

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210795Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 101471

MEETING MINUTES

GlaxoSmithKline Intellectual Property Development Ltd. England
c/o GlaxoSmithKline Research & Development
Attention: Christian Baumann, Ph.D.
Director, Global Regulatory Affairs
1250 S. Collegeville Road, UP4300
Collegeville, PA 19426

Dear Dr. Baumann:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Tafenoquine (SB-252263) capsule.

We also refer to the teleconference between representatives of your firm and the FDA on July 18, 2017. The purpose of the meeting was to discuss the planned NDA for Tafenoquine (SB-252263) capsule.

A copy of the official minutes of the teleconference 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: B

Meeting Category: Pre-NDA

Meeting Date and Time: July 18, 2017, at 9:00 AM to 10:00 AM ET

Meeting Format: Teleconference

Application Number: IND 101471

Product Name: Tafenoquine (SB-252263) capsule

Indication: Radical cure of *P. vivax* malaria

Sponsor Name: GlaxoSmithKline Intellectual Property Development Ltd. England

Meeting Chair: Sumathi Nambiar, M.D., M.P.H.

Meeting Recorder: Gregory DiBernardo

FDA ATTENDEES

Division of Anti-Infective Products

Sumathi Nambiar, M.D., M.P.H.	Director
Dmitri Iarikov, M.D., Ph.D.	Acting Deputy Director
Joseph Toerner, M.D., M.P.H.	Deputy Director for Safety
Yuliya Yasinskaya, M.D.	Clinical Team Leader
Elizabeth M. O'Shaughnessy, M.D.	Clinical Reviewer
Shukal Bala, Ph.D.	Clinical Microbiology Reviewer
Terry Miller, Ph.D.	Pharmacology/Toxicology Team Leader
Owen G. McMaster, Ph.D.	Pharmacology/Toxicology Reviewer
Abimbola Adebawale, Ph.D.	Associate Director for Labeling
Maureen P. Dillon-Parker	Chief, Project Management Staff
Gregory F. DiBernardo	Regulatory Project Manager

Division of Clinical Pharmacology IV

Philip M. Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader
Zhixia (Grace) Yan, Ph.D.	Clinical Pharmacology Reviewer

The meeting minutes include the FDA Preliminary Meeting Responses for those questions where additional clarification was requested (**FDA Response**) followed by the discussion that took place at the meeting (**Meeting Discussion**). Following introductions from Glaxo and FDA representatives the following discussion occurred.

2. DISCUSSION

Question 2: Case Report Forms

Does the FDA agree with the proposal for provision of CRFs for the NDA filing?

FDA Response: *We agree with your proposal to provide case report forms (CRFs) for deaths, serious adverse events, and adverse events leading to discontinuation in the studies supporting the indication of radical cure of P. vivax malaria. Your proposal regarding the older clinical pharmacology studies and studies for the malaria prophylaxis indication is acceptable. As previously agreed, you will provide datasets for us to create a 10% random sample of patients for whom CRFs will be included in the NDA.*

Meeting Discussion:

Glaxo sought clarification on the studies from which the random sample of CRFs would be created. Glaxo stated they assumed that the 10% sample would be from the Phase 2b/3 studies TAF112582 part 2 (DETECTIVE part 2) and TAF116564 (GATHER), excluding TAF112582 Part 1). FDA confirmed that the 10% sample based on DETECTIVE Part 2 and GATHER was acceptable. GSK stated they could have the datasets ready within the next week for FDA to create the random sample. Glaxo also asked FDA if they had an estimated time frame for responding to GSK with the random sample to be included with the NDA. FDA stated they would be able to provide the requested random sample within 2 weeks of receipt of the datasets.

Question 13: OSI Request Clarity (Statistics Team)

Does the FDA and/or the OSI agree with this proposal for provision of information for the OSI request for this planned NDA submission.

FDA Response: *We acknowledge your plan to provide general study information and specific clinical investigator information, subject data listings by sites, and a site level dataset for TAF112582 (DETECTIVE) part 2. The Office of Scientific Investigations (OSI) has been consulted and we will provide a written response as soon as possible. We recommend that you refer to FDA Guidance for Industry Providing Submissions in Electronic Format —Summary Level Clinical Site Data for CDER's Inspection Planning found at <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf> to facilitate FDA selection of clinical study sites for inspection.*

Meeting Discussion:

Glaxo sought clarification on when OSI would provide a follow-up communication to the Division. The FDA stated they expected a response from OSI in one week.

