
1) To assess the effect of the proposed three-day therapy on the signs and symptoms of P. vivax or P. falciparum malaria infection up to Day 42
2) To assess the effect of the proposed three-day therapy on treatment outcomes in patients with P. vivax or P. falciparum malaria infection at Days 28, 35, and 42
3) To describe parasite clearance kinetics in patients with P. vivax or P. falciparum malaria infection
4) To describe the pharmacokinetics of SJ733 and its primary metabolite SJ506 during the three-day dosing period and for 7 additional days in patients with P. falciparum and P. vivax malaria infection.

Exploratory Objectives:
1) To assess the effect of the proposed three-day therapy on PCR adjusted outcomes in patients with P. vivax or P. falciparum malaria infection:
a. With PCR-adjustment at Days 7, 14, 28, 35, and 42 (P. falciparum only)
b. PCR adjusted rates of recurrence (P. vivax or P. falciparum), up to Day 42.

Study Design: Describe the study design (e.g., single/double blind, parallel, crossover, etc.). Indicate whether or not the subjects will receive placebo medication at some point in the research procedures. Also, indicate whether or not the subjects will be randomized in this study. You may reference sponsor's protocol pages and attach as an appendix in the E-IRB "Additional Information" section, however, a summary paragraph must be provided in the text box below. (Including the study design table from a sponsor's protocol is

helpful to IRB members.)

Community-Based Participatory Research: If you are conducting community-based participatory research (CBPR), describe strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.

Research Repositories: If the purpose of this submission is to establish a Research Repository (bank, registry) indicate whether the material you plan to collect would or would not be available from a commercial supplier, clinical lab, or established IRB approved research repository. Provide scientific justification for establishment of an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance [PDF] or the UK Research Registry Guidance [PDF]

The present proof-of-concept Phase 2a trial will be an adaptive, open label study to examine the antimalarial efficacy, safety, and tolerability of SJ733 in adult patients with uncomplicated P. vivax or P. falciparum blood-stage malaria monoinfection. SJ733 will be administered orally once every day for three consecutive days, with or without a fixed dose of the pharmacoenhancer cobicistat, to determine if pharmacoenhancement is required, and if significant improvements in drug efficacy are seen at higher total exposures of SJ733. Success will be defined independently for each treatment arm at Day 14 as: 1) the absence of any repeatable drug-related serious adverse event; and 2) crude ACPR = 80% (equivalent to = 20% recurrence). Crude ACPR is defined as the absence of microscopically determined parasitemia (thick smear), irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure, or late parasitological failure. Additional aims are to characterize the antiparasitic activity, safety, tolerability, and pharmacokinetics of SJ733 over the period of 42 days. The results of this trial will help identify effective, well-tolerated doses for investigation in combination with a partner drug within a Phase 2b clinical study. Study design table can be found on page 23 of the attached clinical protocol.

The overall study design is to demonstrate proof of concept and serves as an exploratory study. It is not intended to demonstrate superiority or non-inferiority against a control. Rather, the goal is to establish preliminary data for planning future studies and to assess whether SJ733 is safe, well tolerated, and the estimated crude ACPR equals or exceeds 80%. As such, there will be no statistical testing of hypotheses. This exploratory proof of concept study is based on using fixed Day 14 clinical safety and parasitological response (primary endpoints) to determine dosing regimen and schedules. If patients drop out for reasons unconnected to safety and efficacy, attempts will be made to replace them to try to ensure the maximum number in each cohort. In total, there will be a minimum of 20 and a maximum of 60 patients.

Attachments

Attach Type	File Name
StudyDesign	20200406_SJ733_Clinical_Protocol_V1.0_en.docx
StudyDesign	20200430_SJ733_Clinical_Protocol_V1.0_es.docx
StudyDesign	20200430_SJ733_Clinical_Protocol_V1.0_Cert_of_Translation.pdf

Back to Top

Study Population: Describe the characteristics of the subject population, such as anticipated number, age range, gender, ethnic background and health status. Identify the criteria for inclusion and exclusion. Explain the rationale for the use of special classes such as fetuses, pregnant women, children, institutionalized, adults with impaired consent capacity, prisoners, economically or educationally disadvantaged persons or others who are likely to be vulnerable.

If women or minorities are included, please address how the inclusion of women and members of minority groups and their subpopulations will help you meet your scientific objectives. Exclusion of women or minorities requires clear and compelling rationale that shows inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be excluded routinely from participation in clinical research.

Provide the following information:

- A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design;
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group;
- The proposed dates of enrollment (beginning and end);
- The proposed sample composition of subjects.

You may reference grant application/sponsor's relevant protocol pages and attach as an appendix using the below attachment button, however, a summary paragraph must be provided in the text box below.

Proposed dates of enrollment: November 1st, 2020 to December 31st, 2021

The trial will be conducted in Iquitos, Peru. Patients will be recruited from the community, local health-care clinics, and post-secondary educational institutions through word-of-mouth, active recruitment by study staff, and self-referral in response to advertisements. Verbal permission will be sought at private locations where advertisements will be posted, and a signed letter of authorization will be obtained from any performance site where recruitment activities take place. Men and women between the ages of 18 and 70 years with P. falciparum or P. vivax malaria monoinfection living in Peru. 2-6 cohorts of adult patients (10 patients per cohort) with acute,

uncomplicated P. falciparum or P. vivax malaria monoinfection. In total, there will be a minimum of 20 and a maximum of 60 patients. In general, the people who live in these recruitment areas are representative of the general population that suffers malaria in the Amazon region. They are generally mestizo and do not live in extreme poverty. Their educational level includes completion of primary or high school.

Inclusion Criteria:
1) Male or female, aged 18 to 70 years of age (inclusive) at screening.
2) Body weight between 45 kg and 90 kg inclusive
3) Presence of mono-infection of P. falciparum or P. vivax confirmed by:
a. Fever, as defined by axillary temperature = 37.5°C or oral/rectal/tympanic temperature = 38°C, or history of fever in the previous 24 hours (history of fever must be documented) and,
b. Microscopically confirmed parasite infection: 1,000 to 40,000 asexual parasite count/µL blood
4) Written informed consent provided by participant, in accordance with local practice. If the participant is unable to write, witnessed consent is permitted according to local ethical considerations.
5) Ability to swallow oral medication.
6) Ability and willingness to participate and to comply with the study requirements
7) Agreement to hospitalization for at least 102 hours and/or until malarial parasites are not detected by microscopy on 2 consecutive occasions.
8) Agreement to come back to the hospital on Days 7, 10 or 11, 14, 17 or 18, 21, 24 or 25, 28, 35, and 42.
9) Women of child-bearing potential, has a negative pregnancy test at screening, and agrees to comply with one of the following during the treatment stage of the study and for a period of 30 days after stopping study drug:
a. Use of oral, implantable, or injectable hormonal contraceptive, either combined or progestogen alone used in conjunction with barrier method as defined below.
b. Use of an intrauterine device with a documented failure rate of <1% per year.
c. Barrier method consisting of either condom or diaphragm.
d. Male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female.
e. Complete abstinence from intercourse for 2 weeks prior to administration of study drug, throughout the study and for a period of 30 days after stopping study drug.

Exclusion Criteria:
1) Signs and symptoms of severe/complicated malaria according to the World Health Organization Criteria 2010 (Attachment 1: Definition of Severe Malaria)
2) Mixed Plasmodium infection.
3) Severe vomiting, defined as more than three times in the 24 hours prior to inclusion in the study, or severe diarrhea defined as 3 or more watery stools per day.
4) Severe malnutrition (defined as the weight-for-height being below -3 standard deviation or less than 70% of median of the NCHS/WHO normalized reference values)
5) Presence of a significant medical or psychiatric condition, or any other serious or chronic clinical condition requiring hospitalization, or any other condition that in the opinion of the investigator precludes participation in the study.
6) Female patients must not be either lactating or pregnant as demonstrated by a negative serum point-of-care pregnancy test pre-dose (the result of the pre-dose assessment must be confirmed negative prior to dosing).
7) Employment under the direct supervision of the investigators or study staff.
8) Clinically significant alterations to hematologic or clinical chemistry parameters that in the opinion of the investigator precludes participation in the study, including:
a. AST/ALT > 3 x upper limit of normal range (ULN) and total bilirubin is normal
b. AST/ALT > 2 x ULN and total bilirubin is >1 and <1.5 x ULN and conjugated bilirubin is > 35% of the total bilirubin
c. Total bilirubin > 1.5 x ULN
d. Serum creatinine levels > 2 x ULN
e. Hb level < 8 g/dL
f. Platelet level < 50,000/mm3
9) Participation in a clinical study of another investigational small molecule within 30 days or investigational biologic within 90 days prior to study enrollment or planning to begin such participation during the study.
10) Have received any antimalarial treatment (alone or in combination) in the past containing:
a. Piperaquine, mefloquine, naphthoquine or sulphadoxine / pyrimethamine within the previous 6 weeks
b. Amodiaquine or chloroquine within the previous 4 weeks
c. Any artemisinin (artesunate, artemether, arteether or dihydroartemisinin) quinine, halofantrine, lumefantrine and any other anti-malarial treatment or antibiotics with antimalarial activity (including cotrimoxazole, tetracyclines, quinolones and fluoroquinolones, and azithromycin) within the past 14 days
11) Any medication from a list of prohibited medications as provided in Section 7.6. (page 65 of the Clinical Protocol)

Attachments

Attach Type	File Name
StudyPopulation	20200406_SJ733_Clinical_Protocol_V1.0_en.docx

Subject Recruitment Methods & Privacy: Using active voice, describe plans for the identification and recruitment of subjects, including how the population will be identified, and how initial contact will be made with potential subjects by those having legitimate access to the subjects' identity and the subjects' information.

Describe the setting in which an individual will be interacting with an investigator or how and where members of the research team will meet potential participants. If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate

populations as participants in clinical research. Describe steps taken to minimize undue influence in recruiting potential participants.

Please note: Based upon both legal and ethical concerns, the UK IRB does not approve finder's fees or "cold call" procedures made by research staff unknown to the potential participant. The ORI/IRB does not control permission to any UK listserv, mass mailing list, etc. Investigators must secure prior approval for access and use from owners/managers.

For additional details, see topic "Recruitment of Subjects/Advertising" on ORI's IRB Survival Handbook web page and the PI Guide to Identification and Recruitment of Human Subjects for Research [PDF].

Patients will be recruited from the community, local health-care clinics, and post-secondary educational institutions through word-of-mouth, active recruitment by study staff, and self-referral in response to advertisements. Verbal permission will be sought at private locations where advertisements will be posted, and a signed letter of authorization will be obtained from any performance site where recruitment activities take place. All recruitment materials will be approved by the EC before use. Advertisements will indicate the nature of the study and provide a phone number for further information. Currently, the recruitment sites include 14 villages that have health posts in the districts of Iquitos, San Juan Bautista, and Punchana. Some are located along the road and others at the edges of the rivers. The distance by land or river to the city of Iquitos is less than 1.5 hours, most less than 1 hour.

In each health post there are health personnel, including a laboratory technician, who will make the initial diagnosis of parasitemia (thick smear). The rate of mixed infections varies between 4% and 6% when thick smear is used as a diagnostic method. When a Patient tests positive for P. vivax malaria or P. falciparum monoinfection, the health personnel will call the study field coordinator by telephone, who can then send a field worker to verify the Patient's willingness to participate in the study. Study investigators or their designees will explain the study to potential research patients including the inclusion and exclusion criteria. Persons who indicate they are interested in participating in the study and are potentially eligible will be offered transport to a screening visit. During the screening visit, study investigators or their designees will assign a participant ID and provide the individuals with information about the study and an opportunity to ask questions. If the individual is willing, written informed consent for study participation will be obtained.

Back to Top

Advertising: Specify if any advertising will be performed. If yes, please see "IRB Application Instructions - Advertisements" for instructions on attaching copies of the information to be used in flyers or advertisements. Advertisements must be reviewed and approved by the IRB prior to use. For additional details, see topic "Recruitment of Subjects/Advertising" on ORI's IRB Survival Handbook web page for the *PI Guide to Identification and Recruitment of Human Subjects for Research* [D7.0000] document [PDF]. If you will be recruiting subjects via advertising at non-UK owned or operated sites, you should include a copy of written permission from that site to place the advertisement in their facilities.

Note: Print and media advertisements that will be presented to the public also require review by UK Public Relations (PR) to ensure compliance with UK graphic standards, and equal opportunity language. See Advertising Instructions for PR contacts.

Please find a copy of the advertisements attached.

The Patient Brochure has been designed in close collaboration with the local Peruvian research team to ensure it is consistent with local expectations and regulations. The Patient Brochure has also been reviewed and approved by UKPR and Communications Director at University of Kentucky Center for Clinical & Translational Science Mallory Powell. Email: mallory.powell@uky.edu Phone: 615.828.0000

Attachments

Attach Type	File Name
Advertising	20200501_Patient_Brochure_Cert_of_Translation.pdf
Advertising	20200615_Patient_Borchure_ES_EN_v2.pdf
Advertising	20200615_Patient_Borchure_ES_EN_v2_PRSTAMPED.pdf

Informed Consent Process: Using active voice, describe the consent/assent procedures to be followed, the circumstances under which consent will be sought and obtained, the timing of obtaining informed consent, whether there is any waiting period between informing the prospective subject and obtaining consent, who will seek consent., steps taken to minimize the possibility of coercion or undue influence, the method used for documenting consent, and if applicable who is authorized to provide permission or consent on behalf of the subject. Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application.

Describe provisions for obtaining consent/assent among any relevant special populations such as children (see Children in Research Policy [PDF] for guidance), prisoners (see Summary of Prisoner Regulations [PDF] for guidance), and persons with impaired decisional capacity (see Impaired Consent Capacity Policy [PDF] for guidance). Describe, if applicable, use of specific instruments or techniques to assess and confirm potential subjects' understanding of the nature of the elements of informed consent and/or a description of other written materials that will be provided to participants or legally authorized representatives. If you have a script, please prepare it using the informed consent template as a guide, and submit it on a separate page.

Informed Consent for Research Involving Emancipated Individuals
If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **when preparing the IRB application and prior to submitting the application to the IRB**. Include legal counsel's recommendations (legal counsel's recommendations may be attached in the E-IRB "Additional Information" section as a separate document, if necessary). For a complete definition of emancipated minors, see the section on *Emancipated Individuals* in the Informed Consent SOP [PDF].

Informed Consent for Research Involving Non-English Speaking Subjects
If you are recruiting non-English speaking subjects, the method by which consent is obtained should be in language in which the subject is proficient. Describe the process for obtaining informed consent from prospective subjects in their respective language (or the legally authorized representative's respective language). In order to ensure that individuals are appropriately informed about the study when English is their second-language, describe a plan for evaluating the level of English comprehension, and the threshold for providing a translation, or explain why an evaluation would not be necessary. For additional information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.

Research Repositories
If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the Sample Repository/Registry/Bank Consent Template [PDF]

Patients will be recruited from the community, local health-care clinics, and post-secondary educational institutions through word-of-mouth, active recruitment by study staff, and self-referral in response to advertisements. Verbal permission will be sought at private locations where advertisements will be posted, and a signed letter of authorization will be obtained from any performance site where recruitment activities take place. In each health post there are health personnel, including a laboratory technician, who will make the initial diagnosis of parasitemia (thick smear). When a Patient tests positive for P. vivax malaria or P. falciparum monoinfection, the health personnel will call the study field coordinator by telephone, who can then send a field worker to verify the Patient's willingness to participate in the study. Study investigators or their designees will explain the study to potential research patients including the inclusion and exclusion criteria. Persons who indicate they are interested in participating in the study and are potentially eligible will be offered transport to a screening visit. During the screening visit, study investigators or their designees will assign a participant ID and provide the individuals with information about the study and an opportunity to ask questions. If the individual is willing, written informed consent for study participation will be obtained.

Back to Top

Research Procedures: Describe the research procedures that will be followed. Identify all procedures that will be carried out with each group of subjects. Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project.

STUDY SPECIFIC PROCEDURES
1) Inclusion/exclusion criteria; Relevant medical history/Current medical conditions
2) Demography
3) Increased number of Physical examinations (body height, body weight, body temperature, blood pressure, pulse rate,)
4) Alcohol, drug and smoking history
5) Pregnancy test at completion or withdrawal
6) Meal record within 3 hours prior to the dose of study medication
7) Investigation New Drug administration (all cohorts will receive SJ733; cohorts 1 and 3 will also receive Cobicistat)
8) Study Completion information
9) ECG evaluation
10) Hematology; Blood chemistry; Urinalysis
11) Adverse Events tracking
12) Concomitant medication/ Significant non-drug therapies
13) Pharmacokinetic (PK) blood collection
14) Increased number of Parasitemia blood collection and assessment (microscopy/qPCR)
15) Parasite genetic assessments (to determine potential mechanisms of resistance)

STANDARD/ROUTINE CLINICAL CARE PROCEDURES
1) Single Physical examinations (body height, body weight, body temperature, blood pressure, pulse rate,)

2) Single Pregnancy test
3) Concomitant medication/ Significant non-drug therapies
4) diagnostic Parasitemia determinations (microscopy/qPCR)
5) Administration of local standard drug therapy

Attachments

Attach Type	File Name
ResearchProcedures	20200406_SJ733_Clinical_Protocol_V1.0_en.docx

Data Collection: List the data or attach a list of the data to be collected about or from each subject (e.g. interview script, survey tool, data collection form for existing data).

If the research includes survey or interview procedures, the questionnaire, interview questions or assessment scales should be included in the application (use attachment button below).

The data collection instrument(s) can be submitted with your application in draft form with the understanding that the final copy will be submitted to the IRB for approval prior to use (submit final version to the IRB for review as a modification request if initial IRB approval was issued while the data collection instrument was in draft form).

Note: The IRB approval process does not include a statistical review. Investigators are strongly encouraged to develop data management and analysis plans in consult with a statistician.

Details regarding the data to be collected throughout the trial from screening to finalization can be found on pages 61 - 65 of the attached Clinical Protocol and include:

• Written informed consent
• Demographic data
• Medical and surgical history and details of current medical conditions
• Social history (including previous and current use of alcohol, tobacco products and drugs of abuse)
• Previous and concomitant medications (medications used currently and in the 28 days prior to screening will be recorded in the patient's CRF)
• Use of herbal products
• Signs and symptoms of malaria
• Height and body weight
• A complete physical examination (excluding genitourinary unless indicated)
• Vital signs (blood pressure, pulse rate and axillary body temperature) after the patient has been resting in the supine position for 5 minutes
• Standard 12-lead ECG (single recording)
• Blood sampling for the following:
- determination of plasma drug concentrations (SJ773 and its primary metabolite SJ506)
- microscopy (thick and thin slides) for parasite counts and parasite species identification
- qPCR determined parasitemia
- hematology and chemistry safety laboratory tests, including methemoglobin
• Point-of-care whole blood/serum pregnancy test (females only)
• Review of eligibility criteria (including review of essential safety laboratory results).
• Monitoring and recording of AEs and SAEs
- G6PD enzyme test (P. vivax Patients only)

Attachments

Attach Type	File Name
DataCollection	20200406_SJ733_Clinical_Protocol_V1.0_en.docx

Resources: Describe what resources/facilities are available to perform the research (i.e., staff, space, equipment). Such resources may include a) staffing and personnel, in terms of availability, number, expertise, and experience; b) psychological, social, or medical services, including counseling or social support services that may be required because of research participation; c) psychological, social, or medical monitoring, ancillary care, equipment needed to protect subjects; d) resources for subject communication, such as language translation services, and e) computer or other technological resources, mobile or otherwise, required or created during the conduct of the research. Please note: Some mobile apps may be considered mobile medical devices under FDA regulations (see FDA Guidance). Proximity or availability of other resources should also be taken into consideration, for example, the proximity of an emergency facility for care of subject injury, or availability of psychological support after participation.

Research activities conducted at performance sites that are not owned or operated by the University of Kentucky, at sites that are geographically separate from UK, or at sites that do not fall under the UK IRB's authority, are subject to special procedures for coordination of research review. Additional information is required (see IRB Application Instructions - Off-Site Research web page); supportive documentation can be attached in the E-IRB "Additional Information" section. Provide a written description of the role of the non-UK site(s) or non-UK personnel who will be participating in your research. The other site may need to complete its own IRB review, or a cooperative review arrangement may need to be established. Contact the Office of Research Integrity at (859) 257-9428 if you have questions about the participation of non-UK sites/personnel.

