CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213036Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 64769

MEETING MINUTES

The Surgeon General, Department of the Army
U.S. Army Medical Research and Materiel Command
Attention: MCMR-ORA c/o Mark S. Paxton, J.D., M.S.
Sponsor's Representative
1430 Veterans Drive
Fort Detrick, MD 21702-5009

Dear Mr. Paxton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Intravenous Artesunate.

We also refer to the meeting between representatives of your firm and the FDA on February 28, 2019. The purpose of the meeting was to discuss the clinical portion of your planned NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B

Meeting Category: Pre-NDA

Meeting Date and Time: February 28, 2019, at 10:00 AM ET

Meeting Location: FDA White Oak Campus, Building 22, Room 1315

Application Number: IND 64769

Product Name: Intravenous Artesunate

Indication: Treatment of severe malaria

Sponsor Name: The Surgeon General, Department of the Army

Meeting Recorder: Gregory DiBernardo

FDA ATTENDEES

Office of Antimicrobial Products (OAP)

John Farley, M.D., M.P.H.	Deputy Director
*Barbara Styrt, M.D., M.P.H.	Medical Officer
Sunita Shukla, Ph.D., M.P.H.	Associate Director for Regulatory Science

Office of New Drugs, Immediate Office (OND IO)

Katherine Schumann, M.S.	OND IO Policy Staff

Division of Anti-Infective Products (DAIP)

Sumathi Nambiar, M.D., M.P.H.	Director
Dmitri Iarikov, M.D., Ph.D.	Deputy Director
Joseph Toerner, M.D., M.P.H.	Deputy Director for Safety
Abimbola Adebowale, Ph.D.	Associate Director for Labeling
Yuliya Yasinskaya, M.D.	Clinical Team Leader
Elizabeth O'Shaughnessy, M.D.	Clinical Reviewer
Shukal Bala, Ph.D.	Clinical Microbiology Reviewer
Terry Miller, Ph.D.	Pharmacology/Toxicology Team Leader
*Kelly Brant, M.P.H., Ph.D., DABT	Pharmacology/Toxicology Reviewer
Leah Rosenfeld, Ph.D.	Pharmacology/Toxicology Reviewer

Ines Pagan, Ph.D., D.V.M.	Pharmacology/Toxicology Reviewer
Maureen Dillon-Parker, M.S.	Chief, Regulatory Project Management Staff
Carmen DeBellas, RPh., Pharm.D.	Chief, Regulatory Project Management Staff
Gregory F. DiBernardo	Regulatory Project Manager

Division of Biometrics IV (DB IV)

Karen M. Higgins, Sc.D.	Biostatistics Team Leader
Xianbin Li, Ph.D.	Biostatistics Reviewer

Division of Clinical Pharmacology IV (DCP IV)

*Philip Colangelo, PharmD., Ph.D.	Clinical Pharmacology Team Leader
Dakshina Chilukuri, Ph.D.	Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality (OPQ)

Erika Englund, Ph.D.	Acting, Chemistry, Manufacturing and Controls (CMC) Lead
George Lunn, Ph.D.	Product Quality Reviewer
Gerlie Gieser, Ph.D.	Biopharmaceutics Reviewer

Office of Drug Shortage

Leo Zadecky, Pharm.D.	Drug Shortage Reviewer

Counter-Terrorism and Emergency Coordination Staff (CTECS)

Rosemary Roberts, M.D.	Director
Gayle Tuckett, Pharm.D., BCGP	Policy and Special Projects Officer

SPONSOR ATTENDEES

United States Army Medical Research and Materiel Command (USAMRMC)

Sai Majji, Ph.D.	Regulatory Affairs Scientist
Mark Paxton, J.D., M.S.	Sponsor's Representative

AMIVAS, LLC

Mark Reid, M.B.A.	Chief Executive Officer
Bryan Smith, M.D.	Chief Medical Officer

United States Army Medical Materiel Development Activity (USAMMDA)

*Major Victor Zottig	IV AS Project Leader
John Clarke	Product Development Support Officer
Kendra Lawrence, Ph.D.	Acting Deputy Project Manager

Fast-Track Drugs and Biologics, LLC

Jonathan Berman, M.D.	Clinical Consultant
Janet Ransom, Ph.D.	Regulatory Consultant

(b) (4)	Consultant

*	(b) (4)	Consultant

*via telephone

1.0 BACKGROUND

On January 11, 2019, The Surgeon General, Department of the Army, U.S. Army Medical Research and Materiel Command (Sponsor) submitted a type B Pre-NDA meeting request to discuss the clinical portion of their planned NDA for Intravenous Artesunate (IV AS). On January 24, 2019, the Division of Anti-Infective Products (FDA) agreed to a February 28, 2019 meeting. On February 25, 2019, the Sponsor provided an updated timeline for the submission of their NDA requested at the February 15, 2019, type C Nonclinical Meeting (see attached). FDA issued Preliminary Meeting Comments on February 27, 2019 (see attached).

2.0 DISCUSSION

Following introductions, the Sponsor provided a brief overview of the timeline provided to FDA on February 25, 2019.

- Submit first section of the application to begin Rolling Review in May 2019
- Submit draft pharmacology/toxicology study reports in November/December 2019; this will be considered the final portion of the rolling review
- Submit 12-month stability data (CMC) and final pharmacology/toxicology study reports in January 2020

FDA sought clarification on whether the final piece of the rolling review would be submitted in November 2019. The Sponsor stated that this is their current plan. FDA agreed with the plan for the rolling review and recommended that the Sponsor submit an official request for the rolling review along with an outline of the complete module content and timeline to the IND for review and agreement.

FDA inquired about the completeness of the modules and stated that for Module 4 to be considered complete, it should at a minimum include an audited draft report of the nonclinical pharmacology studies. The Sponsor stated they did not believe they could have audited draft reports at this time but noted that IV AS had both Fast Track (FT) and Breakthrough (BT) designations.

FDA inquired whether the draft study reports would contain signed, complete histopathology reports. The FDA stated that signed, complete histopathology reports would be needed for the draft study reports submitted to the NDA. The Sponsor stated they anticipated that the signed histopathology reports would be available by November 4th and they hope to have an audited draft study report from the rat study by November 30, 2019. The FDA indicated they would be willing to accept unaudited draft study reports for the pivotal 4-week toxicology studies in rats and dogs containing signed histopathology reports at time of NDA submission. The Sponsor stated they would provide marked-up versions of the reports with any changes noted between the audited draft and final study reports.

FDA clarified that based on the current discussion, the final piece of the NDA starting the PDUFA clock would be expected in November 2019. If IV AS is determined to be a new molecular entity (NME) and a priority review is granted for the NDA, the application would be reviewed under "the Program" on an 8-month clock with the PDUFA goal date falling in July 2020. FDA is willing to consider unaudited draft reports for 4-week toxicology studies in rats and dogs at the time of NDA submission, audited draft reports within 60 days after the submission of the last piece of the NDA and would accept the final study reports if submitted within 30 days after the submission of the audited draft reports.

FDA asked about the drug product/drug substance (DP/DS) stability data and how much information the Sponsor would have in November 2019. The Sponsor stated they would have 6 to 9 months of stability data by November 2019, and 12 months by January 2020. FDA stated that the contents of the stability package to be submitted in the NDA should be discussed at the CMC Pre-NDA meeting. FDA stated if the data are detailed and clear in the meeting package, it will aid in reaching an agreement at the Pre-NDA CMC meeting.