Post Meeting Note: FDA issued an email communication response to Glaxo on July 25, 2017,

that addressed this outstanding issue. Glaxo confirmed receipt of this email communication on July 27, 2017.

Additional FDA Comments

Clinical Microbiology #3:

For all clinical studies, please provide details of the protocols used for the preparation of blood smears, processing, slide reading as well as quality control parameters and measures implemented. If a central laboratory was used for any of the studies, then name and address of the laboratory should also be included.

Meeting Discussion:

Glaxo sought clarification regarding the studies for which details of the protocols used for blood smear preparation should be provided. Glaxo stated they planned to provide this for the two Phase 3 studies TAF112582 part 2 and TAF116564 (excluding TAF116564part 1) in the Integrated Summary of Efficacy and not in the individual Clinical Study Reports for each study. FDA stated this was acceptable noting the methodology for part 1 and part 2 is likely to be the same. GSK stated in a broad sense it was, but quality control and quality assurance was handled separately, and that they would provide FDA with a summary of the differences. FDA agreed.

Clinical #5:

We recommend that you submit a mock safety dataset and efficacy dataset for review, prior to the NDA submission, so that we can provide feedback.

Meeting Discussion:

Glaxo asked if this request for mock datasets was the same as the CDISC sample dataset requested at the Type C meeting held earlier this year. GSK stated they were planning to submit a sample dataset. FDA confirmed that GSK's plan is acceptable.

Clinical Pharmacology #6:

We note that most of the Phase 1 and Phase 2 studies used a capsule formulation of tafenoquine (TQ). An adequate PK bridge needs to be established between the to-be-marketed tablet formulation and the capsule formulation(s). Please clarify if you have conducted a relative BA study or cross-study comparison(s) to evaluate the relative BA between the to-be-marketed 150 mg tablet formulation and the capsule formulation of TQ and provide a detailed descriptive summary of the formulations and the PK results from such relative BA studies upon NDA submission.

Meeting Discussion:

Glaxo stated they sought clarification on the request for adequate PK bridging between capsule and to be marketed tablet drug product. Glaxo stated they were planning for this in agreement with previous discussions (written response to Type C meeting request provided to GSK on January 23, 2012) but want to confirm this with FDA. GSK stated that based on this previous guidance, the relative bioavailability between the to-be-marketed 150mg tablet formulation used in Phase 3 studies and capsule formulation used in previous Phase 1 and Phase 2 studies would

be characterized through population pharmacokinetic (POP-PK) meta-analyses. The POP-PK analyses would utilize data from various studies with sparse and serial PK sampling employing the capsule and tablet formulations. The results will be included in the NDA. GSK provided a table in their July 17, 2017, email communication that provided a summary of studies that will be part of PK meta-analysis. GSK asked FDA if this was acceptable.

FDA accepted GSK's proposal to use a Population PK approach to show comparative BA between the capsule and the to-be-marketed tablet formulations. FDA requested that GSK provide detailed reports including post hoc estimates of AUC, Cmax, etc., with a formal statistical approach for BA comparison between capsule and to-be-marketed tablet formulations. FDA stated that GSK should also provide model control stream and datasets for the Population PK analyses. GSK agreed to add this information.

Additional Meeting Points:

- GSK informed FDA they were planning to submit the NDA by December 14, 2017.
- FDA confirmed that no agreements were made for a late submission; therefore, the NDA is expected to be complete for filing upon submission.