If the University of Kentucky is the lead site in a multi-site study, or the UK investigator is the lead investigator, describe the plan for managing the reporting of unanticipated problems, noncompliance and submission of protocol modifications and interim results from the non-UK sites.

PI: Professor Alejandro Llanos Cuentas, MD, PhD.
Site name: Asociacion Civil Selva Amazonica (ACSA), Iquitos, Loreto-Peru.
Clinic is managed by Dr. Martin Casapia Morales MD

Alejandro Llanos Cuentas, Clinical lead. Dr. Llanos Cuentas has more than 30 years of experience in planning, direction, execution, monitoring and evaluation of clinical trials, research and interventions for the prevention and control of leishmaniasis and malaria. Dr. Llanos Cuentas is a founder and head of the Unit of Leishmania and Malaria, Instituto de Medicina Tropical "Alexander von Humboldt", Universidad Peruana Cayetano Heredia (UPCH), Lima, Peru and also serves as the president of a group of experts working on Malaria Elimination in partnership with the Peruvian Ministry of Health (MoH). Dr. Llanos Cuentas routinely serves on Data Safety Monitoring Boards for the NIH-USA and has been the Principal Investigator or Co-Investigator in more than 50 studies (30 clinical trials), including playing a pivotal role in several recent Phase 2 and 3 trials of antimalarials including tafenoquine and DSM265

The Asociacion Civil Selva Amazonica (ACSA) has been involved in conducting research with outstanding performance and community-wide acceptance since 2002, the site has been devoted to clinical research in the field of HIV, tuberculosis (TB), dengue, zika and malaria. ACSA has been established by DAIDS as a clinical research site for the HIV Vaccine Trials Network (HVTN) and the HIV Prevention Trials Network (HPTN), as result of this the site has big experience conducting clinical trials in high risk population (MSM) participants for different studies sponsored by the NIAID/NIH such as HPTN 039 where 200 HIV-negative, HSV-2 men who have sex with men (MSM) were enrolled, with a HIV incidence of 3.9 per 100 person-year and an incidence of HSV-2 positive genital ulcers by 63% , the site has also performed non-vaccines HIV prevention trials such as “Chemoprophylaxis for HIV Prevention in Men” (iPrEx) study, where it was the second largest enrolling site with 460 enrolled participants, the cohort participants from these studies are at increased risk for STIs, with consistently high incidences of Neisseria gonorrhea and Chlamydia trachomatis1,2,3,4. The site has also expertise enrolling general population for vaccines studies sponsored by the NIAD/NIH5, the site has currently ongoing a candidate Zika vaccine study sponsored by NIAID where 651 participants were enrolled (general healthy population). Recruitment and retention for all studies are achieved through community outreach including peer leaders and informational meetings in bars, nightclubs, and brothels for high risk population and at universities, institutes and neighborhoods for general population. ACSA has been recognized by DAIDS Networks for its outstanding achievements in enrollment, retention rates, and data quality. We have also performed observational studies sponsored by NIH were pregnant women and scholar children have been enrolled for studies related to parasitic infections.

Organizational Structure of the Clinical Site

ACSA is led by the Dr Casapia, who receive support functions from four different areas conformed by the IoRs, CRS Coordinator, Study Coordinators and Logistics. This organizational structure is flexible responsive and adaptable allowing for a cohesive and integrated approach to support the scientific priorities of the research networks. The ability to adapt hinges on having clear lines of authority, organizational components focused on providing centralized, common and standardized services, and organizational components that are focused on the particular needs of specific research projects. This structure is simple but capable of handling highly complex clinical trials, and also capable of responding to rapidly changing network and pharmaceutical industry needs. Clear lines of authority and communication channels reflect such a conceptual framework. The ACSA CRS Leader represented by Dr Casapia and CRS Coordinator provide the overall leadership to ensure cohesive and coordinated functioning of all CRS components in their interaction with the supporting areas. Each network trial is led by an Investigator of Record (IoR) and a Study Coordinator who knows every detail of the study and interacts with the CRS Coordinator and CRS Leader in order to achieve study goals. Alternatively, an experienced Community Advisory Board (CAB) guarantees community engagement in research development and implementation

The site includes Administrative, Clinic, Laboratory, Pharmacy, Data and Community Education areas, each led by an experienced Head of area. Dr Casapia is in daily communication with the Heads of each area by email, telephone, and in-person meetings. In addition, Dr Casapia and all the Heads of area meet at least twice a month to discuss all ongoing studies. The Heads of each area lead the staff in their respective sections, performing monthly meetings. The Clinic Section Head also oversees the Data Manager and the Pharmacist.

The ACSA site is currently housed in five buildings occupying a total area of 22,556 ft2, located 8 blocks from the main square. Their facilities include clinical, research, pharmacy, laboratory, data management, IT, and administration areas. The Clinical area is located in the first floors and has a total area of 8,544ft2, it has rooms for hospilization and an Emergency room. In the first floor we also have vaccination and infusion rooms used according protocol requirements in research. The research area is located in the second (6567ft2), third floor (2487ft2), four (2475ft2) and five floor (2475ft2). The second and third floor have 12 rooms used for counseling, informed consent process and medical examination, 2 waiting rooms, a pharmacy, two specimen collection rooms and vaccination rooms. The layout of the rooms is designed to provide comfort and confidentiality for participants from the different clinical trials. All the rooms used by participants are equipped with computers for the completion of self-administered questionnaires or any other kind of questionnaires according protocol requirements. In the third floor we also have a room designated to receive monitoring, audit or inspection visits from any local or international regulatory entity. The fourth floor has administrative areas, the office of the Principal investigator, the CRS coordinator and study coordinator are located in this floor. The fifth floor has the Data Management office and a room used for staff training.

ACSA provides the community with medical services in multiple specialty areas, outpatient services, hospitalization, surgery, 24-hour emergency, and diagnostic support. This area is comprised of 2 waiting rooms, a pharmacy, medical triage, 6 medical examination rooms, specimen collection room, surgery and recovery room. Within diagnostic support, ACSA provides X-Ray, mammography, ultrasound and EKG. There is also a shock trauma area, topical emergency and administrative offices.

Laboratory:

The ACSA laboratory is located on the second floor and has a total area of 4400 ft2. This area houses 2 areas of PBMC, biochemistry (clinical and research), hematology (clinical and research), immunology, microbiology, sample preparation, storage and laboratory management. The ACSA laboratory complies with international quality control standards and is currently certified by the College of American Pathologists and the UK-NEQAS, Digital PT Oneworld, IQA of DUKE University, who provide external quality control for evidence of competence. The laboratory infrastructure includes fully automated and semiautomatic equipment approved by the FDA of the United States. The entire team has regularly scheduled preventive maintenance.
The ACSA laboratory has a panel of more than 150 diagnostic tests. They include hematology (complete blood count, hemoglobin, ESR, hematocrit, platelet count, corpuscular constants, WBC, direct and indirect Coombs tests, TP, TPT, CD4 / CD8 counts, cell isolation and cryopreservation); Biochemistry (liver, lipids, thyroid and pregnant profile, glucose, urea, creatinine, arterial blood gases, troponin I); Immunology (rapid HIV tests, syphilis, C-reactive protein, ASO, latex, hCG, viral hepatitis B ELISA, viral hepatitis C, confirmatory HIV immunoblot test and tumor markers); Bacteriology (culture and sensitivity for urine, blood and bone marrow); Mycology (cultivation and isolation of fungi); and Parasitology (direct examination, concentration methods, stool culture and isolation). In addition, the ACSA Laboratory has agreed with an external laboratory for backup tests, IMPACTA Barraco Laboratory, Anglolab laboratory.

Pharmacy:

The ACSA Research Pharmacy is located on the second floor of the research clinic. There are 4 areas in total that are divided into: 2 storage areas, 1 preparation area for intravenous infusions and 1 area for pharmacy management. The pharmacy has 10.76 ft2 of total area with restricted access for all storage areas of study products, preparation of infusions and pharmacy files (insured by alarms and electric locks). The main door has an electric lock whose access is exclusive only to the Pharmaceuticals.

In the Management area, the administrative pharmacy tasks are performed, in this area there are cabinets with double keys for the documentation of the different protocols, Internet access, fax equipment, photocopier, telephone, computer equipment for every pharmacist also there is an air conditioning

The storage area is divided in two, one destined to store the products that need refrigeration or lower temperatures and the other area is for the products that are stored at room temperature. The room and equipments temperature are monitored 24 hours a day, 365 days a year through a system of automatic monitoring called Sensaphone. Additionally, all freezers and refrigerators are equipped with a continuous temperature monitoring and recording system that records the temperature in a circular format. This record is changed every week and stored in a closed cabinet. The equipment includes hygrometers and memory thermometers that measure the minimum and maximum temperature as backup monitoring.
The Infusion Preparation Area has a Biosafety Cabin, air filter system. (HEPA) This area has the accreditation of Microbiological Control (annual) and Particle Count (semi-annual)

Data:

The ACSA Data Management Area (AMDA) has the function of ensuring the quality of clinical research data, which are expressed in the functions of its members. Currently this area works with a data management scheme regulated by a Plan called Clinical Quality Management Plan (CQMP) and by the standard procedures called SOP of data management. The characteristic regulations of each protocol, of each network, are explained in the data management plans for the specific protocol.

ACSA data management Head of area has 15 years of experience performing QC/QA activities in different clinical trials obtaining a good data performance record. A Clinical Quality Management Plan is in place that governs the QC/QA activities.
The data management area has an appropriate infrastructure to maintain study documentation in optimal conditions and assure confidentiality. The data management area has a file area where is the documentation of protocols that were already closed is located on the third floor and the office area together with the documentation file of the active protocols located on the fifth floor. Access is restricted to data managers only. This office is fully equipped with a Multi-functional Printer, computers and air conditioner.

Currently this area has 23 highly trained professionals among data managers and data entries to perform Quality Assurance (QA) and Quality Control (QC) activities for the different research protocols. They are divided into three teams, each one for a defined protocol and all of them led by a protocol head.

Staffing Plans:

ACSA clinical area has a staff of physicians that offer care for cardiology, pulmonology, pediatrics, surgery, internal medicine, infectious diseases, neurology, and dermatology. The ACSA clinical research area has a staff of 20 physicians, 7 of them specialist in infectious diseases. The staff is also comprised of 10 nurses, 4 pharmacists, 6 medical technologists and 8 lab technicians.

Compliance Procedures and Capabilities of Clinical Site Related to IND Submissions:
The daily clinical research operations in the ACSA site are in full compliance with Good Clinical Practices (GCP), Good Clinical Laboratory Practices (GCLP), Human Subjects Protection (HSP), and U.S. FDA, NIAID and Peruvian regulations. Standard Operating Procedures, Pharmacy Establishment Plans, Quality Management Plans and an Evaluation Plan have been implemented, following DAIDS guidelines. The CRS Coordinator is responsible for overseeing, following and enforcing institutional, sponsor, local and federal regulatory policies. The CRS Coordinator is also responsible for delivering high-level quality data as well as secure and confidential study documents in compliance with Quality Standards from the DAIDS scientific research networks. Additionally, the ACSA Laboratory Director is responsible for performing assays under Good Clinical Laboratory Practices (GCLP). All research staff

are trained and certified in Research with Human Subjects and GCP, including refresher training every two years. Research at the site must be approved by an IRBs as a general rule. Standard operating procedures (SOPs) in place for all research activities are reviewed and updated as needed. Assessment of patient safety, treatments, and outcomes is performed by the study clinicians, overseen by Dr Casapia. Reporting of adverse events follows the guidelines of both IRBs; additional reporting to sponsors (e.g. DAERS) is performed for specific studies.
Data management is handled by a Data Manager overseen by the Head of area. For studies with onsite data entry, hard copies of the case report forms (CRFs) are reviewed at the end of each day by the Study Clinician. A second review is performed by the Data Manager, and data are entered in a secure, password-protected database.

Data and sample collection:

Collection of questionnaire data is performed by study clinicians, nurses, and counselors. Data management procedures are detailed above. Collection, labeling, storage, tracking, and transfer of samples are performed according to SOPs at the site. Briefly, samples are labeled by lab trained staff at the time of collection and in some cases by the study nurse; a log of collected samples is created simultaneously. The samples and log are processed or transferred according study requirements. Samples for storage or other tests (e.g. PBMC separation, nucleic acid amplification) are shipped and sent to the corresponding laboratory for processing. Lab staff has a big expertise in sending samples locally or internationally, most of lab staff has IATA training. When the samples are processed on site, there is a staff that receives the sample and verifies the samples and the documents received with it. Samples for cryopreservation are barcode labelled and entered into a Freezerworks sample tracking, biorepository, and freezer inventory program (LDMS). Shipments are prepared with a shipping manifest and transported internationally according to IATA regulations. Depending on required shipping conditions, samples are shipped at ambient temperature or on dry ice, using a commercial vendor (World Courier). These procedures have been highly successful for >15 years of research at the clinical site, and will be used to support VTEU studies.

Potential Risks: Describe any potential risks or likely adverse effects of the drugs, biologics, devices or procedures subjects may encounter while in the study. Please describe any physical, psychological, social, legal or other risks and assess their likelihood and seriousness.

SJ733 is a new investigational drug that has not yet been approved by the US Food and Drug Administration (FDA) or any other regulatory authority for commercial use. Therefore, there may be risks associated with SJ733 that are not foreseen, known, or understood at this time.

SJ733 has been well tolerated in clinical studies with 51 human volunteers including those experimental infected with malaria (P. falciparum). During the Phase 1a trial, all subjects tolerated the study drug well with no serious adverse events or dose limiting toxicities noted following receipt of the drug. Two adverse events (AEs) were judged to be possibly related to SJ733: 1) grade 1 low leukocyte count first noted on day 7 post dose in a clinically asymptomatic participant; 2) grade 2 proteinuria (2+ urine protein noted on urinalysis) at 24 h post dose in an otherwise asymptomatic participant with urine specific gravity of 1.023 (range 1.020–1.025) that was judged to be not clinically significant (trace proteinuria on days 2 and 7 post-dose, resolved by day 14 post dose). No Grade 3 or Grade 4 AEs were noted. There were no clinically significant ECG or methemoglobin formation findings.

During the Phase 1b the only SJ733-related adverse event observed was mild bilateral foot paraesthesia (Grade 1) seen in a single patient in the 150 mg cohort that lasted 3·75 h and resolved spontaneously. Transient asymptomatic inoculum-related clinical and laboratory adverse effects were observed in the 150 mg cohort but not with the higher dose of 600 mg. Laboratory changes observed in the first cohort included significant elevations in ALT in 3 subjects (> 5x ULN) where early and rapid recrudescence occurred. Clinical and laboratory adverse events were less common in cohort 2 (600 mg of SJ733), with only 1 subject experiencing ALT > 3x ULN. These transient and isolated ALT/AST elevations with no change in bilirubin have been observed in other malaria challenge studies including studies using registered antimalarials and are believed to be inoculum-related. No subjects had out of normal range methemoglobin values.

In studies in dogs, SJ733, at dose exposure levels much higher than what are expected in this study, caused reversible (temporary) methemoglobinemia after a single dose. Methemoglobinemia is a blood disorder in which an abnormal amount of methemoglobin, a form of hemoglobin, is produced. Hemoglobin is the protein in red blood cells that carries and distributes oxygen to the body. With methemoglobinemia, the hemoglobin can carry oxygen but is unable to release it so the body can use it. Early symptoms of methemoglobinemia include pale, gray or blue colored skin, lips, and nail beds, lightheadedness, headache, tachycardia (rapid heart rate), fatigue, shortness of breath, and lethargy. These symptoms in otherwise healthy people with methemoglobinemia are seen when methemoglobin levels are 20-30%. As part of this study patient methemoglobin levels will be closely followed before and after administration of SJ733.

Cobicistat (Tybost®) is a potent CYP3A4 inhibitor used as "pharmacoenhancer" for boosting exposures to CYP3A4 substrates and more particularly human immunodeficiency virus (HIV) drugs. Cobicistat was shown to be well tolerated in healthy subjects after both single dose (50-400 mg) and multiple dose (50-300 mg for 14 days) administration. After single dose administration all the AEs observed were of Grade 1. The most frequently reported AEs (in only 2 subjects) were headache, somnolence, and abnormal dreams. No notable changes in biology parameters, vital signs or ECGs (QTc) were detected in the first-in-man study. In subsequent studies with multiple dose administration of cobicistat, it was shown that the drug increases serum creatinine concentration by decreasing its elimination, resulting in a decrease in estimated glomerular filtration rate (eGFR). The rise in serum creatinine concentration and decline in eGFR was reversible within 7 days after the discontinuation of cobicistat. Cobicistat is approved in the USA. This study will use 3-consecutive daily doses of 150 mg of cobicistat. No significant changes have been observed in blood, hepatic, renal, or cardiac function attributable to SJ733 in people that have taken SJ733 or SJ733 in combination with cobicistat

As with all new drugs and combinations, unexpected and unforeseen adverse events can result. If the proposed therapy is ineffective

or not tolerated, patients will receive standard treatment from the study physicians following the protocol for treating malaria according to current Peruvians standards (see Available Alternative Treatment).

Back to Top

Safety Precautions: Describe the procedures for protecting against or minimizing any potential risks, *including risks of breach of confidentiality or invasion of privacy*. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects. Also, where appropriate, describe the provisions for monitoring the data collected to ensure the safety of subjects. If vulnerable populations other than adults with impaired consent capacity are to be recruited, describe additional safeguards for protecting the subjects' rights and welfare.

Established antimalarial therapy will be given if a patient meets any of the following criteria:
1) Clinical decline or lack of clinical improvement or decrease in platelets by > 20% for Patients with a platelet count at inclusion of between 50,000/mm3 and 74,999/mm3 (thrombocytopenia grade 2) or a drop in platelet count to < 50,000/mm3 for
Patients with a platelet count of > 75,000/mm3 at inclusion, at 24 hours for P. vivax malaria and 12 hours for P. falciparum malaria
Patients with a = 25% increase in parasitemia in comparison to baseline with or without fever.
2) Development of any clinical complications (WHO definition of complicated/severe malaria, WHO [2013])
3) Parasitemia > 100,000/µL for P. falciparum at any time with or without fever
4) Parasitemia > baseline (from the slides taken 30 min before start of treatment) with or without fever, 48 hours after first dose for P. vivax and 36 hours after first dose for P. falciparum
5) Failure to clear all parasites by microscopy associated with axillary fever > 37.5°C between 72 hours and 7 days for P. vivax and 60 hours and 5 days for P. falciparum
6) Failure to clear all P. vivax parasites by microscopy with or without fever on Day 7 and P. falciparum parasites by microscopy with or without fever on Day 5
7) Patient exhibits a rise of microscopically detectable parasitemia between Day 7 and Day 42 with or without fever
Following discharge, the patient will be monitored as an out-patient every 3-4 days: (on Days 7, 10 or 11, 14, 17 or 18, 21, 24 or 25, 28, and 35) until the final clinic visit on Day 42. At each visit the patient will be accompanied by the health care professional to Clínica de la Asociación Civil Selva Amazónica (ACSA) in Iquitos for the following examinations:
• Physical examinations and body temperature measurements will be conducted at every visit (Days 7, 10 or 11, 14, 17 or 18, 21, 24 or 25, 28, 35, 42).
• Blood samples will be taken for parasitology (microscopy and qPCR) at every visit (Days 7, 10 or 11, 14, 17 or 18, 21, 24 or 25, 28, 35, and 42).
• Additional blood samples for hematology and clinical chemistry assessments will be taken on Days 7, 14, 28, 35, and 42.
After discharge (negative microscopy), and during the 42 day follow up period, if a study subject displays parasitological signs (as confirmed by positive microscopy) or develops clinical signs of malaria, he/she will be given standard of care according to the national treatment guidelines and supervised by the investigator.

Patient data will be logged into an Electronic Data Capture system at site by the site. Where the data violate validation checks queries will fire within the system for the Investigator to address and respond. Medications will be coded using the WHO-drug dictionary. Medical conditions and AEs will be coded using the latest version of the MedDRA dictionary.

When data entry has been completed and all outstanding queries have been resolved for a CRF, the CRF will be eligible for QC checking. A sample of 9 (i.e. ?n + 1) Patients will be selected for QC checks and 100% of these Patients' data will be audited. In addition, 100% of demography, parasite count, AEs and withdrawal data will be checked for all Patients. The highest acceptable error rate for QC is 0.5%. A higher error rate will prompt a review of a further sample of 9 Patients. If the error rate remains above 0.5%, a 100% QC check of all data will be conducted.