FDA stated that the information shared at the meeting had been discussed with the Office of New Drugs (OND) leadership, including OND Director, Dr. Peter Stein, and FDA's position is based on those discussions.

Pre NDA Meeting Background Materials Questions:

1. Does the agency agree that the pharmacology, pharmacokinetic and toxicology studies that have already been completed are sufficient to support the NDA filing presuming that there are no review issues?

FDA Response:

Pharmacology Toxicology:

In your draft NDA timeline analysis that describes the status of ongoing CMC studies and the proposed timeline for submission of the nonclinical study reports (4-week repeat-dose toxicology studies in rats and dogs with IV AS), it appears that the draft study reports will be submitted close to the end of the review cycle leaving insufficient time to conduct a substantial review of the study findings. We typically require complete study reports at the time of NDA submission. Given significant unmet need and the breakthrough status of IV AS, we are willing to consider Module 4 of the NDA submission complete if you include unaudited draft reports with signed histopathology reports, in the initial NDA submission and agree to submit the audited study reports within 60 days of the NDA submission and the final study reports no later than 30 days after the audited draft reports. We recommend that you contact the CRO that will be carrying out these studies to see if they could provide you with the unaudited draft reports at an earlier date to facilitate the submission of a complete Module 4 in your initial NDA submission. Both audited draft reports and final study reports should be accompanied by a list of changes from the previously submitted draft reports.

Meeting Discussion:

The Sponsor stated the response to Question 1 was acknowledged and will be addressed.

Clinical Microbiology:
The clinical microbiology response was communicated in the preliminary comments and discussed with you at the meeting on February 15, 2019. We assume that nonclinical information will be based on the active metabolite in addition to artesunate.

Meeting Discussion:
The Sponsor stated the response to Question 1 was acknowledged and will be addressed.

2. Amivas is planning to conduct a [redacted] (b) (4) so as not to delay the review and approval of this drug. This timing would address concerns expressed by the Drug Shortages Divisions regarding the imminent absence of an approved drug in the US to treat severe [redacted] (b) (4) malaria. Is this acceptable at the time of filing the NDA?

FDA Response:

Pharmacology Toxicology:

Please see response to Question 1.

Clinical Pharmacology:
[redacted] (b) (4)

Meeting Discussion:
The Sponsor stated the responses to Question 2 are acknowledged and will be addressed.

3. Alternatively, to the proposal in question #2, as IV AS has received both Fast Track designation and Breakthrough designation, information such as the results of the proposed studies could possibly be submitted during the review period, if FDA agrees to this possibility. As the nonclinical section that is ready for submission now is otherwise complete, would the Agency consider a late submission of these reports if the proposed PMR is rejected?

FDA Response:

Clinical Pharmacology:
We agree with your proposal to [redacted] (b) (4) *Please see our response to the question 2.*

Meeting Discussion:
The Sponsor stated the response to Question 3 was acknowledged and will be addressed.

Clinical Questions:
Amivas plans to provide the results of 3 pivotal clinical trials (R-CDC-060, SEAQUAMAT, and AQUAMAT) that studied IV AS in patients with complicated or severe malaria and several supportive clinical trials including 2 Phase 1 (study 1128 and study 1142) pharmacokinetic (PK) single and multiple dose studies and 2 Phase 2 (study 1168 and study 1263ab) clinical trials in patients with uncomplicated malaria, along with a summary of the relevant literature as sufficient evidence of product efficacy. As evidence of product safety, Amivas will provide safety data from all subjects who received at least one dose of IV AS in one of the Phase 1 studies (n=50), Phase 2 studies (n=130), or in Study R CDC-060 (n=102). In addition, safety data will be referenced from a randomized, double-blind, Phase 2 clinical trial conducted by EDCTP-MMV that compared 2 different dosing regimens of IV AS in African children (n=194) with severe *Pf* malaria (Study EDCTP-MMV07- 01, Kremsner-2012). Final clinical study reports will be provided for all of the above studies with the exception of the SEAQUAMAT and AQUAMAT studies. These study's results are available as publications, Dondorp-2005 and Dondorp-2010, respectively. Of the three pivotal clinical trials, complete CDISC compliant SDTM and ADaM datasets including define files, annotated CRFs and reviewer's guide are available for the R-CDC-060 clinical trial and will be submitted. Likewise complete CDISC compliant SDTM and ADaM datasets will also be provided for Phase 1 and 2 studies 1128, 1142, 1168, and 1263ab. The SEAQUAMAT group provided a single legacy dataset for all 1461 subjects enrolled in the SEAQUAMAT trial and the blank case report forms (CRFs). We plan to submit these legacy data as CDISC SAS.xpt files, along with annotated CRFs, Reviewer's guide, and define.xml file. Source data for the R-CDC-060 study are available for review at CDC headquarters in Atlanta, GA. The SEAQUAMAT and AQUAMAT data are not available for source data review as these were conducted by another sponsor. Although datasets from the EDCTP-MMV07-01 study are not available, safety data from the study's clinical study report will be referenced in the IV AS safety discussions.

4. Is the above plan for submission of clinical study reports, supporting literature, and datasets acceptable to the Agency? Electrocardiograms (ECG) were administered during the conduct of the two Phase 1 clinical trials sponsored by the Army (Studies 1128 and 1142). Besides the evaluation of the ECGs by a cardiologist at the clinical site, all ECG tracings were digitized and analyzed by a Cardiologist at (b) (4) prepared a separate Cardiac Safety Report evaluating the ECGs for QTc prolongation and other cardiac clinically significant changes. The Cardiac Safety Reports are included in an Appendix to the final clinical study reports for these studies. (b) (4) also provided digital ECGs as pdf files. The sponsor does not have xpt files for these ECGs to submit to through the FDA gateway, but is providing them as Appendices (Appendix 16.3) to each of the clinical study reports. In addition, the digital ECG data are provided with the datasets for these studies.

FDA Response:

Clinical/ Statistical:
According to your meeting package, your NDA will include data and information from R-CDC-060 and Phase 1 and 2 studies 1128, 1142, 1168, and 1263ab, as well as published studies including SEAQUAMAT (Dondorp et al. 2005) and AQUAMAT (Dondorp et al. 2010). Please

note that the decision regarding the adequacy of the submitted data and published studies to support the safety and effectiveness of IV AS for the treatment of severe malaria will be made upon the review of the NDA. For guidance on FDA's expectations regarding clinical evidence of effectiveness for human drug products, please refer to: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072008.pdf.

Please see our comments below:

- *The SEAQUAMAT and AQUAMAT studies could potentially serve as adequate and well-controlled trials. It will be important to submit complete patient level data, protocols, statistical analysis plans, and complete study reports for both trials. Please discuss if you are unable to submit this information and the efforts you have made, if any, to obtain such information.*
- *Whether or not the SEAQUAMAT study alone can support the efficacy of IV artesunate for the proposed indication will depend on the adequacy of the datasets, the strength of the results, and the consistency across subgroups.*

Meeting Discussion:
The Sponsor stated they had concerns about whether the NDA should be submitted as a 505(b)(1) or 505(b)(2) application. FDA directed the Sponsor to review the FDA Guidance on submission of an NDA and determining 505(b)(1) vs. 505(b)(2) status. FDA emphasized that any information that is not owned by an applicant but required for approval of an NDA, would make the NDA a 505(b)(2).