All errors discovered will be corrected on the database and the corrections will be audit-trailed and will undergo a QC check. On satisfactory completion of the QC checks, the database will be locked.

Analytic data management will be performed by faculty and staff at the University of Kentucky. Methods for data transfer will involve a secure platform (e.g. REDCap SendIt! Feature). Data transfer protocols from independent CRO to UK faculty and staff data management team will be described in the data management plan (DMP).

Analytic data management will utilize Research Electronic Data Capture (REDCap) as an electronic data management system. REDCap is a software toolset and workflow methodology to manage research data for research studies. The consortium, initiated in August 2006, has shared the software and methodology with the larger research community of CTSA-, GCRC- and RCMI-participating institutions. The consortium is open to any academic institution, and members are provided with software and support at no charge, with the expectation that participants will contribute back to the overall project.

Limited study personnel will have administrative rights to make changes to the data, and all changes will be tracked through the REDCap audit trail. The data entered into the REDCap database is stored on servers in the UK Research Data Management Center and is backed-up on a regular basis. All raw datasets exported from REDCap as well as all analysis datasets are stored on UKHealthcare servers behind the medical center firewall. Access will be limited to study personnel involved with data management and data analysis.

SAS v9.4 or higher will be used to create and integrate any resulting datasets. SAS analysis datasets will be created, and SAS programs will be developed to further investigate potential data issues via simple descriptive statistics and plots. Summary reports will be provided periodically during the course of the project to verify accuracy of data entry and provide early opportunities for

clarification of questions and correction of errors and omissions. For analysis datasets, Data Definition Tables (DDTs) are included to document all variables (both raw and derived) included in the analysis datasets. This includes the variable name, label, type, length, format, coded values and logic for creating derived variables. All derived variables are independently programmed by two SAS programmers and then compared using SAS PROC COMPARE. All differences are documented and changes are made to the SAS code as necessary until the PROC COMPARE output is clean, i.e. showing no differences. For raw data, a data dictionary is available through REDCap. The data dictionary provides a description of all data fields including the field name, label, field type, response option coding and branching logic.
Project data will include raw survey data stored in REDCap and analysis. All project data will be maintained on UK Healthcare servers as described in the following section.

EDT Security: The EDT maintains a 900 square feet data center with independent power, cooling, and humidity control on the UK campus. The entire workspace is secured by electronic access with logged entry and exit to all facility offices and monitored with a security camera. The internal communication network is protected by multiple firewalls. All data on servers are sent to off-site backup each day. The network is managed by a full-time staff to support file servers, virtual machines, and the physical network. EDT undergoes periodic comprehensive audits in addition to a security risk assessment through UK HealthCare IT Security that is delivered bi-weekly. This includes a thorough review of Privacy and Confidentiality policies and procedures in addition to hardware security. The objective of the security risk assessment is to identify opportunities for improvement, prioritize any needed remediation activities, scope, and plan and remediate any found deficiencies. All source data, clinical records and laboratory data relating to the study will be retained in the archive for a minimum of 15 years after the completion of the study. Written agreement from the Sponsor must precede destruction of the same.

Benefit vs. Risk: Describe potential benefits to the subject(s); include potential benefits to society and/or general knowledge to be gained. Describe why the risks to subjects are reasonable in relation to the anticipated benefit(s) to subjects and in relation to the importance of the knowledge that may reasonably be expected to result. If you are using vulnerable subjects (e.g., impaired consent capacity, pregnant women, etc…), justify their inclusion by describing the potential benefits of the research in comparison to the subjects' vulnerability and the risks to them. For information about inclusion of certain vulnerable populations, see the IRB/ORI Standard Operating Procedure for Protection of Vulnerable Subjects [C3.0100] [PDF].

Malaria is a devastating disease inflicting high social and economic impact worldwide. To combat increasing levels of drug resistance, the WHO recommends combinations of artemisinin derivatives, the most potent and rapidly acting anti-malarial agents available, with long-acting antimalarials (ACT) for the treatment of uncomplicated P. falciparum malaria (e.g. Coartem® (artemether-lumefantrine), Eurartesim® (dihydroartemisinin-piperaquine), artesunate-mefloquine, etc.). Mutations continue to emerge that mediate resistance to artemisinin, delay parasite clearance upon artemisinin treatment, and may ultimately lead to treatment failures, suggesting artemisinin resistance is rapidly becoming a global issue. In addition, emerging cases of resistance to piperaquine in combination with dihydroartemisinin in Cambodia (unpublished results) as well as undesired side effects of mefloquine underline the need for development of a novel, safe, rapidly acting antimalarials, not subject to current resistance mechanism.

The clinical candidate SJ733 is an orally bioavailable, rapidly acting compound that targets PfATP4, a mechanism for which there is currently no resistance in the field. SJ733 is active against all drug-resistant malaria strains tested. It acts against both the blood and sexual stages of the parasite life cycle and is active against both Plasmodium falciparum and Plasmodium vivax. No significant toxicological responses have been seen in humans to date that can be attributed to SJ733 administration. SJ733 has been demonstrated to block the proliferation of the parasite causing malaria in human subjects. Overall, SJ733's excellent tolerability and safety profile, combined with its rapid antiparasitic effect and reduced susceptibility to resistance, support its candidacy as an antimalarial therapy and suggest it may afford a viable replacement for artemisinin in current treatment therapies.

The results of this study will help to find new treatments for malaria. The results of the study will help to see if SJ733 with or without cobicistat can be a new treatment for malaria. If SJ733 with or without cobicistat is shown to be safe and effective for the treatment of malaria, it may help other patients with malaria that cannot be cured with the currently available drugs.

SJ733 is a new investigational drug that has not yet been approved by the US Food and Drug Administration (FDA) or any other regulatory authority for commercial use. Therefore, there may be risks associated with SJ733 with or without combination with Cobicistat that are not foreseen, known, or understood at this time. If the proposed therapy is ineffective or not tolerated, patients will receive standard treatment from the study physicians following the standard protocol for treating malaria according to current Peruvians standards. A review of each study cohort will be conducted by the safety review team and the data and safety monitoring board and a decision reached as to whether the dose for the next cohort should be implemented. This decision will be based on change in parasitemia from baseline, safety and tolerability, and exposure up to Day 14. 2-6 cohorts of adult patients (10 patients per cohort) with acute, uncomplicated P. falciparum or P. vivax malaria will be run. In total, there will be a minimum of 20 and a maximum of 60 patients.

If success criteria for Cohort 1a are met, Cohort 2a will proceed with a lower exposure of SJ733. Likewise, if success criteria for Cohort 1b are met, Cohort 2b will proceed with a lower dose of SJ733. For the purposes of this decision, a-series cohorts (falciparum) will be treated independently from b-series (vivax) cohorts. If data from the first pair of cohorts do not meet the success criteria, but are inconclusive, the same dosing regimen may be repeated. The same approach will be used for progress from the second pair of cohorts to the third, but with the addition of the option to initiate a 3rd pair of cohorts, re-escalating SJ733 exposure by dosing the combination of SJ733 (300 mg) + cobicistat (150 mg) for three consecutive days. Established antimalarial therapy will be given if a patient meets any of the defined treatment failure criteria.

Dosing within a dose cohort will be paused if one serious adverse event (SAE; Section 8.1.2) is noted while determination of relatedness to study drug is being made. For a SAE, the decision of relatedness to study drug will ultimately be approved by the SRT and DSMB. The DSMB will determine if the nature of the event allows continuation. No additional subjects in the cohort will be dosed

if it is determined that the graded event meets the definition for stopping or if a second drug-related SAE is observed within that cohort.

Cohorts 1a and 1b are expected to achieve roughly five-fold higher plasma exposure of (+)-SJ733 than Cohorts 2a and 2b. Thus, if Cohorts 1a and 1b prove efficacious but repeated drug-related adverse events are observed, the Investigator, DSMB, and SRT may unanimously agree that no further patients should be recruited to Cohorts 1 but that patient recruitment to Cohorts 2 should still be pursued. In this scenario, the Investigator will assess the severity/intensity of the adverse reactions and clinical laboratory changes using the DMID Toxicity Grading Scale for Determining the Severity of Adverse Events provided in Attachment 3 and Section 8.1.2. This information will be relayed to the DSMB and SRT, who will make recommendations regarding further conduct of the trial, and if considered necessary, may recommend pausing or stopping further administration of the investigational product. Cohort progression will only be explored if the Investigator, DSMB, and SRT unanimously agree it is warranted and appropriate. These recommendations will also be communicated to the Ethics Committee and Regulatory Authority and any necessary updates will be made to the patient consent form.

Available Alternative Treatment(s): Describe alternative treatments and procedures that might be advantageous to the subjects, should they choose not to participate in the study. This should include a discussion of the current standard of care treatment(s).

The alternative is to not participate in the study and receive the standard medical attention currently available for the treatment of malaria. If the proposed experimental therapy is ineffective or not tolerated, patients will receive standard treatment from the study physicians following the standard protocol for treating malaria according to current Peruvians standards. Patients maintain the right to withdraw from the study and will receive the standard therapy at the conclusion of the study or at withdrawal to ensure resolution of their malaria. Even if the experimental therapy is effective, all patients will receive the standard therapy at the completion of the trial.

For P. falciparum mono-infection, a combination of Artesunate (AS) and Mefloquine (MQ), known as ASMQ, will be administered as two fixed dose tablets (100 mg AS and 200 mg of MQ) given daily for three consecutive days and supplemented with three tablets (15 mg each) of Primaquine phosphate (PQ) taken on the first day.

For P. vivax mono-infection, patients will be dosed with 25 mg/kg of Chloroquine (CQ) given over three days (day 1: 4 tablets, day 2: 4 tablets, and day 3: 2 tablets) supplemented with two tablets (15 mg each) of Primaquine phosphate (PQ) taken daily for seven consecutive days.

In the case of P. falciparum and P. vivax mixed infections, the ASMQ treatment regimen will be supplemented with two tablets (15 mg each) of Primaquine phosphate (PQ) taken daily for seven consecutive days.

Back to Top

Research Materials, Records and Privacy: Identify the sources of research material obtained from living human subjects. Indicate what information (specimens, records, data, genetic information, etc.) will be recorded and whether use will be made of existing specimens, records or data. Explain why this information is needed to conduct the study.

Return of Research Results or Incidental Findings (if applicable):
If research has the potential to identify individual results or discover incidental findings that could affect the health of a subject, describe plans to assess, manage, and if applicable disclose findings with individual subjects or provide justification for not disclosing. For IRB expectations, refer to the UK IRB “Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings" [PDF].

The medical records gathered during this study will be obtained and processed in electronic form that is used only for investigative purposes related to this study. These records may be reviewed by the Sponsor or their representatives, the, study team, Covance Inc., the Peruvian Ministry of Health through known agencies like the National Health Institute (INS); the Director General autoridad Nacional de Productos Farmacéuticos, Dispositivos médicos y productos sanitarios (ANM) (formerly DIGEMID, the United States Food and Drug Administration (FDA), the regulatory authorities of other countries, and the Ethics Committee (both Peru and the University of Kentucky located in the United States) in order to verify that the study is being carried out in the proper manner.

Any information or specimens that are collected will be identified only by a number code assigned to each patient's file. The study physician is responsible for tracking the list of codes that allow assigned number to be connected to individual patients. This list will be kept at the study site to guarantee that in case of an emergency they can be identified and contacted. The list of codes will be kept until the last request for commercialization of the research product has been received.

Blood samples (Safety, Efficacy, and Pharmacokinetic analysis) will be processed and de-identified at the ACSA site laboratory and the Universidad Peruana Cayetano Heredia Laboratory. Samples will be stored for up to five years and then will be destroyed following the destruction guidelines of the laboratory. Sample analysis will also be conducted at Instituto de Medicina Tropical Alexander von Humboldt de la Universidad Peruana Cayetano Heredia located at located in Av. Honorio Delgado 430, San Martín de Porres, Lima, Peru and Pyxant in Colorado, USA. The storage time allows the Sponsor to respond to regulatory questions related to the study and re-check specific protocol parameters. After that time, any remaining samples will be destroyed following the guidelines of the laboratory. Pyxant laboratories have processed pharmacokinetic samples for both the previously completed Phase 1a and Phase 1b trials. They have a well validated analytical method and will continue to analyze the pharmacokinetic samples to enable direct comparison to previously gathered data.

Patients will have the right to see and photocopy study-related records if the study physician has this information in his possession. At

the end of the study worldwide, the study results will be available for the different national regulatory entities, including the INS in Peru's case, who will have the information available in Spanish on this webpage http://www.ensayosclinicos-repec.ins.gob.pe. In addition, patients may ask the research doctor about the study results.

Confidentiality: Specify where the data and/or specimens will be stored and how the researcher will ensure the privacy and confidentiality of both. Please address the following items or indicate if the following has been addressed in a HIPAA or Limited Review form:

- physical security measures (e.g., locked facility, limited access);
- data security (e.g., password-protection, data encryption);
- who will have access to the data/specimens and identifiers;
- safeguards to protect identifiable research information (e.g., coding, links, certificate of confidentiality);
- procedures employed when sharing material or data, (e.g., honest broker if applicable, written agreement with recipient not to re-identify, measures to ensure that subject identifiers are not shared with recipients).
- management after the study

Describe whether data/specimens will be maintained indefinitely or destroyed. If maintained, specify whether identifiers will be removed from the maintained information/material. If identifiers will not be removed, provide justification for retaining them. If the data/specimens will be destroyed, describe how and when the data/specimens will be destroyed. For multi-site studies, the PI consults the study sponsor regarding retention requirements, but must maintain records for a minimum of six years after study closure. Also, specify who will access the identified data/specimens, and why they need access. If applicable, describe what measures will be taken to ensure that subject identifiers are not given to the investigator. If applicable, describe procedures for sharing data/specimens with entities not affiliated with UK.

HIPAA/FERPA Minimal Access Standards: The IRB expects researchers to access the minimal amount of identifiers to conduct the study and comply with applicable HIPAA and Family Educational Rights and Privacy Act (FERPA) requirements. If data are going to be collected, transmitted, and/or stored electronically, for appropriate procedures please refer to the guidance document "Confidentiality and Data Security Guidelines for Electronic Data" [PDF].

Cloud storage: For storage of data on cloud services other than UK OneDrive, please verify security settings are sufficient and in accordance with respective departmental, UK Corporate Compliance, and/or UK Information Technology requirements.

Creation of digital data application/program: If a research protocol involves the creation and/or use of a computer program or application, mobile or otherwise, please specify whether the program/application is being developed by a commercial software developer or the research team and provide any relevant information regarding the security and encryption standards used, how data is stored and/or transmitted to the research team, what information about the subjects the program/application will collect, etc. For relevant information to include, see Considerations for Protocol Design Concerning Digital Data [PDF]. The IRB may require software programs created or used for research purposes be examined by a consultant with appropriate Internet technology expertise to ensure subject privacy and data are appropriately protected.

NIH-funded genomic research: The National Institutes of Health (NIH) Genomic Data Sharing (GDS) Policy sets forth expectations that ensure the broad and responsible sharing of genomic research data consistent with the informed consent of study participants from which the data was obtained. If you are submitting genomic data to an NIH data repository, describe your NIH data sharing plan.

Management after study: Describe how the collected data/specimens will be managed after the end of the study. Specify whether identifiers will be removed from the maintained information/material. If identifiers will not be removed, provide justification for retaining them and specify what steps will be taken to secure the data/specimens (e.g., maintaining a coded list of identifiers separate from the data/specimens).

If the data/specimens will be destroyed, describe how, when, and why this will be done. Note that destruction of primary data may violate NIH and NSF retention and sharing requirements, journal publication guidance, and University Data-Retention policies. Additionally, primary data may be necessary for other purposes (to validate reproducibility, for data sharing, or for evidence in various investigations). PIs should carefully consider whether the destruction of data is justified.

The investigator is responsible for retaining signed consent and assent documents and IRB research records for at least six years after study closure, as outlined in the Study Closure SOP [PDF]. If the research falls under the authority of the FDA or other regulatory agencies, or a study sponsor is involved, additional requirements may apply.

Back to Top

By signing the informed consent form, volunteers will give their consent for the study physician and his team to review their medical records gathered during this study. These records, and the information in them, will be obtained and processed in electronic form that is used only for investigative purposes related to this study. When we write about or share the results from the study, we will remove any personal information and communicate about the combined information. The volunteer's name and other information that may identify them will be kept private.

The volunteer's medical records may also be reviewed by the Sponsor (R. Kiplin Guy) or his representatives, the study team, Covance Inc., the Peruvian Ministry of Health through known agencies like the National Health Institute (INS); the Director General autoridad Nacional de Productos Farmacéuticos, Dispositivos médicos y productos sanitarios (ANM) (formerly DIGEMID, the United

States Food and Drug Administration (FDA), the regulatory authorities of other countries, and the Ethics Committee (both Peru and the University of Kentucky located in the United States) in order to verify that the study is being carried out in the proper manner. These professionals have a commitment to respect the confidentiality of the information and will keep the volunteer's identity and personal information confidential to the extent that the law permits.

Peruvian regulations require that the study physician and/or study personnel protect the privacy of patients information. We will do everything we can to prevent anyone who is not on the research team from knowing that the patients gave us information, or what that information is. All the information collected will be assigned a number code and the patient's identity will remain unknown. The patient's name and address will not be on the information that comes from the study center, so that they cannot be recognized by it. Any information collected that may be transferred outside of the country to the University of Kentucky will be identified only by the number code assigned to the patient's file. Still, absolute confidentiality cannot be guaranteed due to the need to share information in the matters previously described.

The study physician (Dr. Llanos) is responsible for tracking the list of codes that allow the volunteer's assigned number to be connected to their name. This list will be kept at the study site to guarantee that in case of an emergency they can be identified and contacted. The list of codes will be kept until the last request for commercialization of the research product has been received.

The volunteer's samples will be processed at the ACSA site laboratory and the Universidad Peruana Cayetano Heredia Laboratory. The samples will be stored for up to five years and then will be destroyed following the destruction guidelines of the laboratory

The coded samples will be stored for a maximum of five years after the last patient visit for the study at Instituto de Medicina Tropical Alexander von Humboldt de la Universidad Peruana Cayetano Heredia located at located in Av. Honorio Delgado 430, San Martín de Porres, Lima, Peru. The storage time allows the Sponsor to respond to regulatory questions related to the study and re-check specific protocol parameters. After that time, any remaining samples will be destroyed following the guidelines of the laboratory.

Patient data will be logged into an Electronic Data Capture system at the site by the site. Where the data violate validation checks queries will fire within the system for the Investigator to address and respond.
Medications will be coded using the WHO-drug dictionary. Medical conditions and AEs will be coded using the latest version of the MedDRA dictionary.

When data entry has been completed and all outstanding queries have been resolved for a CRF, the CRF will be eligible for QC checking. A sample of 9 (i.e. ?n + 1) Patients will be selected for QC checks and 100% of these Patients' data will be audited. In addition, 100% of demography, parasite count, AEs and withdrawal data will be checked for all Patients. The highest acceptable error rate for QC is 0.5%. A higher error rate will prompt a review of a further sample of 9 Patients. If the error rate remains above 0.5%, a 100% QC check of all data will be conducted.

All errors discovered will be corrected on the database and the corrections will be audit-trailed and will undergo a QC check. On satisfactory completion of the QC checks, the database will be locked.
Analytic data management will be performed with faculty and staff at the University of Kentucky. Methods for data transfer will involve a secure platform (e.g. REDCap SendIt! Feature). Data transfer protocols from independent CRO to UK faculty and staff data management team will be described in the data management plan (DMP).

Analytic data management will utilize Research Electronic Data Capture (REDCap) as an electronic data management system. REDCap is a software toolset and workflow methodology to manage research data for research studies. The consortium, initiated in August 2006, has shared the software and methodology with the larger research community of CTSA-, GCRC- and RCMI-participating institutions. The consortium is open to any academic institution, and members are provided with software and support at no charge, with the expectation that participants will contribute back to the overall project.

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each day. The network is managed by a full-time staff to support file servers, virtual machines, and the physical network. EDT undergoes periodic comprehensive audits in addition to a security risk assessment through UK HealthCare IT Security that is delivered bi-weekly. This includes a thorough review of Privacy and Confidentiality policies and procedures in addition to hardware security. The objective of the security risk assessment is to identify opportunities for improvement, prioritize any needed remediation activities, scope, and plan and remediate any found deficiencies. All source data, clinical records and laboratory data relating to the study will be retained in the archive for a minimum of 15 years after the completion of the study. Written agreement from the Sponsor must precede destruction of the same.

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

Long term storage of the trial data will utilize the University of Kentucky's (UK) Center for Clinical and Translational Science (CCTS) Biomedical Informatics (BMI) Core and CCTS Enterprise Data Trust (EDT). The EDT was developed by the CCTS Biomedical Informatics (BMI) Core. The EDT combines operational data from a number of different electronic systems into a single, data store, where the data is placed into standard forms, integrated, validated, and optimized for efficient, accurate retrieval. The EDT infrastructure includes a virtualized environment that supports individual virtual machines (VM) for researchers accessing data and resources. Each VM is configured with the preferred operating system (Windows, Ubuntu, Linux) and statistical software or tools (Excel, R, SAS, SPSS, Tableau) required for each project. VM's are configured/provisioned to best practice and continually monitored via VROP for compliance and performance. In most cases, VM's can be modified to optimize performance if necessary. The EDT provides highly secure and monitored environments to support special data collections included Center for Medicare & Medicaid Services (CMS) datasets for several investigators.

Back to Top

Payment: Describe the incentives (e.g., inducements) being offered to subjects for their time during participation in the research study. If monetary compensation is offered, indicate how much the subjects will be paid and describe the terms and schedule of payment. (It is IRB policy that provision should be made for providing partial payment to subjects who withdraw before the completion of the research. Monetary payments should be prorated or paid in full.)

There will be no monetary incentives for participation itself. There will be reimbursement of up to 85 Peruvian soles (~$25 USD) for each day that the patient misses work (lost wages) to go to the site for participating in the study, either for admission to study, receiving treatment, and follow-up appointments. In addition, they will be reimbursed up to a maximum of 50 Peruvian soles (~$15 USD) per visit for any transportation expenses, communication and food expenses incurred for the visits related to the study.

The reimbursement amounts were suggested by the clinical lead and his team and are based on clinical trials conducted at ACSA with the same target patient population over the last 5 years. These amounts have also been reviewed by the local Peruvian ethics committee (latest communication included as an attachment in the Additional Information Section). Patients will be recruited from 14 villages that have health posts in the districts of Iquitos, San Juan Bautista, and Punchana. Some are located along the road and others at the edges of the rivers. The distance by land or river to the city of Iquitos is less than 1.5 hours, most less than 1 hour. In general, the people who live in these recruitment areas are representative of the general population that suffers malaria in the Amazon region. They are generally mestizo and do not live in extreme poverty. However, they do depend on daily wages to support their family and most do not have personal vehicles and therefore must hire a combination of water taxi and rickshaw drivers to travel to the clinical site.

Costs to Subjects: Describe any costs for care associated with research (including a breakdown of standard of care procedures versus research procedures), costs of test drugs or devices, and research procedure costs that are the subject's responsibility as a consequence of participating in the research. Describe any offer for reimbursement of costs by the sponsor for research related injury care.

There will be no cost to subjects for participating in the trial. They may incur lost wages and travel costs when staying at the clinic or visiting test site for follow-up visits and they will be reimbursed as outlined above.

Data and Safety Monitoring: The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk research, clinical research, or NIH-funded/FDA-regulated clinical investigations.

If you are conducting greater than minimal risk research, clinical research, or your clinical investigation is NIH-funded/FDA-regulated, describe your Data and Safety Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.

If this is a *non-sponsored investigator-initiated* protocol considered greater than minimal risk research, clinical research, or your clinical investigation is FDA-regulated, *and* if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

If relying on an independent agent or committee for DSMB services, it is the PI's responsibility to establish the services with the agent or committee. Please be reminded that the PI must submit DSMB reports to the IRB via modification or continuing review.

We have contracted Covance to oversee Peruvian work, including regulatory submissions, medical and safety monitoring, pharmacovigilance, and site monitoring.

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

All SAEs, occurring after the signing of the ICF until the End of Study visit or up to 42 days after last dose of study drug, and regardless of study drug relationship, must be reported, within 24 hours of obtaining knowledge of the event, to the Contract Research Organization (CRO). The CRO will inform the Sponsor on the same day.

The SAE form will collect data surrounding the event (e.g. the nature of the symptom[s], time of onset in relation to initiation of therapy, duration, intensity, and whether or not therapy was interrupted or discontinued). The Investigator's assessment of the probable cause of the event will also be included. In addition, relevant medical history, concomitant medications, laboratory and diagnostic tests reports, and procedures as well as all pertinent medical information related to the event will also be collected.

The investigator or study site personnel will provide the initial notification by completing the SAE page in the eCRF. The SAE form must include the investigator's assessment of the relationship of the event to the study drug and must include the investigator's signature. Even if minimal information is available, it is imperative that the investigator always makes an assessment of causality, as causality assessment is one of the requirements for regulatory reporting. Based on the follow up information received the investigator can change his/her causality assessment and amend the SAE form accordingly.

Covance Pharmacovigilance will forward SAE queries directly to the investigator requesting additional information. It is the investigator's responsibility to be diligent in providing this information as soon as it is available.

If an event meets serious criteria and it is not possible to access the EDC, the SAE will be submitted electronically using this email address: SAEIntake@covance.com or FAX# 1 609 419 2609. If email access is not available, the SAE will be reported telephonically using a toll free number corresponding to the country (see Safety Management Plan)

If Covance Pharmacovigilance becomes aware of the case via a telephone call, the pharmacovigilance representative will document the event details on a telephone contact log which will be filed with the case. A request for a completed SAE form will be emailed to the Investigator site and the Covance Project Manager and Site Monitor will be notified.

Dates should be recorded in the DD/MMM/YYYY format, e.g. 01/JAN/2012. All personal health identifying information (PHI) must be deleted, which may identify the patient from supporting documents. (e.g. patient name, address). The investigator or study site personnel to call the site monitor with any questions regarding the completion of the SAE form.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable.

It is the responsibility of the Sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the investigator of their decision as soon as possible. It is the responsibility of the Sponsor to determine whether an event requires expedited reporting and to notify the investigator of their decision as soon as possible.

Any SAE/SAR/SUSAR, irrespective of causality assessment to study drug and expectedness per IB, must be reported to the Regulatory Authority by University of Kentucky or delegate and to the relevant EC by the PI or delegate within 7 calendar days after the Sponsor becomes aware of the event. If the initial report is incomplete, a complete report must be submitted within 8 days of sending the first response. If significant new information is received by University of Kentucky on a case already reported, the clock starts again, and this should be provided as a follow-up report within 15 calendar days of receipt of the information.

A SUSAR that is not fatal or life-threatening must be reported to the Regulatory Authority by University of Kentucky or delegate and to the EC by the PI or delegate and in any event within 15 calendar days after University of Kentucky first becomes aware of the event.

SAEs/SARs/SUSARs must be recorded and reported whether or not the investigator considers the SAE/SARs/SUSAR to be related to SJ733.

Photocopies of results, consultant report(s), a summary of the outcome of the reaction and the investigator's opinion of SJ733 relationship to the SAE/SUSAR will accompany the SAE form if and when available.

If any information relating to the study drug in a study becomes available after the submission of a final protocol to the competent authority, which may impact on the conduct of the study, including but not limited to the risk and benefit evaluations underpinning approvals and volunteers consent, University of Kentucky will notify the Investigator in writing as soon as practically possible and the parties will agree, in writing, what steps need to be taken, if any.

The Investigator will be required to provide the following information:
• Patient's ID number, date of birth and gender
• Description of the event

o Date, time of onset
o Clinical history
o Associated signs and symptoms
o Temporal association with the study drug
o Medical management, including rationale
o Pertinent laboratory tests
o Severity (see definition or toxicity score)
o Causal relationship to the study drug with investigator's rationale for causality assessment
• Other information
o Relevant past medical history
o Concomitant medications
o Autopsy report or expectation of an autopsy in the case of death
• Outcome of the event
o Date, time of resolution, if resolved
• Documentation of notification to the EC by the Investigator

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Additionally the Study will have an SRT and DSMB. The members of the Safety Review Team (SRT) are responsible for decisions related to the safety of patients and the continuation of the study. The SRT will assess preliminary safety, efficacy and pharmacokinetic data (if available) up to Day 14 of the first four patients enrolled, and thereafter upon completion of Day 14 assessments of each cohort and whenever else indicated as a result of safety concerns. The SRT will decide on the appropriateness of subsequent doses to be administered and continuation of the study.

The SRT will consist of the following people:
• the Principal Investigator (clinical lead - Dr. Llanos)
• the Sponsor (Dr. Guy)
• the Medical Monitor
• the Project Director

The SRT will be advised by the Data and Safety Monitoring Board (DSMB) and will attend the non-voting sessions of the DSMB Meetings. During the study, an external and independent DSMB appointed by the Sponsor will meet to review study data. The board will consist of at least the following voting members:
• a Statistician
• two independent Medical Experts

The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study Sponsor.

The timing of the DSMB reviews and scope of the data review will be detailed in the DSMB Charter. The DSMB will be required to review the safety and efficacy data upon completion of Day 14 assessments of each cohort, and whenever else as indicated by safety concerns. The DSMB members will also be informed of and review all SAEs and AESIs as and when they are reported. All procedures associated with DSMB reviews, including objectives, data handling and elements for review will be documented in the DSMB Charter. Meeting discussions and decisions will be documented in DSMB minutes. Voting sessions of the DSMB will be attended only by designated DSMB members.

Based on its review, the DSMB will make recommendations to the SRT regarding further conduct of the trial, and if considered necessary, may recommend pausing or stopping further administration of the investigational product. These recommendations will also be communicated to the Ethics Committee and Regulatory Authority as required.

Back to Top

Subject Complaints: Describe procedures (other than information provided in consent document) for handling subject complaints or requests for information about the research. The procedures should offer a safe, confidential, and reliable channel for current, prospective, or past research subjects (or their designated representative) permitting them to discuss problems, concerns and questions, or obtain information.

If the patients have any questions, comments, or complaints regarding any part of the study, or in case of harm related to the trial, or if they have an adverse reaction, they are requested to immediately contact:

Dr. Elmer Alejandro Llanos-Cuentas
Address: Asociación Civil Selva Amazónica (ACSA)
Urb. Jardín N.° 27 (altura cuadra 4 Av. Fanning)
Iquitos - Loreto
Telephone: 994 273 050
E-mail: elmer.llanos@upch.pe

If they have any concerns or questions about their rights as a volunteer in this research, they are encouraged to contact staff at the Comité Institucional de Bioética (CIB) de VÍA LIBRE:
• Ethich Committe Chairman: Lic. Karen Cruz Azaña
• Telephone: (+511) 203-9900 Monday to Friday from 09 am to 18 hrs
• Address: Jr. Paraguay 490, Cercado de Lima, Lima, Perú
• e-mail: comitebioetica@vialibre.org.pe

An Ethics Committee is a group of members who are impartial and independent to the medical investigators, and their function is overseeing the respect of the dignity and rights of the participants in the design and performance of the research projects.

Finally, if they believe their rights are violated or for any complaint, they can contact the National Institute of Health (General Office of Research and Technology Transfer, OGITT) regulatory agency for Peruvian clinical trials, through the following telephone number: 748 1111 extension 2191 or by written communication through the following e-mail: consultaensayos@ins.gob.pe, or by a formal document submitted through the Filing Desk of the institution or by appearing in person to the OGITT at the following address: Capac Yupanqui 1400, Jesús María, Lima 11.

Does your research involve **Non-English Speaking Subjects or Subjects from a Foreign Culture**?

(•) Yes ( ) No

Non-English Speaking Subjects or Subjects from a Foreign Culture

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.

Include contact information for someone who can act as a cultural consultant for your study. The person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted. The consultant should not have any direct involvement with the study. If you do not know someone who would be willing to act as your cultural consultant, the Office of Research Integrity will try to find someone to fill this role (this may delay the approval process for your protocol). Please include the name, address, telephone number, and email of the person who will act as the cultural consultant for your study. For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

For recruitment of Non-English speaking subjects, the consent document needs to be in the subject's native language. Download the informed consent template available in the E-IRB "Informed Consent/Assent Process" section and use it as a guide for developing the consent document. (Note: Your translated consent document can be attached to your application in the "Informed Consent" section; **be sure to save your responses in this section first**.)

If research is to be conducted at an international location, identify local regulations, laws, or ethics review requirements for human subject protection. If the project has been or will be reviewed by a local Ethics Committee, attach a copy of the review to the UK IRB using the attachment button below. You may also consult the current edition of the International Compilation of Human Research Standards

All documents pertaining to the study have been translated to Spanish, the local language in Iquitos, Peru by an independent certified translator. Translator asked a Peruvian colleague to be a cultural consultant to ensure the Spanish would be familiar to the people of Iquitos, Peru. Contact information is:
Daniella Razuri Váquez
Francisco de Zela 2086 - Lince - Lima - Lima - Perú
(+51)959392674
daniella.razuri@gmail.com

Study is currently being reviewed by the Peruvian Ethics Committee and CRO Covance Peru Services, S.A. is the Legal Representative in country and has facilitated the submission to the Peruvian EC ensuring local regulations, laws, and ethics review requirements are met.

Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis C, etc…)**?

○ Yes ◉ No

HIV/AIDS Research

If you have questions about what constitutes a reportable disease and/or condition in the state of Kentucky, see ORI's summary sheet: "Reporting Requirements for Diseases and Conditions in Kentucky" [PDF].

HIV/AIDS Research: There are additional IRB requirements for designing and implementing the research and for obtaining informed consent. Describe additional safeguards to minimize risk to subjects in the space provided below.

For additional information, visit the online IRB Survival Handbook to download a copy of the "Medical IRB's requirements for Protection of Human Subjects in Research Involving HIV Testing" [D65.0000] [PDF], and visit the Office for Human Research Protections web site for statements on AIDS research, or contact the Office of Research Integrity at 859-257-9428.

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:

Back to Top

1) involves testing a Nonsignificant Risk (NSR) Device, or
2) is being conducted under an investigator-held Investigational New Drug (IND) or Investigational Device Exemption (IDE)?

◉ Yes ○ No

PI-Sponsored FDA-Regulated Research

If the answer above is yes, then the PI assumes the regulatory responsibilities of both the investigator and sponsor. The Office of Research Integrity provides a summary list of sponsor IND regulatory requirements for drug trials [PDF], IDE regulatory requirements for SR device trials [PDF], and abbreviated regulatory requirements for NSR device trials [PDF]. For detailed descriptions see FDA Responsibilities for Device Study Sponsors or FDA Responsibilities for IND Drug Study Sponsor-Investigators.

- Describe your (the PI's) experience/knowledge/training (if any) in serving as a sponsor (e.g., previously held an IND/IDE); and
- Indicate if you have transferred any sponsor obligations to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity (provide details or attach FDA 1571).

The Sponsor, Rodney Kiplin Guy, is acting as individual person. He is the current holder of the US IND under which SJ733 is being developed.

The Sponsor´s research is focused on the discovery and development of novel small molecules that target the pathophysiology of oncology and protozoal infectious diseases. The Sponsor's work places a major focus on discovering new therapeutic chemotypes, determining their mechanism of action, and conducting proof-of-concept studies in pharmacokinetic/pharmacodynamic (PK/PD) models of disease. All the projects are intended to deliver well-validated compounds that have suitable pharmacokinetic and toxicology profiles for detailed in vivo studies and provide a chemical lead to start drug discovery. To date, the Sponsor's work has identified dozens of potential new leads for these diseases with novel mechanisms of action or novel applications. The Sponsor has contributed to repurposing drugs for clinical trials for ependymoma, infantile ALL, and medulloblastoma; contributed a repurposed clinical candidate for retinoblastoma; and produced a novel clinical candidate for malaria, (+)-SJ733, which is the subject of the proposed clinical trial.

Most relevant publications selected from over 150 peer reviewed papers:
a. Guiguemde WA, et al. Chemical genetics of Plasmodium falciparum. Nature 2010, 465, 311-331.
b. Jimenez-Diaz, M.B et al. (+)-SJ733, a clinical candidate for malaria that acts through ATP4 to induce rapid host-mediated clearance of Plasmodium. Proc. Natl. Acad. Sci. U. S. A., 2014, 111, E5455-E5462.
c. Floyd, D.M. et al Hit-to-Lead Studies for the Antimalarial Tetrahydroisoquinolone Carboxanilides. J. Med. Chem., 2016, 59, 7350-7362.
d. Gaur, A.H. et al. Safety, tolerability, pharmacokinetics, and antimalarial efficacy of a novel Plasmodium falciparum ATP4 inhibitor (SJ733): a first-in-human and induced blood stage malaria phase 1a/ 1b study. Lancet Infect. Dis., 2020, Published Online April 7, 2020: https://doi.org/10.1016/S1473-3099(19)30611-5.

He has been intimately involved in the previously completed Ph1a/1b trials:
NCT02661373 - Phase 1a, First-In-Human, Dose-Escalation Study of (+)-SJ000557733 (SJ733), an Oral, Novel Inhibitor of Plasmodium Falciparum Plasma Membrane Protein PfATP4
NCT02867059 - A Proof-of-concept Study to Assess the Effect of (+)-SJ000557733 (SJ733) Against Early Plasmodium Falciparum Blood Stage Infection in Healthy Participants

IRB policy requires mandatory training for all investigators who are also FDA-regulated sponsors (see Sponsor-Investigator FAQs). A sponsor-investigator must complete the applicable Office of Research Integrity web based training, (drug or device) before final IRB approval is granted.

Has the PI completed the mandatory PI-sponsor training prior to this submission?

◉ Yes ○ No

If you (the PI) have completed equivalent sponsor-investigator training, you may submit documentation of the content for the IRB's consideration.

Attachments

HIPAA

Is HIPAA applicable? ○ Yes ◉ No

(Visit ORI's Health Insurance Portability and Accountability Act (HIPAA) web page to determine if your research falls under the HIPAA Privacy Regulation.)

If yes, check below all that apply and attach the applicable document(s):

- ☐ HIPAA De-identification Certification Form
- ☐ HIPAA Waiver of Authorization

Attachments

STUDY DRUG INFORMATION

The term drug may include:

- FDA approved drugs,
- unapproved use of approved drugs,
- investigational drugs or biologics,
- other compounds or products intended to affect structure or function of the body, and/or
- complementary and alternative medicine products such as dietary supplements, substances generally recognized as safe (GRAS) when used to diagnose, cure mitigate, treat or prevent disease, or clinical studies of e-cigarettes examining a potential therapeutic purpose.

Does this protocol involve a drug including an FDA approved drug; unapproved use of an FDA approved drug; and/or an investigational drug?

◉ Yes ○ No

If yes, complete the questions below. Additional study drug guidance.

LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW

Drug Name:

SJ733 ((+)-SJ000557733) in an investigational new drug
cobicistat (Tybost®) is an FDA approved CYP3A4 inhibitor used as "pharmacoenhancer" for boosting exposures to CYP3A4 substrates and more particularly human immunodeficiency virus (HIV) drugs. In our study it will be used to boost exposure of SJ733.

Note: Inpatient studies are required by Hospital Policy to utilize the Investigational Drug Service (IDS). Use of IDS is highly recommended, but optional for outpatient studies. Outpatient studies not using IDS services are subject to periodic inspection by the IDS for compliance with drug accountability good clinical practices.

Indicate where study drug(s) will be housed and managed:

☐ Investigational Drug Service (IDS) UK Hospital

Other Location:

This is an international study only. There will be no participants enrolled at the University of Kentucky

Is the study being conducted under a valid Investigational New Drug (IND) application?

◉ Yes ○ No

If Yes, list IND #(s) and complete the following:

IND# 126652

IND Submitted/Held by:

Sponsor:	☑	Held By:	Rodney Kiplin Guy
Investigator:	☑	Held By:	Rodney Kiplin Guy
Other:	☐	Held By:	

☐ Checkmark if the study is being conducted under FDA's Expanded Access Program (e.g., Treatment IND) or if this is an Individual Patient Expanded Access IND (FDA Form 3926).

FDA's Expanded Access Program Information for Individual Patient Expanded Access INDs, and attach the following:

- FDA Form 3926;
- FDA expanded access approval or correspondence;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the "Expanded Access SOP" [PDF].