FDA stated they needed to know what kind of data were available for SEAQUAMAT and AQUAMAT studies. FDA also stated that if data were missing, FDA would need to know the steps the Sponsor took to acquire the data including efforts made to contact the investigators or authors to obtain source data and identify and address data gaps.

The Sponsor stated they have SEAQUAMAT data from the Wellcome Trust. The Sponsor stated that Wellcome Trust provided these data in a single SAS dataset, and the Sponsor is proposing to submit the data separated into several ADaM datasets: baseline information, follow-up for clinical endpoints, prior and concomitant medications (without start or stop dates), laboratory data, and adverse event (AE) dataset. The Sponsor said they could submit the legacy data and the derived analysis datasets to the IND for FDA review. FDA requested the legacy dataset for SEAQUAMAT as an xpt file be included in the NDA. FDA inquired if the Sponsor had the SEAQUAMAT protocol. The Sponsor replied that they have the protocol. FDA requested this information be submitted.

The Sponsor stated they did not have any AQUAMAT datasets. FDA reiterated that the Sponsor document their efforts in obtaining the patient level data from the AQUAMAT study.

FDA stated they understood the cutoff for the CDC-060 study data was 2010, but they would like to see more contemporary data from this study. The Sponsor stated they can focus data extraction on deaths and other serious AEs and they will work with the CDC to get these data,

but noted they cannot obtain more detailed data as that will require significant resources to review and extract information from the patients' medical records, which may not be feasible.

Clinical Pharmacology:

- *The proposal to provide study reports and data for PK studies 1128, 1142, 1168 and 1263ab is acceptable.*
- *We recommend that along with the complete study reports for such PK studies, you also provide complete PK bioanalytical assay reports for AS and DHA associated with each study.*
- *We recommend that you submit full clinical study reports, along with the PK bioanalytical assay reports for AS and DHA, for the drug-drug interaction studies conducted with IV AS.*
- *We recommend that you submit the study reports, NONMEM codes, and datasets for the population PK analyses.*
- *We recommend that you provide dosage adjustment recommendations for IV AS in malaria patients with renal or hepatic impairment and provide data and/or other information to support your proposed recommendations in such organ impaired patients.*

Meeting Discussion:
The Sponsor stated that they did not plan on a dosage adjustment in renal or hepatic impairment because the AUC for DHA is similar in patients with severe malaria compared to patients with uncomplicated malaria. Thus, no dosage adjustment for IV AS is needed in severe malaria patients who have either renal or hepatic impairment. FDA stated that the Sponsor should submit their plan and justification to the NDA for review.

FDA asked if any renal or hepatic studies or mass balance study(ies) were done or any analysis to address this concern. The Sponsor stated they have not conducted such studies, but that the AUC for DHA is similar for severe malaria vs. uncomplicated malaria.

5. Is the above plan for submission of digital ECGs as pdf files for these Phase 1 studies acceptable to the Agency?

FDA Response:
In general, for most new molecular entities, a Thorough QT (TQT) study is required prior to approval. While your plan includes submission of digital ECGs as pdf files from two Phase 1 studies, the adequacy of these in characterizing the QT prolongation potential for IV AS will be determined upon review of the data. We refer you to the ICH guideline E14, Clinical Evaluation of QT/QTC Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic drugs for additional information; see https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf.

We are seeking additional input from CDER's QT Interdisciplinary Review Team on your proposed ECG submission plan.

Meeting Discussion:
The Sponsor asked when feedback from the FDA QT Interdisciplinary Review Team would be expected. FDA stated they expect the review to be completed shortly and plan to share the response with the Sponsor as soon as information is available. [See Post Meeting Note]

Post Meeting Note: FDA QT Interdisciplinary Review Team (IRT) completed the review and have the following comments:

QT-IRT's response:
We generally do not accept digitized ECGs in TQT studies or other QT studies designed to exclude a 10-ms increase in the QTc interval. Without the original digital ECG waveforms, it cannot be determined whether the redigitization process may have increased the variance in the QT, which would have reduced the power to detect a small treatment effect Stockbridge, N., J Electrocardiol 2005; 38, 319-20). Therefore, the sponsor must also submit the automatic ECGs readings prior to digitization (e.g., from the ECG device in the clinical site) to support their evaluation. The adequacy of the data collected in studies 1128 and 1142 to be used as a substitute for a TQT study as per ICH E14 Q&A (R3) 5.1 will be a review issue**.** Additionally, we have the following comments for the sponsor to consider:

1. The doses included in studies 1128 and 1142 should characterize the QTc at sufficiently high multiples of the clinically relevant exposure (e.g., twice the supratherapeutic dose) to waive the need for a separate positive control (ICH E14 Q&A (R3) 5.1).
2. If your product is likely to increase or decrease the heart rate significantly (e.g., >10 bpm) in the study, you will need to consider the use of alternative methods for assessing changes in the QT interval, such as QTcI (individualized QT correction). To support alternative methods, it is important that drug-free baselines are available from a wide enough span of heart rates to cover on treatment changes in heart rate, within each individual. For additional information, please see "*Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects*" (Garnett, C. et al., Am Heart J 2012;163(3):912-30). In the absence of significant heart rate effects, we recommend the use of QTcF for the primary analysis.
3. For exposure-response analysis, we recommend the analysis and reporting of results follow the recommendations described in "*Scientific white paper on concentration-QTc modeling"* (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2017; doi 10.1007/s10928-017-9558-5) and "*Correction to: Scientific white paper on concentration-QTc modeling*" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6).
4. We are also interested in the effects of the test substance on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.
5. When you submit your QT study reports, please include the following items:
   a. Study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
   b. Study report
   c. Statistical analysis plan
   d. Clinical study protocol

e. Investigator's Brochure
f. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table
g.Annotated CRF
h. A data definition file which describes the contents of the electronic data sets
i. Electronic data sets as SAS.xpt transport files (in CDISC SDTM and ADAM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable).
j. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
k. Adverse Event analysis using the MedDRA SMQ "Torsade de pointes/QT Prolongation" and include the preferred term "Seizure" by treatment and dose level.
l. Narrative summaries and case report forms for any
    i. Deaths
    ii. Serious adverse events
    iii. Episodes of ventricular tachycardia or fibrillation
    iv. Episodes of syncope
    v. Episodes of seizure
    vi. Adverse events resulting in the subject discontinuing from the study

6. Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

Submission Specific Questions:
The proposed content of the submission is provided in section Appendix 6.

6. Amivas does not intend to submit separate ISS or ISE as the module 2 summaries (module 2.7.3 and module 2.7.4) are comprehensive with respect to data integration. Is the plan to not submit an ISS and ISE acceptable to the agency?

FDA Response:
We strongly encourage submission of an ISE. If all the information noted below can be provided within the space limitations of the Summary of Clinical Efficacy (SCE), with relevant tabulations in Module 5, section 5.3.5.3, cross-linked with relevant 2.7.3 SCE sections, your proposal may be acceptable.

It is critical that you include and synthesize additional sources of information such as clinical pharmacology studies, relevant nonclinical and in vitro studies, and other evidence from the literature, along with the clinical studies discussed. Results should be compared and pooled where possible, and important similarities and differences in patient populations (e.g., demographics, disease severity), control groups (if any), doses, durations of exposure, inclusion and exclusion criteria, length of follow up, etc., should be highlighted. For full details, please refer to the Guidance for Industry on Integrated Summary of Effectiveness: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf. In particular, all content suggestions outlined in Section III (Format and

Content of the ISE) should be addressed. Missing information and analyses could be a filing issue. The same concerns and caveats apply to the SCS/ISS.