Please also complete and attach the Study Drug Form (PDF) (required):

Attachments

Attach Type	File Name
StudyDrug	300mg capsule CofA L0700840.pdf
StudyDrug	300mg capsule CofA L0700840_ES-LA.docx
StudyDrug	Eisai Label Text_United States_en_es.docx
StudyDrug	Tybost latest product label.pdf
StudyDrug	Tybost latest product label(es)-proofread.pdf
StudyDrug	SJ733_UK_Study_Drug_Form.pdf
StudyDrug	Cobi_UK_Study_Drug_Form.pdf
StudyDrug	20200501_SJ733_Investigators_Brochure_en.docx
StudyDrug	20200501_SJ733_Investigators Brochure_es.docx
StudyDrug	GMP Certificate_KCM_18FEB16.pdf
StudyDrug	SN0023 (2020 Ann Rpt).pdf

STUDY DEVICE INFORMATION

A DEVICE may be a:

- component, part, accessory;
- assay, reagent, or in-vitro diagnostic device;
- software, digital health, or mobile medical app;
- other instrument if intended to affect the structure or function of the body, diagnose, cure, mitigate, treat or prevent disease; or
- a homemade device developed by an investigator or other non-commercial entity and not approved for marketing by FDA.

For additional information, helpful resources, and definitions, see ORI's Use of Any Device Being Tested in Research web page.

Does this protocol involve testing (collecting safety or efficacy data) of a medical device including an FDA approved device, unapproved use of an approved device, humanitarian use device, and/or an investigational device?

○ Yes ◉ No

[Note: If a marketed device(s) is only being used to elicit or measure a physiologic response or clinical outcome, AND, NO data will be collected on or about the device itself, you may answer "no" above, save and exit this section, (Examples: a chemo drug study uses an MRI to measure tumor growth but does NOT assess how effective the MRI is at making the measurement; an exercise study uses a heart monitor to measure athletic performance but no safety or efficacy information will be collected about the device itself, nor will the data collected be used for comparative purposes against any other similar device).]

If you answered yes above, please complete the following questions.

LIST EACH DEVICE BEING TESTED IN STUDY IN THE SPACE BELOW

Device Name:

Is the study being conducted under a valid Investigational Device Exemption (IDE) or Humanitarian Device Exemption (HDE) application? See UK HUD SOP (PDF) for guidance.

○ Yes ○ No

If Yes, list IDE or HDE #(s) and complete the following:

IDE/HDE Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Check if this is a Treatment or Compassionate Use IDE under the Food and Drug Administration (FDA) Early Expanded Access program.

For Individual or Small Group Expanded Access, see FDA's Early Expanded Access Program Information, and attach the following:

- FDA expanded access approval or sponsor's authorization;
- An independent assessment from an uninvolved physician, if available;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the "Medical Device Clinical Investigations, Compassionate Use, and Treatment IDE SOP" [PDF]

Does the intended use of any device used in this study meet the regulatory definition of Significant Risk (SR) device?

- Yes. Device(s) as used in this study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- No. All devices, as used in this study do not present a potential for serious risk to the health, safety, or welfare of subjects/participants.

Please also complete and attach the Study Device Form (PDF) (required):

Attachments

RESEARCH SITES

In order for this section to be considered complete, you must click "SAVE" after ensuring all responses are accurate.

A) Check all the applicable sites listed below at which the research will be conducted. If none apply, you do not need to check any boxes.

UK Sites

- ☐ UK Classroom(s)/Lab(s)
- ☐ UK Clinics in Lexington
- ☐ UK Clinics outside of Lexington
- ☐ UK Healthcare Good Samaritan Hospital
- ☐ UK Hospital

Schools/Education Institutions

- ☐ Fayette Co. School Systems *
- ☐ Other State/Regional School Systems
- ☐ Institutions of Higher Education (other than UK)

***Fayette Co. School systems, as well as other non-UK sites, have additional requirements that must be addressed. See ORI's IRB Application Instructions - Off-site Research web page for details.**

Other Medical Facilities

- ☐ Bluegrass Regional Mental Health Retardation Board
- ☐ Cardinal Hill Hospital
- ☐ Eastern State Hospital
- ☐ Norton Healthcare
- ☐ Nursing Homes
- ☐ Shriner's Children's Hospital
- ☐ Veterans Affairs Medical Center
- ☐ Other Hospitals and Med. Centers

- ☐ Correctional Facilities
- ☐ Home Health Agencies
- ☑ International Sites

List all other non-UK owned/operated locations where the research will be conducted:*

*A letter of support and local context is required from non-UK sites. See *Letters of Support and Local Context* on the IRB Application Instructions - Off-Site Research web page for more information.

Clínica de la Asociación Civil Selva Amazónica (ACSA), Iquitos, Loreto - Peru

Attachments

Attach Type	File Name
-Letter of Support & Local Context	Letter of support ALLC 22May2020.pdf
-Letter of Support & Local Context	ACSA Clinical Site detailed.docx

B) Is this a multi-site study for which you are the lead investigator or UK is the lead site? ○ Yes ◉ No

If **YES**, you must describe the plan for the management of reporting unanticipated problems, noncompliance, and submission of protocol modifications and interim results from the non-UK sites in the E-IRB "Research Description" section under *Resources*.

If the non-UK sites or non-UK personnel are ***engaged*** in the research, there are additional federal and university requirements which need to be completed for their participation, such as the establishment of a cooperative IRB review agreement with the non-UK site. Questions about the participation of non-UK sites/personnel should be discussed with the ORI staff at (859) 257-9428.

RESEARCH ATTRIBUTES

Indicate the items below that apply to your research. Depending on the items applicable to your research, you may be required to complete additional forms or meet additional requirements. Contact the ORI (859-257-9428) if you have questions about additional requirements.

☐ Not applicable

Check All That Apply

	Click applicable listing(s) for additional requirements and/or information:
☐ Academic Degree/Required Research	
☐ Aging Research	
☐ Alcohol Abuse Research	
☐ Cancer Research	• Cancer Research (MCC PRMC)
☐ Certificate of Confidentiality	• Certificate of Confidentiality (look up "Confidentiality/Privacy...")
☑ CCTS-Center for Clinical & Translational Science	• CCTS (Center for Clinical and Translational Science)
☐ Clinical Research	• Clinical Research (look up "What is the definition of....)
☑ Clinical Trial	• Clinical Trial (look up "What is the definition of....) Determine if research meets NIH definition of clinical trial; *Reminder: Ensure compliance with applicable requirements including: • Clinicaltrials.gov registration; • Good Clinical Practice (GCP) training; and • Consent Posting Requirement [PDF] for federal funded trials.
☐ Clinical Trial Multicenter(excluding NIH Cooperative Groups)	
☐ Clinical Trial NIH cooperative groups (i.e., SWOG, RTOG)	
☐ Clinical Trial Placebo Controlled Trial	
☐ Clinical Trial UK Only	
☑ Collection of Biological Specimens	• Collection of Biological Specimens for Banking (look up "Specimen/Tissue Collection...") • Collection of Biological Specimens (look up "Specimen/Tissue Collection...")
☐ Collection of Biological Specimens for Banking	
☐ Community-Based Participatory Research	• Community-Based Participatory Research (look up "Community-Engaged...")
☑ Data & Safety Monitoring Board	• Data & Safety Monitoring Board (DSMB) *For Medical IRB: Service Request Form for CCTS DSMB
☐ Data & Safety Monitoring Plan	• Data & Safety Monitoring Plan
☐ Deception	• Deception* *For deception research, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"
☐ Drug/Substance Abuse Research	
☐ Educational/Student Records (e.g., GPA, test scores)	
☐ Emergency Use (Single Patient)	• Emergency Use (Single Patient) [attach Emergency Use Checklist] (PDF)
☐ Genetic Research	• Genetic Research (look up "Specimen/Tissue Collection...")
☐ Gene Transfer	• Gene Transfer
☐ GWAS (Genome-Wide Association Study) or NIH-funded study generating large scale genomic data	• HIV/AIDS Research (look up "Reportable Diseases/Conditions") • Screening for Reportable Diseases [E2.0000] (PDF)
☑ International Research	• International Research (look up "International & Non-English Speaking") • NIH Genomic Data Sharing (GDS) Policy (PDF)
☐ Internet Research	
☐ Planned Emergency Research Involving Waiver of Informed Consent	• Planned Emergency Research Involving Waiver of Informed Consent* *For Planned Emergency Research Involving Waiver of Informed Consent, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"
☐ Pluripotent Stem Cell Research	
☐ Recombinant DNA	
☐ Survey Research	
☐ Transplants	
☐ Use of radioactive material, ionizing radiation, or x-rays [Radiation Safety Committee review required]	
☐ Vaccine Trials	

- Use of radioactive material, ionizing radiation or x-rays for research

FUNDING/SUPPORT

If the research is being submitted to, supported by, or conducted in cooperation with an external or internal agency or funding program, indicate below all the categories that apply.

☐ Not applicable

Check All That Apply

☐ Grant application pending
☐ (HHS) Dept. of Health & Human Services
☐ (NIH) National Institutes of Health
☐ (CDC) Centers for Disease Control & Prevention
☐ (HRSA) Health Resources and Services Administration
☐ (SAMHSA) Substance Abuse and Mental Health Services Administration
☐ (DoJ) Department of Justice or Bureau of Prisons
☐ (DoE) Department of Energy
☐ (EPA) Environmental Protection Agency
☐ Federal Agencies Other Than Those Listed Here
☐ Industry (Other than Pharmaceutical Companies)
☐ Internal Grant Program w/ proposal
☐ Internal Grant Program w/o proposal
☐ National Science Foundation
☐ Other Institutions of Higher Education
☐ Pharmaceutical Company
☐ Private Foundation/Association
☐ U.S. Department of Education
☐ State

Other:

Global Health Innovative Technology Fund (GHIT) is an international public-private partnership between the Government of Japan, multiple pharmaceutical companies, the Bill & Melinda Gates Foundation, Wellcome Trust, and United Nations Development Programme (UNDP)

Click applicable listing(s) for additional requirements and/or information:

- (HHS) Dept. of Health & Human Services
- (NIH) National Institutes of Health
- (CDC) Centers for Disease Control & Prevention
- (HRSA) Health Resources & Services Administration
- (SAMHSA) Substance Abuse & Mental Health Services Administration
- Industry (Other than Pharmaceutical Companies) [IRB Fee Info]
- National Science Foundation
- (DoEd) U.S. Department of Education [PDF]
- DoJ) Department of Justice or Bureau of Prisons ([PDF]
- (DoE) Department of Energy Summary [PDF] and Department of Energy Identifiable Information Compliance Checklist [PDF]
- (EPA) Environmental Protection Agency [PDF]

Specify the funding source and/or cooperating organization(s) (e.g., National Cancer Institute, Ford Foundation, Eli Lilly & Company, South Western Oncology Group, Bureau of Prisons, etc.):

Global Health Innovative Technology Fund (GHIT) - Awarded
Grant# 3048113588
Grant title: Phase 2 Trial of SJ733, a Novel PfATP4 Inhibitor for Malaria

Add Related Grants

If applicable, please search for and select the OSPA Account number or Electronic Internal Approval Form (eIAF) # (notif #) associated with this IRB application using the "Add Related Grants" button.

If required by your funding agency, upload your grant using the "Grant/Contract Attachments" button.

Add Related Grants

Grant/Contract Attachments

Attach Type	File Name
GrantContract	G2016-226_R1.pdf

The research involves use of Department of Defense (DoD) funding, military personnel, DoD facilities, or other DoD resources. (See DoD SOP [PDF] and DoD Summary [PDF] for details)

○ Yes ◉ No

Using the “attachments” button (below), attach applicable materials addressing the specific processes described in the DoD SOP.

DOD SOP Attachments

Additional Certification: (If your project is federally funded, your funding agency may request an Assurance/ Certification/Declaration of Exemption form.) Check the following if needed:

☐ Protection of Human Subjects Assurance/Certification/Declaration of Exemption (Formerly Optional Form – 310)

OTHER REVIEW COMMITTEES

If you check any of the below committees, additional materials may be required with your application submission.

Does your research fall under the purview of any of the other review committees listed below? [*If yes, check all that apply and attach applicable materials using the attachment button at the bottom of your screen.*]

○ Yes ◉ No

☐ Institutional Biosafety Committee
☐ Radiation Safety Committee
☐ Radioactive Drug Research Committee
☐ Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)
☐ Graduate Medical Education Committee (GME)
☐ Office of Medical Education (OME)

Additional Information

- Institutional Biosafety Committee (IBC)--Attach required IBC materials
- Radiation Safety Committee (RSC)-- For applicability, see instructions and/or upload form [WORD] [PDF]
- Radioactive Drug Research Committee (RDRC)--information
- Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)**--Attach MCC PRMC materials, if any, per instructions
- See requirement of Office of Medical Education (OME)
- See requirement of Graduate Medical Education Committee (GME)

Attachments

**** If you are proposing a study involving cancer research, be sure to have "Cancer Research" marked in the E-IRB "Research Attributes" section.** If your study involves cancer research, ORI will provide a copy of your research protocol to the Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC). The MCC PRMC is responsible for determining whether the study meets the National Cancer Institute (NCI) definition of a clinical trial and for issuing documentation to you (the investigator) which confirms either that PRMC approval has been obtained or that PRC review is not required. Your IRB application will be processed and reviewed independently from the PRMC review.

ADDITIONAL INFORMATION/MATERIALS

Do you want specific information inserted into your approval letter? ◉ Yes ○ No

Approval Letter Details (e.g., serial #):

Submission Description: If you wish to have specific details included in your approval letter (e.g., serial #, internal tracking identifier, etc…), type in the box below exactly what you wish to see on the approval letter. What you type will automatically appear at the top of all approval letters, identical to how you typed it, until it is changed by you (Hint: don't include instructions or questions to ORI staff as those will appear in your approval letter). **If these details need to be changed as a result of revisions, continuation review, or modifications to the application, you are responsible for updating the content of the field below accordingly.**

Please note: All of the documents have received extensive input from the clinical PI and his team as well as from our CRO partner (Covance Inc). Additionally, they have been informally reviewed by several malaria focused physician scientists from various countries around the world.

As part of the Peruvian regulations, these documents are currently being reviewed by the Peruvian ethics committee Comité Institucional de Bioética (CIB) de VÍA LIBRE, which is acting as a local IRB. After their approval, we will apply to the Peruvian Ministry of Health for approval as well as through the Perurvian National Institute of Health (General Office of Research and Technology Transfer, OGITT), the regulatory agency for Peruvian clinical trials. Pending the outcome of these submissions and the UK IRB decision, we will be able to apply for our import license and hope to start the trial in early November. Due to the seasonality of Malaria, it is critical that we are actively recruiting patients during the rainy season (November - April).

On May 14th we received initial feedback from the Peruvian ethics committee Comité Institucional de Bioética (CIB) de VÍA LIBRE (attached below). These initial changes are included in this submission and have been resubmitted for final review by the Peruvian committee later this month.

Serial #000
Protocol Version 1.0
Consent Version 1.0
Investigator Brochure Version 1.0
Study Ads dated April 20,2020

Protocol/Product Attachments - For each item checked, please attach the corresponding material.

- ☑ Detailed protocol
- ☐ Dept. of Health & Human Services (DHHS) approved protocol (such as NIH sponsored Cooperative Group Clinical Trial)
- ☑ Drug Documentation (e.g., Investigator Brochure; approved labeling; publication; FDA correspondence, etc.)
- ☐ Device Documentation (e.g., Manufacturer information; patient information packet; approved labeling; FDA correspondence, etc.)
- ☐ Other Documents

Protocol/Product Attachments

Attach Type	File Name
AddInfoProduct	Eisai Label Text_United States_en_es.docx
AddInfoProduct	300mg capsule CofA L0700840_ES-LA.docx
AddInfoProduct	20200501_SJ733_Investigators_Brochure_en.docx
AddInfoProduct	20200501_SJ733_Investigators Brochure_es.docx
AddInfoProduct	PNAS_SJ733.pdf
AddInfoProduct	2020_LancetID.pdf
AddInfoProduct	300mg capsule CofA L0700840.pdf
AddInfoProduct	Tybost latest product label.pdf

AddInfoProduct	Tybost latest product label(es)-proofread.pdf
AddInfoProduct	20200615_Patient_Borchure_ES_EN_v2.pdf
AddInfoProtocol	EC comment letter_SJ733-2001 Dr. Elmer Llanos_14May20(en).pdf
AddInfoProtocol	20200406_SJ733_Clinical_Protocol_V1.0_en.docx
AddInfoProtocol	20200430_SJ733_Clinical_Protocol_V1.0_es.docx

NOTE: Instructions for Dept. of Health & Human Services (DHHS)-approved protocol]

If you have password protected documents, that feature should be disabled prior to uploading to ensure access for IRB review.

Additional Materials:

If you have other materials you would like to include in your application for the IRB's consideration, please attach using the Attachments button below.

[To view what materials are currently attached to your application, go to "Application Links" in the menu bar on the left and click "All Attachments".]

Attachments

Attach Type	File Name
AdditionInfoConsiderations	20200430_Peru_SJ733-2001_Insurance.pdf
AdditionInfoConsiderations	20200430_Peru_SJ733-2001_Insurance_Policy_es.PDF
AdditionInfoConsiderations	20200414_SJ733 Patient_Alert_Card_en.docx
AdditionInfoConsiderations	20200414_SJ733 Patient_Alert_Card_es.docx
AdditionInfoConsiderations	20200430_SJ733_Clinical_Protocol_V1.0_Cert_of_Translation.pdf
AdditionInfoConsiderations	20200501_Patient_Brochure_Cert_of_Translation.pdf
AdditionInfoConsiderations	20200501_Phase2a_Main_Consent_Cert_of_Translation.pdf
AdditionInfoConsiderations	20200501_SJ733_Investigators_Brochure_Cert_of_Translation.pdf
AdditionInfoConsiderations	20200501_Phase2a_PK_Consent_Cert_of_Translation.pdf
AdditionInfoConsiderations	EC GCP letter_16Jun20.pdf
AdditionInfoConsiderations	EC membership list 16Jun20.pdf
AdditionInfoConsiderations	Initial EC approval letter_16Jun20.pdf
AdditionInfoConsiderations	Institutional approval letter_09Jun20.pdf
AdditionInfoConsiderations	Main ICF SSV1.0_stamped 16Jun20.pdf
AdditionInfoConsiderations	PAC V1.0_stamped 16Jun16.pdf
AdditionInfoConsiderations	patient Brochure_Stamped 16Jun16.pdf
AdditionInfoConsiderations	PK ICF V1.0_stamped 16Jun16.pdf
AdditionInfoConsiderations	IRB Requested Revisions.pdf
AdditionInfoConsiderations	20201009_SJ733-2001_INS_Submission_full.pdf

SIGNATURES (ASSURANCES)

On all IRB applications there is a requirement for additional assurances by a Department Chairperson (or equivalent) [hereafter referred to as "Department Authorization" (DA)], and when applicable, a Faculty Advisor (FA) (or equivalent), which signifies the acceptance of certain responsibilities and that the science is meritorious and deserving of conduct in humans. Note: the individual assigned as DA *should not* also be listed in the Study Personnel section, the individual assigned as FA *should* be listed in the Study Personnel section.

For a list of responsibilities reflected by signing the Assurance Statement, download the guidance document "What does the Department Chairperson's Assurance Statement on the IRB application mean? [PDF]"

Required Signatures:

First Name	Last Name	Role	Department	Date Signed	
Joseph	Chappell	Department Authorization	Pharmaceutical Sciences	06/22/2020 11:47 AM	View/Sign
Rodney	Guy	Principal Investigator	Pharmaceutical Sciences	06/22/2020 11:21 AM	View/Sign

Department Authorization

☑ This is to certify that I have reviewed this research protocol and that I attest to the scientific validity and importance of this study; to the qualifications of the investigator(s) to conduct the project and their time available for the project; that facilities, equipment, and personnel are adequate to conduct the research; and that continued guidance will be provided as appropriate. When the principal investigator assumes a sponsor function, the investigator has been notified of the additional regulatory requirements of the sponsor and by signing the principal investigator Assurance Statement, confirms he/she can comply with them.

*If the Principal Investigator is also the Chairperson of the department, the Vice Chairperson or equivalent should complete the "Department Authorization".

**IF APPLICABLE FOR RELIANCE: I attest that the principal investigator has been notified of the regulatory requirements of both the Reviewing and Relying IRBs, according to the information provided in the E-IRB application. The attached Reliance Assurance Statement, signed by the principal investigator, confirms that he/she can comply with both sets of IRB requirements.