Meeting Discussion:
The Sponsor stated they do not plan to include ISS and ISE since section 2.7.3 includes all information that would be provided in the ISS and ISE. FDA responded that the Sponsor must have an integrated summary of publicly available data and the Sponsor generated data related to the efficacy and safety of their product. The Sponsor stated they will closely examine all available data and construct an overview of clinical efficacy and safety sections accordingly. The Sponsor will consider inclusion of the meta-analysis as proposed by FDA. The Sponsor noted that they have more AE data than what can be found in the public domain.

7. Amivas and USAMMDA would both like to ensure continuity of IV AS supply to the US market during the transition of IND lots (with (b) (4) (b) (4) API) to commercial lots (with (b) (4) semi-synthetic API). Is continued supply of IND lots acceptable until commercial product can be supplied post-NDA approval?

FDA Response: *This is acceptable from a CMC perspective.*

Meeting Discussion:
The Sponsor acknowledged the response to Question 7.

8. Does the Agency have any comment regarding the proposed content of the NDA?

FDA Response:

***Clinical Microbiology*:**
All details of the parasitological methods used in the clinical trials such as preparation of blood smears, slide reading, number of slide readers, and quality control measures implemented should be included. Additionally, please clarify if slide reading was performed at the site laboratories and/or a central laboratory. If central laboratory was used, then name and address of the laboratory should also be included.

Biopharmaceutics:
In Section 3.2.P.2 Pharmaceutical Development, provide a standalone file that includes a summary table for the IV AS formulations/drug products used in the literature and/or Applicant-sponsored clinical efficacy and safety (as well as clinical PK) studies being used to support the marketing application for the proposed IV AS developed. To the extent possible, the following information should be included in the summary table: clinical study number and status (i.e., completed/ongoing), formulation identifier (i.e., brand/generic name), manufacturer information, drug product batch/lot number, expiration date, formulation composition (i.e., active and inactive ingredients and amount of each ingredient), dosage form, strength and presentation (e.g., powder for reconstitution, mg per vial), storage conditions, instructions for preparation and administration, vehicles for powder reconstitution and further dilution, physico-chemical properties of the powder and the reconstituted product, drug substance source (e.g., (b) (4) *or semi-synthetic) and batch/lot number, etc. Provide also the Certificates of Analysis of the drug products, if available.*

For each formulation/drug product in the summary table that is not the same as the final proposed to-be-marketed IV AS formulation/drug product, provide justification that any differences in such formulations/drug products would not impact PK, efficacy and safety, and/or the ability of FDA to rely on the efficacy and safety information from the literature studies, for example, the IV AS formulations/drug products used in the SEAQUAMAT and AQUAMAT studies. This information should establish that reliance on the studies described in the literature is scientifically appropriate.

Clinical:

1. *For each of your studies, please submit the study protocol and amendments, sample case report form, statistical analysis plan, and any publications based on the study, as relevant. In addition, please identify the duration of follow up for each study.*

2. *According to your background materials, the proposed indication for IV AS is for the initial treatment of severe* (b) (4) *malaria in adults and children, and your definition of severe malaria includes the presence of Plasmodium falciparum, P. vivax, or P. knowlesi. The SEAQUAMAT and AQUAMAT studies, required diagnosis of P. falciparum at enrollment, and your two Phase 2 studies 1168 and 1263 enrolled patients with uncomplicated P. falciparum malaria. Study R-CDC-060 (Twomey 2015) reported that only 12 of the 102 patients had species other than P. falciparum or an unknown species. Please clarify which studies you intend to submit to support the efficacy and safety of severe malaria caused by species other than P. falciparum.*

3. *Your planned NDA submission includes Study R-CDC-060 (Twomey et al. 2015), which enrolled 102 patients from 2007 until the end 2010. As the CDC study is ongoing, please clarify if you will have data on patients enrolled from 2011 to 2018. If possible, we recommend that your application includes data and analysis from study initiation through the most recent data available. As described in Twomey et al. 2015, subjects were followed for a maximum of 7 days; we are also interested in any safety information from CDC-060 on patients followed for longer than 7 days, including any patients who experienced post-artesunate delayed hemolysis.*

4. (b) (4)

5. *We note that your IND included three reports titled "Retrospective Data Abstraction Study of CDC Treatment Protocol CDC-060: Intravenous Artesunate for treatment of Severe Malaria in the United States", "*(b) (4) *and "Meta-analysis of Intravenous Artesunate in Complicated or severe malaria" (IND 64769 SDN 103 received August 29, 2014) that described and analyzed the occurrence of PADH and other safety endpoints following IV AS. Please clarify whether you intend to submit the data and information characterizing PADH including the above-mentioned analyses in the NDA.*

6. *We note you plan to submit legacy datasets for SEAQUAMAT. According to the briefing document, pdf p. 359, you intend to submit the following .xpt files: adsl.xpt, adlb.xpt, advs.xpt, admb.xpt, adce.xpt. Please indicate whether you are able to provide additional files including adae.xpt, (adverse event), adcm.xpt (concomitant medication), adex.xpt (exposure to treatment), and admh.xpt (medical history). We recommend that you submit the legacy dataset for review to the IND prior to NDA submission.*

7. *Every effort should be made to provide source data for clinical studies supporting the submission, including patient level data. Please clarify your efforts to obtain access to the source data for SEAQUAMAT and AQUAMAT.*

8. *We recommend you plan to organize and submit your NDA in electronic format according to FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submission Using the eCTD Specifications, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.*

Meeting Discussion:
The Sponsor acknowledged the responses to Question 8 and stated they will provide the available information. Additionally, the Sponsor stated that they plan to seek an indication for severe malaria and not a species-specific indication in the product labeling.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  Agreement was reached that all NDA Modules will be submitted as complete modules, except for the Nonclinical module and CMC module (pending agreement with OPQ at the CMC only pre-NDA meeting)

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was not held on the need for a REMS, other risk management actions and, the development of a Formal Communication Plan. The need for a REMS and a Formal Communication Plan will be a review issue.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following application components may be submitted within the below specified calendar days after the submission of the original application:

- Complete audited 4-week rat and dog toxicology draft study reports must be submitted within 60 days of the NDA submission date
- The final 4-week rat and dog toxicology study reports must be submitted within 30 days following the submission of the audited draft reports.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - NONCLINICAL
NDA NUMBER: LATE COMPONENT - QUALITY

In addition, we note that a chemistry pre-submission meeting is planned. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

4.0 OTHER IMPORTANT APPLICATION INFORMATION (not discussed at the meeting)

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format.

Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108,

until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue meeting minutes	FDA	March 30, 2019
Submit updated NDA timeline to IND.	Sponsor	Within 1 month
Submit a rolling review request to the IND.	Sponsor	Prior to May 2019

6.0 ATTACHMENTS

- Sponsor's February 25, 2019, NDA Timeline
- FDA's February 27, 2019, Preliminary Meeting Comments

6 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 64769

MEETING PRELIMINARY COMMENTS

The Surgeon General, Department of the Army
U.S. Army Medical Research and Materiel Command
Attention: MCMR-ORA c/o Mark S. Paxton, J.D., M.S.
Sponsor's Representative
1430 Veterans Drive
Fort Detrick, MD 21702-5009

Dear Mr. Paxton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Intravenous Artesunate.