Principal Investigator's Assurance Statement

I understand the University of Kentucky's policies concerning research involving human subjects and I agree:

1. To comply with all IRB policies, decisions, conditions, and requirements;
2. To accept responsibility for the scientific and ethical conduct of this research study;
3. To obtain prior approval from the Institutional Review Board before amending or altering the research protocol or implementing changes in the approved consent/assent form;
4. To report to the IRB in accord with IRB/IBC policy, any adverse event(s) and/or unanticipated problem(s) involving risks to subjects;
5. To complete, on request by the IRB for Full and Expedited studies, the Continuation/Final Review Forms;
6. To notify the Office of Sponsored Projects Administration (OSPA) and/or the IRB (when applicable) of the development of any financial interest not already disclosed;
7. Each individual listed as study personnel in this application has received the mandatory human research protections education (e.g., CITI);
8. Each individual listed as study personnel in this application possesses the necessary experience for conducting research activities in the role described for this research study.
9. To recognize and accept additional regulatory responsibilities if serving as both a sponsor and investigator for FDA regulated research.

☑ Furthermore, by checking this box, I also attest that:

- I have appropriate facilities and resources for conducting the study;
- I am aware of and take full responsibility for the accuracy of all materials submitted to the IRB for review;
- If applying for an exemption, I also certify that the only involvement of human subjects in this research study will be in the categories specified in the Protocol Type: Exemption Categories section.
- If applying for an Abbreviated Application (AA) to rely on an external IRB, I understand that certain items above (1, 3, 4, 7-8) may not apply, or may be altered due to external institutional/IRB policies. I document my agreement with the Principal Investigator Reliance Assurance Statement by digitally signing this application.

*You will be able to "sign" your assurance after you have sent your application for signatures (use Submission section). Please notify the personnel required for signing your IRB application after sending for signatures. Once all signatures have been recorded, you will need to return to this section to submit your application to ORI.

SUBMISSION INFORMATION

Each Section/Subsection in the menu on the left must have a checkmark beside it (except this Submission section) indicating the Section/Subsection has been completed; otherwise your submission for IRB review and approval will not be able to be sent to the Office of Research Integrity/IRB.

Please remember to update, when applicable, the Approval Letter Details text box under the Additional Information section to ensure verbiage you want on your approval letter is accurate.

If your materials require review at a convened IRB meeting which you will be asked to attend, it will be scheduled on the next available agenda and a message will be forthcoming to notify you of the date.

If you are making a change to an attachment, you need to delete the attachment, upload a highlighted version that contains the changes (use Document Type of "Highlighted Changes"), and a version that contains the changes without any highlights (use the appropriate Document Type for the item(s)). Do **not** delete approved attachments that are still in use.

Your protocol has been submitted.

MAIN INFORMED CONSENT

TITLE:	An Open Label Phase 2a Study to Assess the Efficacy, Safety, Tolerability and Pharmacokinetics of (+)-SJ000557733 (SJ733), with or without Combination with Cobicistat, in Adult Patients with Acute, Uncomplicated Plasmodium Falciparum or Vivax Malaria Mono-Infection over a 42 Day Period
PROTOCOL NO.:	SJ733-2001
SPONSOR:	Rodney Kiplin Guy 789 South Limestone Lexington, KY 40536 United States of America (USA)
LEGAL REPRESENTATIVE:	Covance Perú Services S.A. Av. De La Floresta 497, Int. 201, Edificio Parque Las Lomas, San Borja, ZIP 15038, Perú
INVESTIGATOR:	Dr. Elmer Alejandro Llanos-Cuentas Telephone: 994 273 050 E-mail: alejandro.llanos.c@upch.pe
SITE NAME:	Asociación Civil Selva Amazónica (ACSA) Centro de Investigacion: Asociación Civil Selva Amazónica. RCI - 287 Urb. Jardín N.° 27 (altura cuadra 4 Av. Fanning) Iquitos, Loreto – Perú
IRB NAME:	Comité Institucional de Bioética (CIB) de VÍA LIBRE Jr. Paraguay 490, Cercado de Lima, Lima, Perú
REGULATORY AUTHORITY:	Instituto Nacional de Salud

PATIENT INFORMATION FOR AN OPEN LABEL PHASE 2A STUDY TO ASSESS THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF (+)-SJ000557733 (SJ733), WITH OR WITHOUT COMBINATION WITH COBICISTAT, IN ADULT PATIENTS WITH ACUTE, UNCOMPLICATED PLASMODIUM FALCIPARUM OR VIVAX MALARIA MONO-INFECTION OVER A 42 DAY PERIOD

INTRODUCTION

We are inviting you to volunteer for an experimental research study authorized by the Comité Institucional de Bioética VÍA LIBRE (CIB) and Instituto Nacional de Salud (INS). The study will test a newly discovered research product called SJ733 with or without cobicistat as a new treatment for malaria. Cobicistat blocks the body's ability to metabolize (break-down) other medicines. The study will test SJ733 with or without cobicistat to see if SJ733 with cobicistat is safe and if cobicistat can increase the amount of SJ733 that remains in the body and therefore improve the effect that SJ733 may have on malaria.

We are asking you to participate because you have been diagnosed with malaria. To assure your voluntary participation without being obligated by someone (coercion), please take the time to carefully understand the information about the two research products SJ733 and cobicistat as well as the study. The team will answer any questions you have. The contact information for the investigator in charge of the study is given below.

It is very important that you fully understand the study before agreeing to participate.

Rodney Kiplin Guy is supporting this research by providing funding, SJ733, and cobicistat for use in this study and is sometimes referred to as "Sponsor". The study doctor will receive payment/compensation for conducting this study.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

This study will help us learn more information about whether SJ733 (research product) when given with or without cobicistat (research product) is safe and can effectively treat malaria. SJ733 is new and not approved by the United States Food and Drug Administration (FDA) or the autoridad Nacional de Productos Farmacéuticos, Dispositivos médicos y productos sanitarios (ANM; formerly DIGEMID). Cobicistat is not approved by the FDA nor by the ANM for the treatment of malaria. Your participation in this research will last about 42 days.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

The results of the study will help to see if SJ733 with or without cobicistat can be a new treatment for malaria. SJ733 may help you with your malaria but there is no guarantee it will work. If SJ733 with or without cobicistat is shown to be safe and effective for the treatment of malaria, it may help other patients with malaria that cannot be cured with the currently available drugs.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

There are possible side effects of SJ733 including nausea (feeling sick to the stomach), dizziness, loss of appetite, vomiting, diarrhea, fever, headaches, fatigue (tiredness or low energy). These effects have been mild to moderate and have not stopped previous volunteers from taking SJ733. In dogs, large amounts of SJ733 affected the way blood cells carry oxygen to the body. The effects went away after SJ733 was stopped. This has never been seen in humans. Cobicistat can cause jaundice (yellowing of the skin and/or whites of the eyes) and skin rash. It can also decrease how well your kidneys work. We will closely

monitor your health during the study. There is more information about the risks of the study later in this consent. If you are pregnant or nursing, you cannot participate. You or your partner should not become pregnant during this study. The complete study will take a lot of your time and you will need to remain in Iquitos for five consecutive days and return to Iquitos for some follow-up visits.

DO YOU HAVE TO TAKE PART IN THE STUDY?

You do not have to take part in the study. If you take part in the study, it should be because you want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer. If you do not participate in the study, you will receive the standard treatment for malaria in Peru.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study contact Elmer Alejandro Llanos-Cuentas MD, Ph.D. at 994 273 050 or alejandro.llanos.c@upch.pe.

If you have any concerns or questions about your rights as a volunteer in this research, contact staff at the Vía Libre Ethics Committee at 511 203-9900 ext. 131.

DETAILED INFORMED CONSENT

1. STUDY PURPOSE

People get malaria after a bite from a mosquito infected with the malaria parasite. The malaria first infects the liver and then the blood. The most common symptoms of malaria (fever, chills, general discomfort, headaches, muscle aches) are caused by the infected blood cells bursting. Malaria can make someone very sick and even cause death if not treated with medicine.

The goal of this study is to test if a newly discovered research product called SJ733 taken with or without cobicistat is safe and if it kills the parasites that cause malaria. Cobicistat blocks the body's ability to metabolize (break-down) other medicines. The study will test SJ733 with or without cobicistat to see if SJ733 with cobicistat is safe and if cobicistat can increase the amount of SJ733 that remains in the body and therefore improve the effect that SJ733 may have on malaria. The study will also determine how much SJ733 a patient must take to work its best.

SJ733 is still being studied and is not yet approved to treat malaria by the United States Food and Drug Administration (FDA), autoridad Nacional de Productos Farmacéuticos, Dispositivos médicos y productos sanitarios (ANM; formerly DIGEMID), or any other regulatory agency for public use. Cobicistat is approved by the ANM and FDA only when combined with several human immunodeficiency virus (HIV) drugs to increase the amount of those HIV drugs that remain in the body. Cobicistat is not approved by the FDA, ANM, or any other regulatory agency for the treatment of Malaria.

2. WILL YOU BENEFIT FROM PARTICIPATING IN THIS STUDY?

We do not know if you will get any direct benefit from participating in this study. SJ733 with or without cobicistat may cure your malaria. The results of the study will help to find new treatments for malaria. If SJ733 with or without cobicistat is safe and cures malaria, this research product could be a great help for other malaria patients. Malaria is becoming resistant to current standard treatments so the number of patients that are not able to be cured is rising worldwide.

3. WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?

This study will take place in Iquitos, Peru at the Asociación Civil Selva Amazónica (ACSA). The complete study will last about 42 days. This study is estimated to include 20 to 60 research subjects (participants) and will be carried out only in Peru.

4. HOW MUCH WILL IT COST YOU TO PARTICIPATE?

You will not be charged for any services specifically required for this study. The Sponsor will cover the cost of the research products, all the associated tests, hospitalization, clinical visits (including transportation costs and food), and any hotel bills (if required) for this study.

5. WILL YOU RECEIVE ANY REWARDS FOR PARTICIPATING IN THIS STUDY?

You will not receive any payment for your participation in the study. However, you will receive up to S/. 85 soles for each day that you miss work (lost wages) to go to the site for participating in the study, either for admission to the study, receiving treatment and/ or follow-up appointments. In addition, you will be reimbursed up to a maximum of S/. 50 soles per visit for any transportation expenses, communication and food expenses incurred for the visits related to the study.

6. ALTERNATIVE TREATMENTS

Your alternative is to not participate in the study and receive treatment according to the malaria regulations of Peru. Your study physician will explain to you what the alternative treatments are and discuss with you their risks and benefits.

7. ARE THERE REASONS WHY YOU DO NOT QUALIFY FOR THIS STUDY?

You should not take part in this study if:

- you are not willing or able to comply with the study requirements
- you are unable to give informed consent
- you are under the age of 18
- you are over the age of 70
- you weigh less than 45 kg
- you weigh more than 90 kg
- you are severely sick including severe vomiting or diarrhea, either because of malaria or another disease
- you are pregnant or breast feeding
- you are unable to remain sexually abstinent or use methods to prevent pregnancy (oral/injectable contraceptives and barrier contraception, e.g. condom)
- you are unable to swallow pills
- you have laboratory tests that do not meet the requirements to remain in the study
- you are unable to remain in Iquitos for at least five days and unable to attend all study visits
- you are an employee under the direct supervision of the investigators or study staff

- you have volunteered for another study with a drug that is not allowed in this study
- your malaria is caused by more than one species of parasite
- you are taking other medications that are not allowed in this study

8. PATIENT RESPONSIBILITIES

To monitor your health, the study will be under the direct supervision of the study physician and will be conducted by trained personnel. Please provide all information about your current and past health (medical) history at the screening visit. We need this information to protect your health.

Your responsibilities as a study patient/participant are the following:

- Provide honest and complete information about your medical history and current medical conditions
- Notify the study physician about any other medications or herbs/home remedies that you have taken, are taking, or plan to take.
- Notify the study physician of any other research studies you have been in during the last three months, are currently in, or plan to be in.
- Notify the study physician if you have had malaria in the last three months and of any other treatments you have received or are receiving.
- Notify the study physician about any problems you have during the study.
- Take the research product as indicated by the study physician and study personnel.
- Remain at the clinic as required by the study.
- Immediately notify study personnel about any side effects that you have, including changes that you may not consider important.
- Follow the instructions and come back for your scheduled visits.

9. WHAT WILL YOU BE ASKED TO DO?

If you choose to participate, you will sign this informed consent form in two copies agreeing to become a research subject (participant). Next, you will have blood samples drawn (about 24 mL or 5 teaspoons) and be asked for a urine sample for routine laboratory tests and to identify the type of malaria you have (there are more than one). You will be asked a series of questions about your medical history. You will have a physical exam and vital signs taken. We will test how your heart is working with an electrocardiogram (ECG).

An ECG involves sticking several monitors (which look like small stickers) onto your chest and monitoring your heartbeat. The study doctor will determine whether you can participate in the study.

We do not know the effects of SJ733 during pregnancy. You cannot participate if you are pregnant or nursing. For this reason, you or your partner will receive counseling on how to avoid pregnancy. Also, you will receive free contraceptives (birth control) that should be used the entire time that you participate in this trial and for 30 days after you stop taking the research product.

If you participate, it is important that you take the research product exactly as indicated by the study physician, return for all follow-up visits, and comply with all study requirements.

If your screening tests show that you can continue in the study, you will be given either SJ733 alone or together with cobicistat once every day for three days in a row. You will remain in Iquitos for five days so the investigators can see how the treatment works. You will also return to the clinic in Iquitos for nine follow-up visits on Days 7, 10 or 11, 14, 17 or 18, 21, 24 or 25, 28, 35, and 42. For more details see to the Appendix: Study Visits & Procedures.

Every day that you are at the clinic, you will have a brief physical examination, your vital signs monitored, and blood samples drawn. The blood samples will measure the amount of research product in your blood, the number of parasites in your blood, and your general health. Each blood draw will be about 5 to 35 mL of blood (1-7 teaspoons). During the entire study of 42 days, about 227 mL (46 teaspoons) of blood will be drawn. This may sound like a lot, but your body will replace the blood drawn and the amount drawn is normal for these types of studies. During this time, you must not take any other medications, unless approved by your doctor. For more details, refer to the Appendix: Study Visits & Procedures.

During the study, if your malaria returns or gets worse, you will be given the standard malaria treatment according to the malaria regulations of Peru. You will be asked to continue in the study with the study visits as defined in the Appendix: Study Visits & Procedures.

If you request it, the study physician will provide the study results to you and discuss them with you when they are available.

10. HOW WILL THE RESEARCH PRODUCT BE GIVEN?

All research subjects in the study are given SJ733, as capsules taken by mouth, either alone or in combination with cobicistat, as tablets taken by mouth, once every day for three days in a row. You will be asked if you have eaten any food within three hours before taking the research product.

The study is designed to only treat research subjects who have one of the malaria parasite species: vivax or falciparum.

The study may contain up to three groups of research subjects. The first group of research subjects will be given SJ733 as two 300 mg capsules along with one 150 mg tablet of cobicistat and about 250 milliliters of water (less than a glass).

The dosage for the other groups will depend on the results of the first group. The study physician will explain what group you will be part of for the study.

If the first group is successful, the second group will be given SJ733 as two 300 mg capsules and about 250 milliliters of water. This group will not be given any cobicistat. This group will test whether cobicistat is needed for SJ733 to have a similar effect as the first group. If the second group is successful, the study will be stopped.

If SJ733 does not work without cobicistat, a third group will be studied who will receive less SJ733 (one 300 mg capsule) along with one 150 mg tablet of cobicistat along and 250 milliliters of water. This group will test whether a combination of cobicistat with less SJ733 has a similar effect as the first group with the

benefit of lower cost and less adverse effects.

After being admitted to the study, you will remain in Iquitos for five days for treatment and evaluation.

Standard Malaria Treatment
If your malaria does not get better within 7 days, you will be given the standard treatment and care according to the national regulations for the treatment of malaria in Peru. You will be asked to continue in the study and return for all follow-up as defined in the Appendix. At the end of the study (Day 42) you will receive the standard treatment recommended by the national regulations for the treatment of malaria in Peru. This will ensure your malaria is successfully treated.

11. WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

SJ733
So far, none of the 51 volunteers who have taken SJ733 have reported any serious problems. In some people, SJ733 may have caused nausea, loss of appetite, vomiting, diarrhea, fever and headaches, all of which have been from mild to moderate in severity. During the previous studies, none of the volunteers chose to stop taking the research product before the end of the study.

In dogs, large amounts of SJ733 temporarily decreased how well the dog's blood cells could carry oxygen to the body. Low levels of oxygen can cause the skin to look blue, headaches, and fatigue (tiredness or low energy). The effects went away after the dogs stopped taking SJ733. This has not been seen in humans. We will closely monitor your oxygen levels and general health during the study.

It is not yet known if SJ733 is an effective treatment against malaria, there is a risk that your condition may not improve or worsen. If your malaria does not get better within 7 days, you will receive treatment from the study physicians following the national regulations for the treatment of malaria in Peru.

Cobicistat
Cobicistat can cause jaundice (yellowing of the skin and/or whites of the eyes) and skin rash. It can also decrease how well your kidneys work. For this reason, your kidneys will be closely monitored throughout the study with blood and urine tests.

Because cobicistat can increase the number of other drugs in your body, it is very important to provide honest and complete information about any other medications or herbs/home remedies that you are taking or plan to take. This is very important for your health.

Blood draw
At the blood draw site swelling, pain, irritation, or infection may occur. During the blood draw, some people may feel dizzy or faint. To avoid these issues, only qualified and experienced professional will take blood samples.

Electrocardiogram
The electrocardiogram (ECG) procedure may cause minimal discomfort when the ECG electrodes (monitors/stickers) are put on or taken off.

Risks related to pregnancy/use of contraceptives (birth control)
We do not know the effects of SJ733 during pregnancy. You cannot participate in the study if you are

pregnant or breastfeeding. If you are male, you should not make your partner pregnant, and if you are female, you should not become pregnant during your participation in this study. You will receive counseling on how to avoid pregnancy. You will be given free contraceptives that should be used the entire time that you participate in this study and for 30 days after your last dose of the research product.

Prior to participation, female participants must take a pregnancy test to show you are not pregnant. It is possible that this test may not detect a pregnancy if you became pregnant too recently.

Your study physician will ensure that you and/or your partner have access to contraceptives (oral/injectable contraceptives and barrier contraceptives, e.g., condoms) that are allowed in this clinical study and are convenient for you and/or your partner at no cost to you.

If you suspect that you may be pregnant (or that your partner may be pregnant) during the study, you should notify the study physician immediately. If you become pregnant during the study, you must tell the study doctor about your pregnancy and stop taking all research product immediately. You will be referred to receive appropriate counseling and you will be monitored to observe any possible pregnancy risks related to research product. In addition, your pregnancy will be followed until the outcome. When you give birth, you should inform the study doctor of your baby's health. Your baby's health will be followed for at least 1 year after its birthday in order to dismiss the possibility that any problems can be detected. As part of the consent, you agree that we will continue collecting information about you at least until the birth or termination of the pregnancy.

Unexpected risks

There may be problems or side effects from the research products and procedures that we do not yet know about. You will be informed about any changes in the way the study will be carried out. We will tell you of any new risks that may make you change your mind about participating in the study. New information will be provided to the Ethics Committee and it is possible that you may be asked to review and sign a new informed consent.

12. CAN YOU CHOOSE TO WITHDRAW FROM OR LEAVE THE STUDY EARLY?

Yes, you can choose to leave the study at any time. If you leave the study, you will be treated by the study physician following the national regulations for the treatment of malaria in Peru. You will not be penalized or treated differently if you decide to stop taking part in the study. If you choose to leave the study early, data collected until that point will remain in the study database and may not be removed.

Also, it is possible that your participation in the study could end at any time without your permission. This could occur if you do not follow the instructions given by the study physician or if the study physician determines that it is best for you. The study could also be interrupted due to administrative, medical, or other reasons as determined by the Sponsor, the Instituto Nacional de Salud — INS, or other regulatory authorities. Once your participation in the study has ended, you will no longer have access to the research product or study procedures.

Your participation in the study will end if:

- You decide to withdraw from the study.
- You show any medical condition that causes you harm or exposes you to unnecessary risks.
- You show unacceptable/harmful side effects.

- There is evidence that your illness has worsened.
- You become pregnant.
- You require other medications that are not allowed in this study.
- You do not comply with scheduled visits/study requirements.
- The Sponsor, the INS, or other regulatory agency determines that it is necessary to limit or suspend the study.

Research subjects who are withdrawn (or leave) from the study will be asked to have the same evaluations at the time of their withdrawal that they would have had upon completing the study (Day 42).

13. ARE YOU PARTICIPATING, OR CAN YOU PARTICIPATE, IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?

It is important to let your study physician know if you are participating in another research study. During this study, it is important to inform the study physician of any other studies you plan to participate in.

14. WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?

If you believe you are hurt or if you get sick because of something that is caused by the study, you should call Elmer Alejandro Llanos-Cuentas at 994 273 050 immediately.

If you suffer an injury or an adverse effect directly caused by the study drug or any procedure specified in the protocol, the Sponsor will pay, or cause others to pay, for your reasonable and necessary medical treatment expenses through the CHUBB insurance policy number 530005238 from the beginning until the end of the clinical trial. This insurance policy will cover such expenses are paid as long as (a) those expenses are not specifically for the symptoms of the condition under study (malaria) or for the expected symptoms of your disease, and (b) the cause of the expenses is not due to your failure to follow the instructions of Elmer Alejandro Llanos-Cuentas MD, Ph.D. The Sponsor will not pay for any wages you may lose if you are harmed by the study.

You, your family, or your legal representative, will receive compensation for medical expenses related to a case of disability or death as result of this clinical trial as required by the laws of Peru. For this to happen, the injury, in the opinion of the study doctor and the Sponsor, must have been caused by your participation in this study. No other payments will be provided by the Sponsor. If you would like further information about being paid for research-related injuries, please ask the study doctor.
You do not give up your legal rights by signing this form.

15. PRIVACY AND CONFIDENTIALITY

By signing this form, you give your consent for the study physician and his team to review your medical records gathered during this study. These records, and the information in them, will be obtained and processed in electronic form that is used only for investigative purposes related to this study. When we write about or share the results from the study, we will remove any personal information and communicate about the combined information. Your name and other information that may identify you will be kept private.

Your medical records may also be reviewed by the Sponsor or their representatives, the, study team, Covance Inc., the Peruvian Ministry of Health through known agencies like the National Health Institute (INS); the Director General autoridad Nacional de Productos Farmacéuticos, Dispositivos médicos y productos sanitarios (ANM) (formerly DIGEMID, the United States Food and Drug Administration (FDA), the regulatory authorities of other countries, and the Ethics Committee (both Peru and the University of Kentucky located in the United States) in order to verify that the study is being carried out in the proper manner. These professionals have a commitment to respect the confidentiality of your information and will keep your identity and personal information confidential to the extent that the law permits. You should understand that by signing this consent form you are granting your permission for this review to happen. If the results of the study are published or presented in meetings, you will not be identified.

Peruvian regulations require that the study physician and/or study personnel protect the privacy of your information. We will do everything we can to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. All the information collected will be assigned a number code and your identity will remain unknown. Your name and address will not be on the information that is obtained about you that comes from the study center, so that you cannot be recognized by it. Any information collected that may be transferred outside of the country to the University of Kentucky will be identified only by the number code assigned to your file. Still, absolute confidentiality cannot be guaranteed due to the need to share information in the matters previously described.

Your study physician is responsible for tracking the list of codes that allow your assigned number to be connected to your name. This list will be kept at the study site to guarantee that in case of an emergency you can be identified and contacted. The list of codes will be kept until the last request for commercialization of the research product has been received.

You have the right to see and photocopy your study-related records if the study physician has this information in his possession. By signing this form, you accept the possibility that it may not be possible to review some of your study-related records until after the study has been completed, at which time you will once again be able to access those records.

This authorization does not have an expiration date. If you do not revoke (cancel) this authorization, it will remain in effect indefinitely. You can cancel this authorization at any time by notifying the study physician in writing to address Urb. Jardín N.° 27 (altura cuadra 4 Av. Fanning), Iquitos – Loreto. If you cancel this authorization, you will no longer be able to participate in the study and your records will not be shared unless it is necessary to preserve the scientific integrity of the study. The information collected before you cancel the authorization may still be used and shared with the parties mentioned before.

At the end of the study worldwide, the study results will be available for the different national regulatory entities, including the INS in Peru's case, who will have the information available in Spanish on this webpage http://www.ensayosclinicos-repec.ins.gob.pe. In addition, you may ask the research doctor about the study results. You will not be identified in any of these publications or reports.

Your samples will be processed at the ACSA site laboratory and the Universidad Peruana Cayetano Heredia Laboratory. Your samples will be stored for up to five years and then will be destroyed following the destruction guidelines of the laboratory

Your coded samples will be stored for a maximum of five years after the last patient visit for the study at Instituto de Medicina Tropical Alexander von Humboldt de la Universidad Peruana Cayetano Heredia

located at located in Av. Honorio Delgado 430, San Martín de Porres, Lima, Peru. The storage time allows the Sponsor to respond to regulatory questions related to the study and re-check specific protocol parameters. After that time, any remaining samples will be destroyed following the guidelines of the laboratory.

16. QUESTIONS/INFORMATION

If you have any questions regarding any part of the study, or in case of harm related to the trial, or if you have an adverse reaction, immediately contact:

Dr. Elmer Alejandro Llanos-Cuentas
Address: Asociación Civil Selva Amazónica (ACSA)
Urb. Jardín N.° 27 (altura cuadra 4 Av. Fanning)
Iquitos - Loreto
Telephone: 994 273 050
E-mail: alejandro.llanos.c@upch.pe

You will be informed if during the study there is any other new information that could affect your current decision to participate therein.

If you have any concerns or questions about your rights as a volunteer in this research, contact staff at the **Comité Institucional de Bioética (CIB) de VÍA LIBRE:**

- **Ethich Committe Chairman: Lic. Karen Cruz Azaña**
- **Telephone: (+511) 203-9900 Monday to Friday from 09 am to 18 hrs**
- **Address: Jr. Paraguay 490, Cercado de Lima, Lima, Perú**
- **e-mail: comitebioetica@vialibre.org.pe**

An Ethics Committee is a group of members who are impartial and independent to the medical investigators, and their function is overseeing the respect of the dignity and rights of the participants in the design and performance of the research projects.

When you believe your rights are violated or for any complaint, you can contact the National Institute of Health (General Office of Research and Technology Transfer, OGITT) regulatory agency for clinical trials, through the following telephone number: 748 1111 extension 2191 or by written communication through the following e-mail: consultaensayos@ins.gob.pe, or by a formal document submitted through the Filing Desk of the institution or by appearing in person to the OGITT at the following address: Capac Yupanqui 1400, Jesús María, Lima 11.

Appendix: Study Visits & Procedures

	Screen	**Treatment – Remain in Iquitos**				
Day	**0**	**1**	**2**	**3**	**4**	**5**
Informed Consent	X					
Screening	X					
Pregnancy Test	X					
Physical Exam	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X
ECG	X	X	X	X		
Research Product Dosing		X	X	X		
PK Blood Samples		Pre-dose 0.5, 1, 2, 8 hours after dose 1	Pre-dose, 0.5 hours after dose 2	Pre-dose 0.5, 1, 2, 4, 8 hours after dose 3	24, 26, 28, 30, 32 hours after dose 3	48, 54 hours after dose 3
Safety Blood Samples	X	X	X	X		X
PD Blood Samples	X	Pre-dose 4, 8, 12, 16 hours after dose 1	Pre-dose, 6, 12, 18 hours after dose 2	Pre-dose 6, 12, 18, 24 hours after dose 3	Additional readings every 6-12 hours until two consecutive negative microscopic readings	
Problems or Complaints	X	X	X	X	X	X

	Follow-up – Return to clinic for visits								
Day	**7**	**10 or 11**	**14**	**17 or 18**	**21**	**24 or 25**	**28**	**35**	**42[A]**
Pregnancy Test									X
Physical Exam	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X
ECG									X
PK Blood Sample	X	X							
Safety Blood Sample	X		X				X	X	X
PD Blood Sample	X	X	X	X	X	X	X	X	X
Problems or Complaints	X	X	X	X	X	X	X	X	X
Standard Malaria Treatment									X

A = Day 42, or day of withdrawal (Note: all Day 42 procedures will be done before standard treatment for malaria in Peru is received). Abbreviations: ECG = Electrocardiogram; PK = Pharmacokinetic (how much research product is in the blood); PD = Pharmacodynamic (how many parasites are in the blood).

RESEARCH SUBJECT MAIN INFORMED CONSENT FORM

STUDY TITLE: An Open Label Phase 2a Study to Assess the Efficacy, Safety, Tolerability and Pharmacokinetics of (+)-SJ000557733 (SJ733), with or without Combination with Cobicistat, in Adult Patients with Acute, Uncomplicated Plasmodium Falciparum or Vivax Malaria Mono-Infection over a 42 Day Period

Protocol number: SJ733-2001

This Informed Consent will be signed in two copies and one of them will be delivered to me [research subject] or my [his / her] legal representative.

The patient should check the following:

1. I confirm that I have read and understand the study information sheet above. YES ☐ NO ☐

2. I confirm that the study has been explained to me and that I have had the opportunity to ask questions and enough time to decide if I wish to participate. I know with whom I should communicate in case I have any more questions. YES ☐ NO ☐

3. I understand that the sections of my medical notes may be reviewed by representatives of the Sponsor, University of Kentucky (UK), ethics committees, auditors and national and foreign authorities whenever it is relevant for my participation in the study. I give my permission for these persons to have access to my medical records. YES ☐ NO ☐

4. I agree to the transfer of my personal information, including sensitive information, i.e., race, ethnicity, health, date of birth and diagnostic information to UK and regulatory authorities. YES ☐ NO ☐

5. I agree to the storing of my personal information. YES ☐ NO ☐

6. I allow my primary care physician to be notified about my participation in the study. YES ☐ NO ☐

7. I agree to form part of the study. YES ☐ NO ☐

8. I understand that my participation is voluntary. YES ☐ NO ☐

9. I understand that I can withdraw from the study whenever I want, without having to give explanations and without this affecting my medical care. YES ☐ NO ☐

10. By signing this document, I agree to take part in this clinical trial. I am not renouncing any rights. YES ☐ NO ☐

This consent includes the following:

- **Key Information Page**
- **Detailed Consent**

You will receive a signed and dated copy of this consent form.

Complete Printed Name of Research Subject
(or fingerprint if illiterate)

Signature of Research Subject
(if illiterate, please leave blank)

Date of Signature
(dd / mm / yyyy)

Research Subject's DNI Number
(if illiterate, please leave blank)

Time (am/pm)

I, the undersigned, legally authorized representative, confirm that I agree to the Research subject taking part in this study, as I believe it would be their wish to participate. I understand that if the Research subject expresses a different opinion, that they will be withdrawn from the study without loss of any benefits to which they would otherwise be entitled.

Complete Printed Name of Authorized Representative
(if applicable - fingerprint if illiterate)

Signature of Authorized Representative
(if applicable - if illiterate, please leave blank)

Date of Signature
(dd / mm / yyyy)

Authorized Representative's DNI Number

Time (am/pm)

For the Impartial Witness (where applicable)

- *I have witnessed the accurate reading of the informed consent form to the research subject and he or she has had the opportunity to ask questions.*
- *I confirm that the research subject has freely given his or her consent.*

Complete Printed Name of Impartial Witness
(if applicable - fingerprint if Illiterate)

Signature of Impartial Witness *(if applicable - if illiterate, please leave blank)*	*Date of Signature* *(dd / mm / yyyy)*
Impartial Witness' DNI Number	*Time (am/pm)*

For the Investigator / study personnel

I have explained the clinical trial to the research subject, and I have answered all of his or her questions. I confirm that he or she understands the information described in this document and has voluntarily agreed to take part.

I, the undersigned, investigator / study personnel, confirm that I have verbally given the necessary information about the study, that I answered any additional questions, and that I did not exert any pressure on the research subject to participate in the study.

I declare that I acted in full accordance with the ethical principles described in GCP Guidelines, and other national and international legislation in effect.

Complete Printed Name of Investigator / Study Personnel Obtaining Consent	
Signature of Investigator / Study Personnel Obtaining Consent	*Date of Signature* *(dd / mm / yyyy)*
Investigator / Study Personnel's DNI Number	*Time (am/pm)*

Statistical Analysis Plan

An Open Label Phase 2a Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of (+)-SJ000557733 (SJ733) with or without Combination with Cobicistat in Adult Patients with Acute, Uncomplicated Plasmodium Falciparum or Vivax Malaria Mono-Infection over a 42 Day Period

Date:	11/30/2022
Project Name (PI/Sponsor):	SJ733 (Guy)
IRB Number:	53333
Version:	1.8

Statistical Analysis Plan

Table of Contents

Statistical Analysis Plan

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACPR	Adequate clinical and parasitological response
ACT	Artemisinin-based combination therapies
AE	Adverse Event
ALT	Alanine aminotransferase
ASTAS	Aspartate aminotransferaseArtesunate
AUCAST	Area under the plasma concentration-time curveAspartate aminotransferase
AUCinfAUC	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinityArea under the plasma concentration-time curve
AUClastAUCinf	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentrationThe area under the plasma (or serum or blood) concentration-time curve from time zero to infinity
AUClast	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration
CI	Confidence interval
DDT	Data Definition Tables
Cmax	Maximum measured plasma concentration
DR SAE	Drug-Related Serious Adverse Event
DMC	Data Monitoring Committee
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
ECG	Electrocardiogram
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
F	Bioavailability of a compound
Hb	Hemoglobin
IBSM	Induced Blood Stage Malaria
IRB	Institutional Review Board
L	Liter
LDH	Lactate dehydrogenase
LFT	Liver function test
LOD	Limit of Detection
MEC	Minimum Effective Concentration
MedDRA	Medical Dictionary for Regulatory Activities

MIC	Minimum Inhibitory Concentration
n	Total number observations in the sample
ND	Not detectable
P. falciparum	*Plasmodium falciparum*
P. vivax	*Plasmodium vivax*
PC100	Time to total microscopic clearance of asexual parasites
PC50	Time to microscopic 50% reduction of asexual parasites
PC99	Time to microscopic 99% reduction of asexual parasites
PCR	Polymerase Chain Reaction
PCT	Parasite Clearance Time
PD	Pharmacodynamics(s)
PI	Principal Investigator
PK	Pharmacokinetic
PR	PR interval (ECG)###
PRR	Parasite Reduction Rate
qPCR	Quantitative Polymerase Chain Reaction
QT_cB	QT interval corrected with Bazett's formula
QTcF	QT interval corrected with Fridericia's formula
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SAS	SAS® (Statistical Analysis Software)
SD	Standard deviation
SGPT	Serum glutamic-pyruvic transaminase
SGOT	Serum glutamic-oxaloacetic transaminase
SJ733	(+)-SJ000557733 (study drug)
SRT	Safety Review Team
t1/2	Half-life
Tmax	Time after drug administration when maximum concentration is reached
ULN	Upper Limit of Normal

Statistical Analysis Plan

Introduction

This statistical analysis plan (SAP) outlines the planned analysis for Project SJ733-2001, entitled An Open Label Phase 2a Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of (+)-SJ000557733 (SJ733) with or without Combination with Cobicistat in Adult Patients with Acute, Uncomplicated Plasmodium Falciparum or Vivax Malaria Mono-Infection over a 42 Day Period. This SAP applies to the project as of 11/04/2022 (Version 1.8) and provides a description of the data analysis methods.

1. Project Objectives

Primary:

1) To determine the efficacy of SJ733 with or without combination with the pharmacoenhancer cobicistat, given once per day for three-consecutive days by examining parasitemia 14-days after initiation of therapy for the treatment of uncomplicated *P. vivax* or *P. falciparum* malaria monoinfection.

2) To evaluate the safety and tolerability of SJ733, with or without combination with the pharmacoenhancer cobicistat, given once per day for three-consecutive days in patients with *P. falciparum* and *P. vivax* malaria infection.

Secondary:

1) To assess the effect of the proposed three-day therapy on the signs and symptoms of *P. vivax* or *P. falciparum* malaria infection up to Day 42
2) To assess the effect of the proposed three-day therapy on treatment outcomes in patients with *P. vivax* or *P. falciparum* malaria infection at Days 28, 35, and 42
3) To describe parasite clearance kinetics in patients with *P. vivax* or *P. falciparum* malaria infection
4) To describe the pharmacokinetics of SJ733 and its primary metabolite SJ506 during the three-day dosing period and for 7 additional days in patients with *P. falciparum* and *P. vivax* malaria infection.

Exploratory:

1) To assess the effect of the proposed three-day therapy on PCR adjusted outcomes in patients with *P. vivax* or *P. falciparum* malaria infection:
    a. With PCR-adjustment at Days 7, 14, 28, 35, and 42 (*P. falciparum* only)
    b. PCR adjusted rates of recurrence (*P. vivax* or *P. falciparum*), up to Day 42.

Statistical Analysis Plan

2. Project Description

Background

SJ733 is a new antimalarial drug candidate that has undergone single ascending dose, pharmacoboosted single ascending dose (pharmacoenhancement with cobicistat), food effect single dose, and multiple ascending dose Phase 1 studies in healthy volunteers to demonstrate safety, tolerability, and its pharmacokinetic profile. SJ733 has also been tested in a two-cohort single dose, Phase 1b, human Induced Blood Stage Malaria (IBSM) challenge study. Overall, SJ733's excellent tolerability and safety profile, combined with its rapid antiparasitic effect, support its candidacy as an antimalarial therapy. The Phase 1 clinical data and PK/PD models suggest that SJ733 is most likely to be curative as a 3-daily-dose pharmacoenhanced therapy, due to its moderately rapid clearance.

The present proof of concept Phase 2a trial will be an adaptive, open label study to examine the antimalarial efficacy, safety, and tolerability of SJ733 in adult patients with uncomplicated *P. vivax* or *P. falciparum* blood-stage malaria monoinfection. SJ733 will be administered orally once every day for three consecutive days, with or without a fixed dose of the pharmacoenhancer cobicistat, to determine if pharmacoenhancement is required, and if significant improvements in drug efficacy are seen at higher total exposures of SJ733. Success will be defined independently for each treatment arm at Day 14 as: 1) the absence of any repeated drug-related serious adverse event; and 2) crude ACPR $\geq$ 80% (equivalent to $\leq$ 20% recurrence). Crude ACPR is defined as the absence of microscopically determined parasitemia (thick smear), irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure, or late parasitological failure. Additional aims are to characterize the antiparasitic activity, safety, tolerability, and pharmacokinetics of SJ733 over the period of 42 days. The results of this trial will help identify effective, well-tolerated doses for investigation in combination with a partner drug within a Phase 2b clinical study.

Study Design

This will be a proof-of-concept Phase 2a, adaptive, open label study to examine the efficacy of SJ733 given once per day for three-consecutive days, with or without combination with the pharmacoenhancer cobicistat, in uncomplicated *P. vivax* or *P. falciparum* blood-stage malaria monoinfection in adult patients in Peru. Success will be defined independently for each treatment arm at Day 14 as: 1) the absence of any repeated drug-related serious adverse event; and 2) crude ACPR $\geq$ 80% (equivalent to $\leq$ 20% recurrence). Crude adequate clinical and parasitological response (ACPR) is defined as the absence of microscopically determined parasitemia (thick smear), irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure, or late parasitological failure.