We also refer to your January 11, 2019, correspondence, received January 11, 2019, requesting a meeting to discuss and come to an agreement on the clinical portion of your planned NDA for Intravenous Artesunate.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Gregory F. DiBernardo
Senior Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B

Meeting Category: Pre-NDA

Meeting Date and Time: February 28, 2019, at 10:00 AM

Meeting Location: White Oak Campus, Building 22, Room 1315

Application Number: IND 64769

Product Name: Intravenous Artesunate (IV AS)

Indication: Treatment of severe malaria

Sponsor Name: The Surgeon General, Department of the Army

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 28, 2019, at 10:00 AM, at the White Oak Campus, Building 22, Room 1315 between The Surgeon General, Department of the Army and the Division of Anti-Infective Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

FDA issued a meeting granted letter on January 24, 2019, for a January 11, 2019, Pre-NDA meeting request. We note that in the January 11, 2019, meeting package, Amivas LLC (Amivas) is identified as the co-development partner with the U.S. Army Medical Materiel Development Activity (USAMMDA) for the development of IV AS in the U.S. Amivas plans to submit an NDA for IV AS pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

2.0 DISCUSSION

Pre NDA Meeting Background Materials Questions:

1. Does the agency agree that the pharmacology, pharmacokinetic and toxicology studies that have already been completed are sufficient to support the NDA filing presuming that there are no review issues?

FDA Response:

Pharmacology Toxicology:

In your draft NDA timeline analysis that describes the status of ongoing CMC studies and the proposed timeline for submission of the nonclinical study reports (4-week repeat-dose toxicology studies in rats and dogs with IV AS), it appears that the draft study reports will be submitted close to the end of the review cycle leaving insufficient time to conduct a substantial review of the study findings. We typically require complete study reports at the time of NDA submission. Given significant unmet need and the breakthrough status of IV AS, we are willing to consider Module 4 of the NDA submission complete if you include unaudited draft reports with signed histopathology reports, in the initial NDA submission and agree to submit the audited study reports within 60 days of the NDA submission and the final study reports no later than 30 days after the audited draft reports. We recommend that you contact the CRO that will be carrying out these studies to see if they could provide you with the unaudited draft reports at an earlier date to facilitate the submission of a complete Module 4 in your initial NDA submission. Both audited draft reports and final study reports should be accompanied by a list of changes from the previously submitted draft reports.

Clinical Microbiology:

The clinical microbiology response was communicated in the preliminary comments and discussed with you at the meeting on February 15, 2019. We assume that nonclinical information will be based on the active metabolite in addition to artesunate.

2. Amivas is planning to conduct (b) (4) (b) (4) (b) (4) This timing would address concerns expressed by the Drug Shortages Divisions regarding the imminent absence of an approved drug in the US to treat severe (b) (4) malaria. Is this acceptable at the time of filing the NDA?

FDA Response:

Pharmacology Toxicology:

Please see response to Question 1.

Clinical Pharmacology:

(b) (4) (b) (4)

(b) (4)

3. Alternatively to the proposal in question #2, as IV AS has received both Fast Track designation and Breakthrough designation, information such as the results of the proposed studies could possibly be submitted during the review period, if FDA agrees to this possibility. As the nonclinical section that is ready for submission now is otherwise complete, would the Agency consider a late submission of these reports if the proposed PMR is rejected?

FDA Response:

Clinical Pharmacology:
We agree with your proposal to conduct the transporter studies as PMRs. Please see our response to the question 2.

Clinical Questions:
Amivas plans to provide the results of 3 pivotal clinical trials (R-CDC-060, SEAQUAMAT, and AQUAMAT) that studied IV AS in patients with complicated or severe malaria and several supportive clinical trials including 2 Phase 1 (study 1128 and study 1142) pharmacokinetic (PK) single and multiple dose studies and 2 Phase 2 (study 1168 and study 1263ab) clinical trials in patients with uncomplicated malaria, along with a summary of the relevant literature as sufficient evidence of product efficacy. As evidence of product safety, Amivas will provide safety data from all subjects who received at least one dose of IV AS in one of the Phase 1 studies (n=50), Phase 2 studies (n=130), or in Study R CDC-060 (n=102). In addition, safety data will be referenced from a randomized, double-blind, Phase 2 clinical trial conducted by EDCTP-MMV that compared 2 different dosing regimens of IV AS in African children (n=194) with severe *Pf* malaria (Study EDCTP-MMV07- 01, Kremsner-2012). Final clinical study reports will be provided for all of the above studies with the exception of the SEAQUAMAT and AQUAMAT studies. These study's results are available as publications, Dondorp-2005 and Dondorp-2010, respectively. Of the three pivotal clinical trials, complete CDISC compliant SDTM and ADaM datasets including define files, annotated CRFs and reviewer's guide are available for the R-CDC-060 clinical trial and will be submitted. Likewise complete CDISC compliant SDTM and ADaM datasets will also be provided for Phase 1 and 2 studies 1128, 1142, 1168, and 1263ab. The SEAQUAMAT group provided a single legacy dataset for all 1461 subjects enrolled in the SEAQUAMAT trial and the blank case report forms (CRFs). We plan to submit these legacy data as CDISC SAS.xpt files, along with annotated CRFs, Reviewer's guide, and define.xml file. Source data for the R-CDC-060 study are available for review at CDC headquarters in Atlanta, GA. The SEAQUAMAT and AQUAMAT data are not available for source data review as these were conducted by another sponsor. Although datasets from the EDCTP-MMV07-01 study are not available, safety data from the study's clinical study report will be referenced in the IV AS safety discussions.

4. Is the above plan for submission of clinical study reports, supporting literature, and datasets acceptable to the Agency? Electrocardiograms (ECG) were administered during the conduct of the two Phase 1 clinical trials sponsored by the Army (Studies 1128 and

1142). Besides the evaluation of the ECGs by a cardiologist at the clinical site, all ECG tracings were digitized and analyzed by a Cardiologist at (b) (4) prepared a separate Cardiac Safety Report evaluating the ECGs for QTc prolongation and other cardiac clinically significant changes. The Cardiac Safety Reports are included in an Appendix to the final clinical study reports for these studies. (b) (4) also provided digital ECGs as pdf files. The sponsor does not have xpt files for these ECGs to submit to through the FDA gateway, but is providing them as Appendices (Appendix 16.3) to each of the clinical study reports. In addition, the digital ECG data are provided with the datasets for these studies.

FDA Response:

Clinical/ Statistical:

According to your meeting package, your NDA will include data and information from R-CDC-060 and Phase 1 and 2 studies 1128, 1142, 1168, and 1263ab, as well as published studies including SEAQUAMAT (Dondorp et al. 2005) and AQUAMAT (Dondorp et al. 2010). Please note that the decision regarding the adequacy of the submitted data and published studies to support the safety and effectiveness of IV AS for the treatment of severe malaria will be made upon the review of the NDA. For guidance on FDA's expectations regarding clinical evidence of effectiveness for human drug products, please refer to: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072008.pdf.

Please see our comments below:

- *The SEAQUAMAT and AQUAMAT studies could potentially serve as adequate and well-controlled trials. It will be important to submit complete patient level data, protocols, statistical analysis plans, and complete study reports for both trials. Please discuss if you are unable to submit this information and the efforts you have made, if any, to obtain such information.*
- *Whether or not the SEAQUAMAT study alone can support the efficacy of IV artesunate for the proposed indication will depend on the adequacy of the datasets, the strength of the results, and the consistency across subgroups.*

Clinical Pharmacology:

- *The proposal to provide study reports and data for PK studies 1128, 1142, 1168 and 1263ab is acceptable.*
- *We recommend that along with the complete study reports for such PK studies, you also provide complete PK bioanalytical assay reports for AS and DHA associated with each study.*
- *We recommend that you submit full clinical study reports, along with the PK bioanalytical assay reports for AS and DHA, for the drug-drug interaction studies conducted with IV AS.*
- *We recommend that you submit the study reports, NONMEM codes, and datasets for the population PK analyses.*

- *We recommend that you provide dosage adjustment recommendations for IV AS in malaria patients with renal or hepatic impairment and provide data and/or other information to support your proposed recommendations in such organ impaired patients.*

5. Is the above plan for submission of digital ECGs as pdf files for these Phase 1 studies acceptable to the Agency?

FDA Response:
In general, for most new molecular entities, a Thorough QT (TQT) study is required prior to approval. While your plan includes submission of digital ECGs as pdf files from two Phase 1 studies, the adequacy of these in characterizing the QT prolongation potential for IV AS will be determined upon review of the data. We refer you to the ICH guideline E14, Clinical Evaluation of QT/QTC Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic drugs for additional information; see https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf.

We are seeking additional input from CDER's QT Interdisciplinary Review Team on your proposed ECG submission plan.

Submission Specific Questions:
The proposed content of the submission is provided in section Appendix 6.

6. Amivas does not intend to submit separate ISS or ISE as the module 2 summaries (module 2.7.3 and module 2.7.4) are comprehensive with respect to data integration. Is the plan to not submit an ISS and ISE acceptable to the agency?

FDA Response:
We strongly encourage submission of an ISE. If all the information noted below can be provided within the space limitations of the Summary of Clinical Efficacy (SCE), with relevant tabulations in Module 5, section 5.3.5.3, cross-linked with relevant 2.7.3 SCE sections, your proposal maybe acceptable.

It is critical that you include and synthesize additional sources of information such as clinical pharmacology studies, relevant nonclinical and in vitro studies, and other evidence from the literature, along with the clinical studies discussed. Results should be compared and pooled where possible, and important similarities and differences in patient populations (e.g., demographics, disease severity), control groups (if any), doses, durations of exposure, inclusion and exclusion criteria, length of follow up, etc., should be highlighted. For full details, please refer to the Guidance for Industry on Integrated Summary of Effectiveness: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf. In particular, all content suggestions outlined in Section III (Format and Content of the ISE) should be addressed. Missing information and analyses could be a filing issue. The same concerns and caveats apply to the SCS/ISS.

7. Amivas and USAMMDA would both like to ensure continuity of IV AS supply to the US market during the transition of IND lots (with (b) (4) (b) (4) API) to commercial

lots (with (b) (4) semi-synthetic API). Is continued supply of IND lots acceptable until commercial product can be supplied post-NDA approval?

FDA Response: *This is acceptable from a CMC perspective.*

8. Does the Agency have any comment regarding the proposed content of the NDA?

FDA Response:

***Clinical Microbiology*:**
All details of the parasitological methods used in the clinical trials such as preparation of blood smears, slide reading, number of slide readers, and quality control measures implemented should be included. Additionally, please clarify if slide reading was performed at the site laboratories and/or a central laboratory. If central laboratory was used, then name and address of the laboratory should also be included.

Biopharmaceutics:
In Section 3.2.P.2 Pharmaceutical Development, provide a standalone file that includes a summary table for the IV AS formulations/drug products used in the literature and/or Applicant-sponsored clinical efficacy and safety (as well as clinical PK) studies being used to support the marketing application for the proposed IV AS developed. To the extent possible, the following information should be included in the summary table: clinical study number and status (i.e., completed/ongoing), formulation identifier (i.e., brand/generic name), manufacturer information, drug product batch/lot number, expiration date, formulation composition (i.e., active and inactive ingredients and amount of each ingredient), dosage form, strength and presentation (e.g., powder for reconstitution, mg per vial), storage conditions, instructions for preparation and administration, vehicles for powder reconstitution and further dilution, physico-chemical properties of the powder and the reconstituted product, drug substance source (e.g., (b) (4) *or semi-synthetic) and batch/lot number, etc. Provide also the Certificates of Analysis of the drug products, if available.*

For each formulation/drug product in the summary table that is not the same as the final proposed to-be-marketed IV AS formulation/drug product, provide justification that any differences in such formulations/drug products would not impact PK, efficacy and safety, and/or the ability of FDA to rely on the efficacy and safety information from the literature studies, for example, the IV AS formulations/drug products used in the SEAQUAMAT and AQUAMAT studies. This information should establish that reliance on the studies described in the literature is scientifically appropriate.

Clinical:

1. *For each of your studies, please submit the study protocol and amendments, sample case report form, statistical analysis plan, and any publications based on the study, as relevant. In addition, please identify the duration of follow up for each study.*

2. *According to your background materials, the proposed indication for IV AS is for the initial treatment of severe* (b) (4) *malaria in adults and children, and your*

definition of severe malaria includes the presence of Plasmodium falciparum, P. vivax, or P. knowlesi. The SEAQUAMAT and AQUAMAT studies, required diagnosis of P. falciparum at enrollment, and your two Phase 2 studies 1168 and 1263 enrolled patients with uncomplicated P. falciparum malaria. Study R-CDC-060 (Twomey 2015) reported that only 12 of the 102 patients had species other than P. falciparum or an unknown species. Please clarify which studies you intend to submit to support the efficacy and safety of severe malaria caused by species other than P. falciparum.

3. *Your planned NDA submission includes Study R-CDC-060 (Twomey et al. 2015), which enrolled 102 patients from 2007 until the end 2010. As the CDC study is ongoing, please clarify if you will have data on patients enrolled from 2011 to 2018. If possible, we recommend that your application includes data and analysis from study initiation through the most recent data available. As described in Twomey et al. 2015, subjects were followed for a maximum of 7 days; we are also interested in any safety information from CDC-060 on patients followed for longer than 7 days, including any patients who experienced post-artesunate delayed hemolysis.*

4. *(b) (4)*

5. *We note that your IND included three reports titled "Retrospective Data Abstraction Study of CDC Treatment Protocol CDC-060: Intravenous Artesunate for treatment of Severe Malaria in the United States", (b) (4) ", and "Meta-analysis of Intravenous Artesunate in Complicated or severe malaria" (IND 64769 SDN 103 received August 29, 2014) that described and analyzed the occurrence of PADH and other safety endpoints following IV AS. Please clarify whether you intend to submit the data and information characterizing PADH including the above-mentioned analyses in the NDA.*

6. *We note you plan to submit legacy datasets for SEAQUAMAT. According to the briefing document, pdf p. 359, you intend to submit the following .xpt files: adsl.xpt, adlb.xpt, advs.xpt, admb.xpt, adce.xpt. Please indicate whether you are able to provide additional files including adae.xpt, (adverse event), adcm.xpt (concomitant medication), adex.xpt (exposure to treatment), and admh.xpt (medical history). We recommend that you submit the legacy dataset for review to the IND prior to NDA submission.*