Patients will be recruited as per Figure 1 into one of two treatment arms:

1. Arm A: *P. falciparum* malaria, or
2. Arm B: *P. vivax* malaria

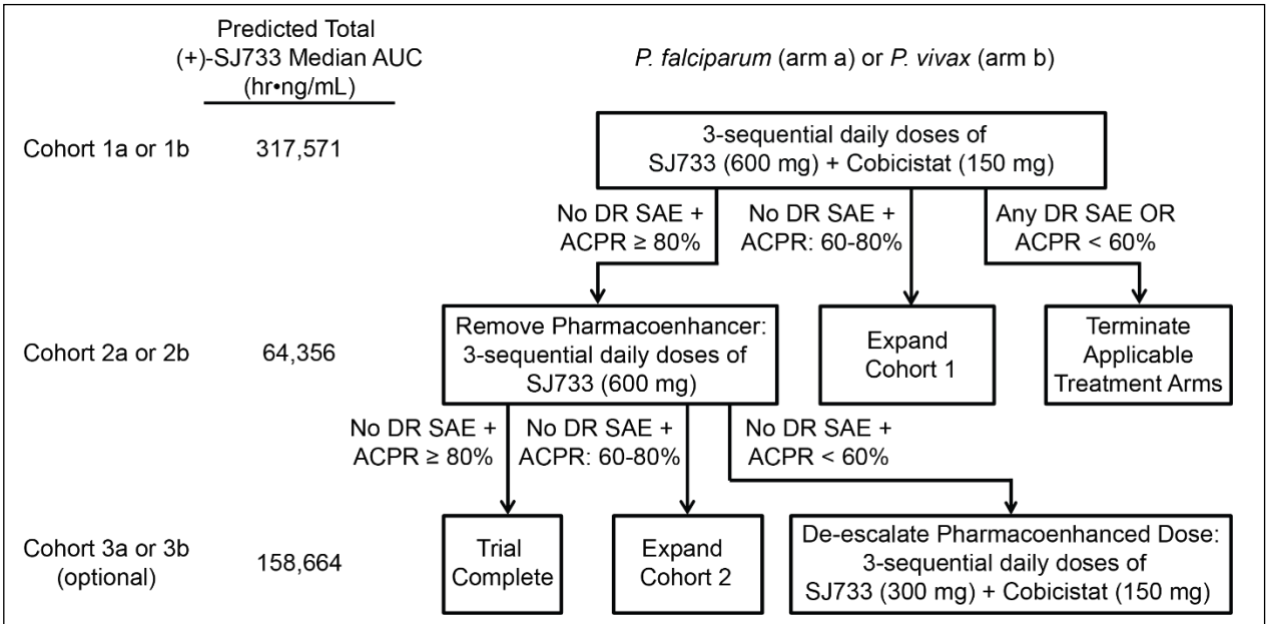

Figure 1. Treatment scheme for cohorts 1-3. Each cohort contains two treatment arms, *P. falciparum* (a) and *P. vivax* (b). Cohort progression will be managed independently for each treatment arm. Interim analysis will determine whether the data for a given treatment arm meets the success criteria, is inconclusive, or meets the failure criteria. Crude adequate clinical and parasitological response (ACPR) is defined as the absence of microscopically determined parasitemia (thick smear), irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure, or late parasitological failure. Success is defined at Day 14 as: 1) the absence of any repeated drug-related serious adverse event (DR SAE); and 2) crude ACPR ≥ 80% (equivalent to ≤ 20% recurrence). An inconclusive result is defined at Day 14 as: 1) the absence of any repeated DR SAE; and 2) ACPR between 60-80%. Failure is defined as: 1) the detection of any repeated DR SAE; or 2) ACPR < 60%.

A minimum of one cohort containing two treatment arms (20 patients; 10 patients per arm) will be investigated with a maximum of 3 cohorts (60 patients; 3 dosing regimens; 2 arms; 10 patients per arm) being tested as shown in Figure 1. The starting dosing regimen for the first *P. vivax* or *P. falciparum* cohorts will be three consecutive daily doses of the combination of SJ733 (600 mg) and cobicistat (150 mg). Based on the results from completed Phase 1a/1b studies, this dose is expected to be well-tolerated and show complete clearance of parasites on Day 7 as determined by microscopy (thick blood smear) and a ≤ 20% recrudescence rate as assessed by microscopy on Day 14.

If the data from the first cohorts of *P. falciparum* (cohort 1A) and *P. vivax* (cohort 1B) respectively meet the success criteria, two other dosing regimens, expected to yield reduced total exposures of SJ733, may be investigated. Each is expected to be efficacious. If data from the first cohorts are inconclusive, an adaptation will be triggered to use the same dosing regimen for a larger number of patients in order to improve statistical power and more accurately classify a potential failure. An inconclusive result will be defined at Day 14 as: 1) the absence of any repeated drug-related SAE; and 2) crude ACPR between 60-80% (equivalent to 20-40% recurrence). If data from the first cohorts result in failure, the trial will be stopped. Failure is defined as: 1) the detection of

any 2 incidents of the same drug-related SAE; or 2) crude ACPR < 60% (equivalent to > 40% recurrence).

Cohort 2 will test whether pharmacoenhancement of SJ733 with cobicistat is required for clinical efficacy. If cohort 2 meets the success criteria, the trial will be complete. If data from cohort 2 are inconclusive, an adaptation will be triggered to use the same regimen for a larger number of patients in order to improve statistical power and more accurately classify a potential failure. If cohort 2 proves safe (no repeated drug-related SAE) but not efficacious (crude ACPR < 60%), an adaptation will be triggered to use an intermediate exposure of SJ733, obtained by pharmacoenhancement of a reduced dose of SJ733 (optional cohort 3). Due to the pharmacoenhancing effects of cobicistat, a co-dose of SJ733 (300 mg) + cobicistat (150 mg) is expected to yield a higher total plasma exposure (median AUC) of SJ733 than a dose of SJ733 (600 mg) alone (Figure 1). The increase in plasma exposure is expected to provide increased efficacy. While cohort 3 requires co-dosing with a pharmacoenhancer, if successful, this regimen would reduce the quantity of SJ733 required by two-fold, lowering cost of goods and potentially improving tolerability.

Cohorts 1a and 1b are expected to achieve roughly five-fold higher plasma exposure of (+)-SJ733 than Cohorts 2a and 2b. Thus, if Cohorts 1a and 1b prove efficacious but repeated drug-related adverse events are observed, the Investigator, DMC, and SRT may unanimously agree that no further patients should be recruited to Cohorts 1 but that patient recruitment to Cohorts 2 should still be pursued. In this scenario, the Investigator will assess the severity/intensity of the adverse reactions and clinical laboratory changes using the DMID Toxicity Grading Scale for Determining the Severity of Adverse Events provided in Protocol Attachment 3 and Section 8.1.2. This information will be relayed to the DMC and SRT, who will make recommendations regarding further conduct of the trial, and if considered necessary, may recommend pausing or stopping further administration of the investigational product. Cohort progression will only be explored if the Investigator, DMC, and SRT unanimously agree it is warranted and appropriate. These recommendations will also be communicated to the Ethics Committee and Regulatory Authority and any necessary updates will be made to the patient consent form.

Each cohort will consist of two treatment arms. Cohort progression for each treatment arm will be managed independently of the other treatment arm. For example, if data from the *P. falciparum* cohort (1A) do not meet the success criteria or are inconclusive, but the data from the *P. vivax* cohort (1B) do meet the success criteria, then the *P. vivax* arm may continue to explore reducing levels of SJ733 exposure according to Figure 1 (cohort 2B and 3B), while the *P. falciparum* initial cohort of the study will be expanded or terminated. Established antimalarial therapy will be given if a patient meets any of the defined treatment failure criteria. Finally, if one treatment arm meets the failure criteria, remaining patients who have not received treatment may be reassigned to the other treatment arm to improve statistical power.

Study Population

Men and women between the ages of 18 and 70 years with *P. falciparum* or *P. vivax* malaria monoinfection living in Peru. 2-6 cohorts of adult patients (10 patients per cohort) with acute, uncomplicated *P. falciparum* or *P. vivax* malaria monoinfection. In total, there will be a minimum of 20 and a maximum of 60 patients.

3. Data Elements

Endpoints

Primary endpoints related to efficacy

For *P. vivax:* Crude Adequate Clinical and Parasitological Response (ACPR) at Day 14 defined as the absence of microscopically determined parasitemia (thick smear) on Day 14, irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure, or late parasitological failure.

For *P. falciparum:* Crude Adequate Clinical and Parasitological Response (ACPR) at Day 14 defined as the absence of microscopically determined parasitemia (thick smear) on Day 14, irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure, or late parasitological failure.

Success criterion: Crude ACPR on Day 14 ≥ 80% (equivalent to ≤ 20% recurrence).

Primary endpoints related to safety and tolerability up to Day 42

- Incidence, severity, drug-relatedness, and seriousness of adverse events
- Proportion of patients with clinically significant abnormal laboratory values including changes from baseline (biochemistry and hematology)
- Proportion of patients with clinically significant abnormal vital signs including changes from baseline
- Proportion of patients with a decrease in hemoglobin (Hb): > 2 g/dL from baseline to an absolute value of < 5 g/dL
- Proportion of patients with an absolute Neutrophil count < 1,000/µL after baseline
- Proportion of patients meeting Hy's law criteria
- Proportion of patients with the following LFT changes:
  - Any ALT or AST ≥ 5 x ULN
  - Any AST or ALT ≥ 3 x ULN together with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (eosinophil percent or count above the ULN)
  - Persistent ALT ≥ 3 x ULN for a period of more than 4 weeks.
- Proportion of patients with clinical signs of possible cutaneous adverse reactions such as dermatitis, rash, erythematous rash, macular rash, papular rash, maculo-papular rash, pruritic rash, pustular rash, vesicular rash
- Proportion of patients with clinically significant increases in venous methemoglobin levels
- Proportion of patients with significant changes in ECG findings, including heart rate, ECG intervals (PR, QTcB, QTcF), conduction changes or abnormalities

Success criterion: No repeated drug-related serious adverse events (Attachment 3, Section 8.1.2).

Secondary Endpoints

Secondary endpoints related to malaria signs and symptoms up to Day 42

- Proportion of patients with symptoms or physical examination signs related to uncomplicated *P. vivax* or *P. falciparum* malaria (dizziness, headache, nausea, anorexia, vomiting, diarrhea, pruritus, urticaria, skin rash, abdominal pain, joint pain, muscle pain, palpitations, sleep disturbance, confusion, hearing disturbance, visual disturbance, fatigue)
- Fever Clearance Time as defined as the time from baseline to the first of two consecutive post-dose axillary temperature measurements < 37.5°C obtained within an interval of 4 to 24 hours of each other.

Secondary endpoints related to secondary treatment outcomes

- Crude ACPR at Days 28, 35, and 42 (*P. vivax* or *P. falciparum)*
- Recurrence (*P. vivax* or *P. falciparum*) up to Day 42

Secondary endpoints related to parasite clearance kinetics by microscopy

- Parasite clearance time (PCT)
- PRR (parasite reduction rate) and parasitemia half life
- Times to microscopic clearance of asexual parasites
  - Total reduction (PC100)
  - 99% reduction (PC99)
  - 90% reduction (PC90)
  - 50% reduction (PC50)
- Microscopically determined percentage reduction in asexual parasites from baseline at:
  - 24 hours after administration of study drug
  - 48 hours after administration of study drug
  - 72 hours after administration of study drug
- Proportion of microscopically determined parasitemia in patients at:
  - 24 hours after administration of study drug
  - 48 hours after administration of study drug
  - 72 hours after administration of study drug

Secondary endpoints related to PK parameters up to Day 42

$AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, t_{max}, $t_{½}$, Cl, F, etc.

Exploratory Endpoints:

- PCR-adjusted ACPR at Days 7, 14, 28, 35, and 42 (*P. vivax* or *P. falciparum*)
- PCR determined recurrence (*P. vivax* or *P. falciparum)* up to Day 42
- Correlation between parasite genotypes of interest and parasite clearance kinetics/efficacy

Data Sources

Data will be entered into REDCap instruments per the Data Management Plan (DMP). Clinical, laboratory, and safety study measures will be entered into the electronic data capture system (REDCap) and assessed for quality as outlined in the DMP.

Statistical Analysis Plan

Creation of Analysis Datasets and Analytic Data Handling

Data from REDCap will be exported and converted to SAS datasets. Analysis datasets will be created, and SAS programs will be developed to further investigate potential data issues via simple descriptive statistics and plots. Summary reports will be provided periodically during the course of the project to verify accuracy of data entry and provide early opportunities for clarification of questions and correction of errors and omissions.

For analysis datasets, Data Definition Tables (DDTs) are included to document all variables (both raw and derived) included in the analysis datasets. This includes the variable name, label, type, length, format, coded values and logic for creating derived variables. For raw data, a data dictionary is available through REDCap. The data dictionary provides a description of all data fields including the field name, label, field type, response option coding and branching logic.

Quality assurance strategies outlined in the DMP will be used to minimize missing data. In general, primary analyses will be conducted as observed. In the event imputation is needed and appropriate, it will be employed using multiple imputation methods. In the presence of imputation, the sample size is not diminished. A description of participant disposition will be included to assess incomplete data, visits, withdrawals, deviations, and discontinuations.

4. Statistical Methods

The overall study design is to demonstrate proof of concept and serves as an exploratory study. It is not intended to demonstrate superiority or non-inferiority against a control. Rather the goal is to establish preliminary data for planning future studies and to assess whether the SJ733 is safe and the observed curative rate equals or exceeds 80%. As such, there will be no statistical testing of hypotheses. This exploratory Proof of Concept study uses a fixed clinical safety and parasitological responses (primary endpoints) defined as the absence of any drug-related SAE or microscopically determined parasitemia 14-days after initiation of therapy in ≥ 80% patients who did not violate any of the inclusion/exclusion criteria.

Statistical Analysis Plan

General Approach

The overall study design involves two cohorts receiving SJ733 doses (600 mg and 300 mg) with and without cobicistat (150 mg) as cohorts. Data subsets (eligible, evaluable and completer) will be used in the potential comparisons.

The primary analytic approaches will be descriptive. All data will be summarized descriptively for the appropriate analysis sets defined below: Continuous variables by descriptive statistics (number of patients [n], mean, standard deviation [SD], minimum, median, maximum); categorical data by absolute and relative frequencies (n and %) or contingency tables.

While this is a proof of concept, exploratory study, any potential comparisons between dose cohorts will be informative. Potential longitudinal data will be described as graphical summaries presented by each group. Unless indicated otherwise, summary statistics will be reported for observed data only, by dose cohort. Missing data will not be imputed. If a baseline value is missing, no change from baseline will be calculated.

Baseline is defined as the last observation prior to the administration of study medication.

SAS v9.4 or higher will be used for all analyses and a significance level of 0.05 will be used for all statistical tests.

Primary Analysis (Efficacy)

Primary analyses will be conducted across the two cohorts and by the two cohorts. Estimates will be presented with 95% confidence intervals.

The primary efficacy endpoints will be summarized descriptively, across the two cohorts and by the two cohorts. A statistical test will not be performed on the Crude ACPR on Day 14. Achieving a rate of 80% will be the decision rule for cohort dose phase. For future study planning, a one-sample z-test will be used to compare the rate of success, as defined by the Crude ACPR on Day 14, to the hypothesized rate of 80%.

Secondary efficacy variables will be summarized descriptively (by cohort; on Days 0, 14, 42) with proportions, means, and medians. To inform future studies, all estimates will be presented with 95% confidence intervals (1.96 ± margin of error). Graphical summaries will be used to describe changes in efficacy endpoints over time.

Exploratory Analysis

Exploratory model-based analyses will be performed as data allows. These will include model-based analyses of PK, PD and PK/PD.

Safety Analysis

Adverse events (AEs) will be summarized in Listing 9: Cumulative Summary of Adverse Events. The listing will include the following information: Patient ID, AE Description, Start Date, Stop Date, Special Interest, Severity, Relationship to Study Drug, Action Taken, Outcome of AE, Expected AE, and if the AE was a Serious Adverse Event (SAE).

Laboratory values that fall outside a clinically accepted reference range must be evaluated and commented on by the Investigator and graded according to the DMID Toxicity Scale for Determining Severity of Adverse Events (Protocol Attachment 3, Section 8.1.2).

All related AEs, AEs with outcome death, AEs leading to permanent discontinuation of treatment, SAEs and related SAEs will be summarized in Listing 10: Cumulative Summary of Serious Adverse Events. The listing will include the following information: Patient ID, Age, Sex, Dose, SAE Description, Start Date, Stop Date, SAE Category, and Relationship to Study Drug.

Treatment related AEs are those rated by the Investigator as “definite”, “probable”, “possible”. In case relationship is unknown or missing the worst case will be assumed and the AE will be considered to be drug related

Planned Interim Analyses

Interim analyses will be made to review parasite reduction, adverse events, and clinical laboratory data. Following review, a decision on cohort progression will be made. However, as this is an exploratory study no formal analyses with adjustments for type I error are planned.

The following rules will be used as general guidelines to aid the decision of cohort progression:

- Curing ≥8/10 patients without any repeated drug-related SAEs then explore lower dose;
- Curing 6/10 or 7/10 patients without any repeated drug-related SAEs would be inconclusive and as a result we would expand the treatment arm;
- Curing ≤5/10 is failure which would stop the trial in Cohort 1.

Strategies to Minimize Bias

Given the nature of the study, issues related to randomization/blinding/masking do not apply.

Sample Size Justification

The sample size for this exploratory Proof of Concept study was based on primary efficacy hypothesis. A one-sample z-test will have at least 85% power to detect the difference between the hypothesized curative rate (80%) with an alternative curative rate of 98%, assuming a one-sided significance level of 0.05, when the sample size is 20. All primary analyses will pool parasite arms within cohort dose. As such, a sample size of 10 patients per dose cohort arm was considered adequate to gain efficacy and safety data in patients with *P. falciparum* and *P. vivax* or to permit evaluation of MIC and MEC as per similar studies conducted. If patients drop out for reasons unconnected to efficacy, attempts will be made to replace them to try to ensure the maximum number in each cohort.

5. Planned Tables, Listings, and Figures.

Number	Tables* *Tables will be provided overall and by cohort
Table 1	Patient Status
Table 2	Patient Demographics and Baseline Characteristics
Table 3	Malaria Sign and Symptoms
Table 4	Clinical Laboratory Summary
Table 5	Vital Signs
Table 6	12-LEAD ECG Summary
Table 7	Primary Endpoint
	Figures
Figure 1	Patient Status
Figure 2a	Efficacy: Asexual Parasite Count Over Time Up to Day 42 – Microscopist Report 1
Figure 2b	Efficacy: Asexual Parasite Count Over Time Up to Day 42 – Microscopist Report 2
Figure 3-	qPCR Values Over Time Up to Day 42
Figure 4a	Crude ACPR – Microscopist Report 1
Figure 4b	Crude ACPR – Microscopist Report 2
Figure 5	eDISH Plot
Figure 5a	Liver Testing by Patient
Figure 6	Total Bilirubin Lab Result (mg/dL) Over Time
Figure 7	Albumin Lab Result (g/dL) Over Time
Figure 8	ALT/SGPT Lab Result (U/L) Over Time
Figure 9	AST/SGOT Lab Result (U/L) Over Time
Figure 10	LDH Lab Result (U/L) Over Time
Figure 11	Alkaline Phosphate Lab Result (U/L) Over Time
Figure 12	Creatine Kinase Lab Result (mg/dL) Over Time
Figure 13a	Creatine Kinase Lab Result (mg/dL) Over Time for Males
Figure 13b	Creatine Kinase Lab Result (mg/dL) Over Time for Females
Figure 14	Urea Lab Result (mg/dL) Over Time
Figure 15	Sodium Lab Result (mmol/L) Over Time
Figure 16	Potassium Lab Result (mmol/L) Over Time
Figure 17	Glucose Lab Result (mg/dL) Over Time
Figure 18	Temperature (ºC) Over Time – Overall
Figure 18a	Temperature (ºC) Over Time – Day 1
Figure 18b	Temperature (ºC) Over Time – Day 1-5
Figure 19	Leukocyte Total (/mm3) Over Time
Figure 20	Erythrocyte Count (/uL) Over Time
Figure 21a	Hemoglobin (g/dL) Over Time for Females
Figure 21b	Hemoglobin (g/dL) Over Time for Females
Figure 22a	Hematocrit (%) Over Time for Males
Figure 22 b	Hematocrit (%) Over Time for Females
Figure 23	Methemoglobin (%) Over Time
Figure 24	Platelet Count (/mm3) Over Time

Figure 25	Haptoglobin (mg/dL) Over Time
Figure 26	Neutrophil (/mm3) Over Time
Figure 27	Absolute Lymphocyte (/mm3) Over Time
Figure 28	Absolute Eosinophils (/mm3) Over Time
Figure 29	Absolute Basophils (/mm3) Over Time
Figure 30	Absolute Monocytes (/mm3) Over Time
Figure 31	Absolute Reticulocytes (%) Over Time
	Listings
Listing 1	Baseline Parasite Count
Listing 2	Efficacy: Asexual parasite count over time up to Day 42
Listing 3	qPCR Value over time up to Day 42
Listing 4	Fever Clearance Time
Listing 5	Medication History
Listing 6	Concomitant History
Listing 7	Malaria Signs and Symptoms
Listing 8	Definitive Antimalarial Treatment
Listing 9	Cumulative Summary of Adverse Events
Listing 10	Cumulative Summary of Serious Adverse Events

6. Planned Start and End of Analysis

Start of analysis: 05/2021
End of analysis: 12/2022