7. *Every effort should be made to provide source data for clinical studies supporting the submission, including patient level data. Please clarify your efforts to obtain access to the source data for SEAQUAMAT and AQUAMAT.*

8. *We recommend you plan to organize and submit your NDA in electronic format according to FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submission Using the eCTD Specifications,*

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our January 24, 2019, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage

between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing

application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUMATHI NAMBIAR
03/28/2019 02:49:25 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND #	64769, SDN 136
Request Receipt Date	07-13-18
Product	Intravenous Artesunate
Indication	Severe malaria
Drug Class/Mechanism of Action	Artemisinin/ antimalarial
Sponsor	U.S. Army Medical Research and Materiel Command (USAMRMC)
ODE/Division	Division of Anti-Infective Products
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	09-11-18

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes,*** *and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)****.*** *Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):** Treatment of severe (b) (4) malaria.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
      ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
      ☐ Undetermined

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- *Information regarding the disease and intended population for the proposed indication.*

In the US, intravenous (IV) artesunate is intended for the treatment of returning travelers who have severe malaria. IV artesunate is currently available from the CDC under IND 76,725 and the drug (known as the WRAIR formulation) is supplied to the CDC by the US Army.[3,4] The dose is four weight-based doses of IV

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf
[3] Twomey PS, Smith BL, McDermott C, et al. Intravenous Artesunate for the Treatment of Severe and Complicated Malaria in the United States: Clinical Use Under an Investigational New Drug Protocol. Annals of internal medicine. 2015;163(7):498-506.
[4] CDC. CDC and Malaria. Updated June 26, 2018: Available at: https://www.cdc.gov/malaria/diagnosis_treatment/artesunate.html

artesunate (2.4 mg/kg) at 0, 12, 24, and 48 h before transitioning to oral antimalarials. IV artesunate (WRAIR formulation) is available to US military personnel under IND 64,769. Intravenous artesunate is recommended by the World Health Organization as the first-line therapy for severe malaria in adults and children, worldwide.[5] Severe malaria is a life-threatening infection and is a medical emergency. Most cases are due to *P. falciparum*. The disease is characterized by hyperparasitemia (≥ 5% parasitized red cells), destruction of parasitized red cells, and sequestration of red cells in small blood vessels causing end-organ dysfunction. Manifestations of severe malaria include, high fever, hemolytic anemia, hypoglycemia, metabolic acidosis, renal failure, hepatic injury/jaundice, pulmonary edema, Acute Respiratory Distress Syndrome, cerebral malaria, convulsions, disseminated intravascular coagulation, circulatory shock, and death.

During 2013, the CDC received 1,727 case reports of a onset of symptoms of malaria in the US.[6] This represents a 2% increase from the 1,687 cases reported for 2012. *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* were identified in 61%, 14%, 3%, and 4% of cases, respectively. Thirty-six cases were reported in pregnant women, none of whom had adhered to malaria chemoprophylaxis. Among the reported cases, approximately 270 (16%) were classified as severe and of these, 10 individuals with malaria due *P. falciparum* died, the highest number since 2001.

- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

There are five known *Plasmodium* species that cause malaria in humans, i.e., *P. falciparum, P. vivax, P. ovale, P. malariae,* and *P. knowlesi*. Most cases of severe malaria are caused by *P. falciparum*; however, some cases of severe malaria have been associated with other species for example, *P. vivax* and *P. knowlesi*. Humans are infected by the bite of an infected mosquito (Anopheles).

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

In two randomized, open-label clinical trials in adults and children (SEAQUMAT[7]) and children (AQUAMAT[8]) with severe malaria, the primary endpoint was death (in-hospital mortality). Secondary endpoints included incidence of neurological sequelae, combined death or neurological sequelae, recovery times, and development of severe complications of malaria.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

The primary endpoint was death from severe malaria which is a meaningful clinical endpoint.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Not applicable.

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[5] WHO. World Malaria Report 2015. Available from: http://www.who.int/malaria/publications/world-malaria-report-2015/report/en/
[6] Cullen K, Mace A, Arguin P. Malaria Surveillance – United States, 2013. MMWR Surveillance Summary. 2016;65(2):1-22.
[7] Dondorp A, Nosten F, Stepniewska K, et al. (South East Asian Quinine Artesunate Malaria Trial or SEAQUAMAT group). Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet (London, England) 2005; 366: 717–25
[8] Dondorp AM, Fanello CI, Hendriksen IC, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet (London, England) 2010;376:1647-1657.

A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and

Intravenous quinine is not available in the USA. Intravenous quinidine (isomer of quinine) gluconate, an anti-arrhythmic, has an indication for treatment of severe *P. falciparum* malaria and it is the only available drug in the US for this indication. The sponsor's assumption is reasonable that quinine efficacy is an appropriate surrogate for quinidine efficacy and comparison of quinine to artesunate closely predicts data if quinidine had been compared to artesunate. Quinidine gluconate IV is not readily available in all US hospitals because newer antiarrhythmic drugs are used in clinical practice. Cardiac monitoring is advised because quinidine is associated with hypotension, hypoglycemia, ventricular arrhythmia, and prolongation of the QTc interval at the doses required for the treatment of *P. falciparum* malaria. On December 1, 2017, Eli Lilly announced discontinuation of the manufacture of quinidine gluconate injectable. The distribution of quinidine gluconate will continue in the US until its labeled expiry in March 2019.

- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Oral antimalarials such as artemether/lumefantrine, mefloquine hydrochloride, atovaquone/proguanil, or quinine sulfate are indicated for treatment of uncomplicated malaria, not severe malaria. These antimalarials could be used off-label for severe malaria but they would be likely to lead to treatment failures because they would not act fast enough to achieve clearance of the hyperparasitemia associated with severe malaria and oral therapy is often difficult to administer and tolerate in sick patients.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[9].

None.

10. Information related to the preliminary clinical evidence:

a. Two phase 1 and two phase 2 studies were conducted by the Sponsor, (Table 1). Artesunate IV (WRIAR formulation) was generally well tolerated. Artesunate IV was associated with 100% malaria parasite clearance in all patients in two phase 2 studies. The sponsor is planning to rely on two published phase 3 studies funded by the Wellcome Trust for their NDA. It is not clear if patient level data from these two trials will be provided in the US Army's NDA.

[9] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

Table 1. IND 64,769: Overview of Phase 1 and 2 Clinical Studies conducted by the Sponsor

Study No.	Design	Objectives	Population	Dosage	Results
US Army 1128	Phase 1a, randomized, double-blind, placebo-controlled, dose-escalation	Safety, tolerability, pharmacokinetics of single IV doses of AS	Healthy adult men and women N=40 enrolled (30 AS, 10 placebo), 39 completed the study (30 AS, 9 placebo)	**Single IV dose of AS or placebo** Doses: 0.5, 1.0, 2.0, 4.0, or 8.0 mg/kg	Well-tolerated and safe at all dose levels. Mild, transient headache, and transient dizziness were noted, together with transient dysgeusia at higher dose levels
US Army 1142	Phase 1b, double-blind, placebo-controlled, randomized, multiple dose escalation	Safety, tolerance, pharmacokinetics of multiple IV doses of AS in a dose-escalation design	Healthy adult men and women N=26 enrolled (20 AS, 6 placebo), 24 completed the study (18 AS, 6 placebo)	**Multiple IV doses of AS or placebo** Doses: 2.0, 4.0, or 8.0 mg/kg on 3 consecutive days	Well-tolerated and safe at all dose levels with no cumulative effects observed. Mild, transient headache noted, and transient dysgeusia at higher dose levels.
US Army 1168	Phase 2, open-label	Safety, tolerability, efficacy, pharmacokinetics	Adult men and women with uncomplicated malaria N=30 enrolled, 30 completed the study Conducted in Kenya	**2.4 mg/kg IVAS for 3 days** followed by oral Malarone for 3 days	100% parasite clearance in all patients by end of Day 2. Safe and well tolerated. One SAE occurred, Stevens-Johnson syndrome considered probably related to Malarone and possibly related to IV AS.
US Army 1263A/1263B	Phase 2 open-label, dose-ranging	Identification of most efficacious treatment regimen, tolerability, safety	Patients with acute symptomatic, uncomplicated *Pf* malaria Adult men and women (Thailand sites), adult men and women and children (Kenya sites) N=100 enrolled, 97 completed the study	**IVAS at 1.2, 2.4, or 4.8 mg/kg once daily for 3 days or 2.4 mg/kg twice on Day 0 then once daily for 2 days.** Follow-on treatment with oral mefloquine or Malarone	100% parasite clearance in all patients by 72 hours in all dosing cohorts. All dosing regimens safe, generally well tolerated. Mild, resolvable adverse events with neutropenia, anemia most common.

Source: Adapted from Table 3, IND 64796, SDN 136

- b. Additional relevant information

Results from two published phase 3 trials in adults and pediatric patients demonstrated a substantial improvement in mortality with IV artesunate over quinine for the treatment of severe malaria. In the SEAQUAMAT trial (adults and children), the mortality rate was 22% (164/731) in the quinine group and 15% (107/730) in the IV artesunate group (odds ratio[OR] 0·60, 95% CI (0·45–0·79); p = 0.0002). Approx. 70% of the participants in the trial had severe malaria and mortality in this subgroup of patients was 28% for those treated with quinine, and 20% for those treated with IV artesunate (OR 0.65, 95% CI (0.48-0.87); p = 0.003). In the pediatric trial (AQUAMAT), 230 (8·5%) patients assigned to artesunate treatment died compared with 297 (10·9%) assigned to quinine treatment (OR 0·75, 95% CI 0·63–0·90; relative reduction 22·5%, 95% CI 8·1-36·9; p=0·0022). Artesunate substantially reduced mortality in adults and children with severe malaria. Artesunate IV used in these trials was manufactured by Guilin Pharmaceuticals, China.

The sponsor referenced a metanalysis of the SEAQUAMAT, AQUAMAT, and six smaller trials which included 7,429 patients (1664 adults and 5765 children).[10] Treatment with artesunate IV significantly reduced the risk of death both in adults (RR=0.61, 95% CI 0.50 - 0.75; 1664 participants, 5 trials) and children (RR=0.76, 95% CI 0.65 - 0.90; 5,765 participants, 4 trials).

The sponsor's formulation of IV artesunate was used in a phase 3 trial of IV artesunate for severe malaria in children. In 171 children (per protocol), 78% of the recipients (95% confidence interval [CI], 69% - 87%) in the 3-dose group achieved ≥ 99% parasite clearance at 24 hours after the start of

[10] Sinclair D, Donegan S, Isba R and Lalloo DG. Artesunate versus quinine for treating severe malaria. Cochrane Database Syst Rev. 2012; (6):CD005967. doi: 10.1002/14651858.CD005967.pub4

treatment, compared with 85% (95% CI, 77% - 93%) of those receiving the conventional regimen (treatment difference, -7.2%; 95% CI, -18.9% to 4.4%). In the ITT population, 76% (95%CI, 69%–86%) of those randomized to receive 3 doses achieved ≥ 99% parasite clearance at 24 hours, compared with 86% (95% CI, 79%–93%) of the 5-dose group, giving a treatment difference of -9.6%, (95% CI, -20.9% to 1.7%).[11]

The sponsor also submitted supportive evidence of efficacy and safety from an observational study of IV artesunate (WRAIR formulation) for treatment of severe malaria conducted by the CDC.[3] Between January 2007 and December 2010, 102 patients aged 1 to 72 years (90% adults; 61% men) with severe or complicated malaria were treated with the WRAIR formulation of IV artesunate under IND via a CDC expanded access protocol (CDC Study 060-2014). Eighty-seven patients were considered evaluable based on parasitemia plus at least one of the following: 1) unable to take oral medications; 2) high density parasitemia (≥5%); and/or 3) severe malaria. Among the 87 evaluable patients, the median time to negative parasitemia was 43 hours. The 43 evaluable patients with quinidine exposure prior to being treated with artesunate had no statistically significant difference in time to negative parasitemia compared with the remaining 44 evaluable patients with no exposure (41 h vs. 50 h, respectively; P=0.608.

- *Safety data:*

Artesunate is generally well tolerated.[7,8,13] Artesunate is associated with post treatment hemolysis/hemolytic anemia known as postartesunate delayed hemolysis (PADH) and monitoring for hemolysis is advised for 30 days post treatment of malaria.[12] The incidence of PADH varies widely (0 to 60%) among studies.[15] Nausea, abdominal pain, diarrhea, dizziness, rash, and elevations in hepatic enzymes have been reported.[13] Neurological adverse events (balance disorder, tremor, seizure, hearing impairment) described in humans treated with IV artesunate appear to be mostly associated with severe malaria.[14,15]

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

Artesunate IV substantially reduced mortality in clinical trials in adults and children with severe malaria due to *P. falciparum* as compared to intravenous quinine. Intravenous artesunate is an important advancement in the treatment of severe malaria.

☐ DENY:

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[11] Kremsner PG, Taylor T, Issifou S, et al. A simplified intravenous artesunate regimen for severe malaria. J Infect Dis. 2012;205(2):312-9.

[12] Roussel C, Caumes E, Thellier M , et al. Artesunate to treat severe malaria in travellers: review of efficacy and safety and practical implications. J Travel Med. 2017; 24 (2):

[13] Adam I, Inrahim Y, Gasim GI. Efficacy and safety of artemisinin-based combination therapy for uncomplicated Plasmodium falciparum malaria in Sudan: a systematic review and meta-analysis. Malar J 2018;17:110. Published online 2018 Mar 13. doi: 10.1186/s12936-018-2265-x

[14] Price R, VanVugt M, Phaipun L, et al. Adverse effects in patients with acute falciparum malaria treated with artemisinin derivatives. Am J Trop Med Hyg 1999; 60(4):547-555.

[15] Jauréguiberry S. Thellier M, Ndour PA et al. Delayed-onset hemolytic anemia in patients with travel-associated severe malaria treated with artesunate, France 2011-2013. Emerg Infect Dis.21(5):804-12.

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The sponsor will be encouraged to schedule pre-NDA meetings with the DAIP and OPQ.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any: See footnotes.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?
YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review): The MPC agreed with DAIP's recommendation to grant USAMRMC's breakthrough therapy designation request and determined that further discussion with DAIP was not required.

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 6/12/18/M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELIZABETH M OSHAUGHNESSY
08/28/2018

SUMATHI NAMBIAR
08/28/2018