3.0 IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. FDA emphasized the NDA would be complete based on current NDA content and format regulations.
- 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.
- The need for a REMS was not discussed but it was conveyed that this would be determined during the application review.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting was held on May 15, 2017. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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. As of **May 5, 2017**, the following submission types: **NDA**, **ANDA**, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. 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>.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

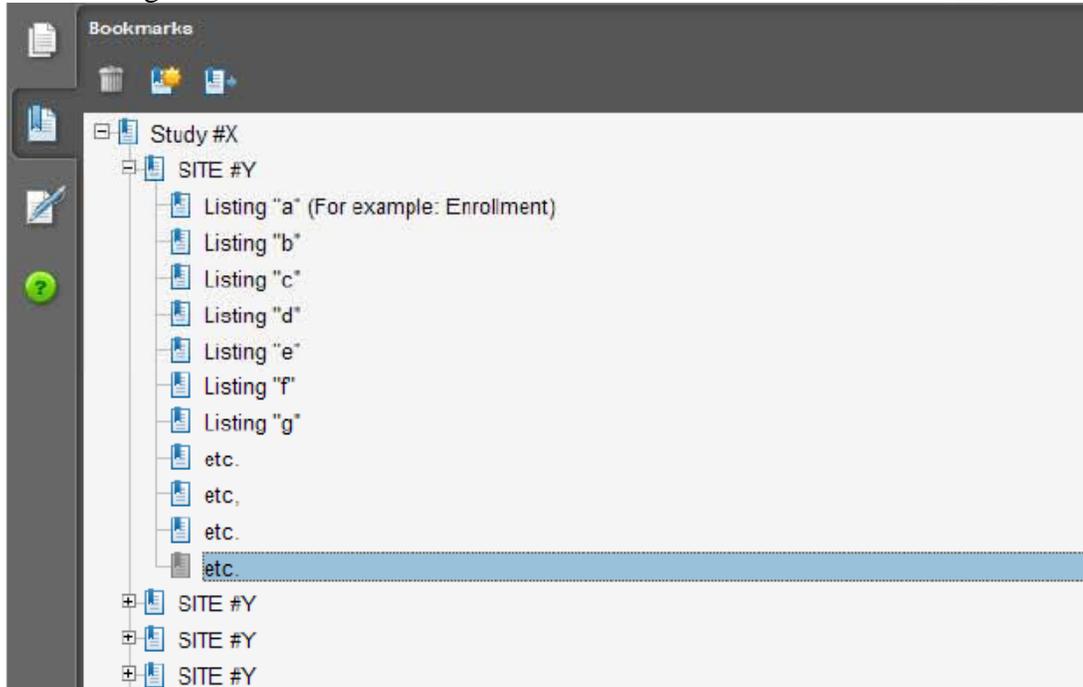
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:

- a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
- a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.

- i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None. See Post Meeting Note for Question 13.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue Meeting Minutes	FDA	August 17, 2017

6.0 ATTACHMENTS

- July 13, 2017, FDA Preliminary Meeting Responses
- July 17, 2017, Glaxo email communication with attachment

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/s/

SUMATHI NAMBIAR
08/16/2017



IND 101471

MEETING MINUTES

GlaxoSmithKline Intellectual Property Development Ltd. England
Attention: Sue. M. Holmes, M.S.
Director, Global CMC Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Holmes:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Tafenoquine (SB-252263).

We also refer to the telecon between representatives of your firm and the FDA on May 15, 2017. The purpose of the meeting was to discuss the proposed content for the CMC section of the planned NDA.

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

If you have any questions, call call LCDR Luz E Rivera, Quality Assessment Lead (Acting) at (301) 796-4013, or luz.e.rivera@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

Balajee Shanmugam, PhD
Branch Chief, Branch I (Acting)
Office of New Drug Products
Office of Pharmaceutical Quality
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: B
Meeting Category: PNDA CMC

Meeting Date and Time: Monday, May 15, 2017, 10:00- 11:00 PM (EST)
Meeting Location: Teleconference

Application Number: 101471
Product Name: Tafenoquine (SB-252263) tablet
Indication: Radical cure (prevention of relapse) of Plasmodium vivax Malaria

Sponsor/Applicant Name: GlaxoSmithKline Intellectual Property Development Ltd. England

Meeting Chair: Balajee Shanmugam
Meeting Recorder: LCDR Luz E Rivera

FDA ATTENDEES

1. Balajee Shanmugam, Ph.D., Branch Chief (Acting), Office of New Drug Product (ONDP), Office of Pharmaceutical Quality (OPQ)
2. Dorota Matecka, Ph.D., CMC Lead, ONDP, OPQ
3. Benjamin Stevens, Ph.D., Branch Chief (Acting), ONDP, OPQ
4. Rajan Pragani, Ph.D., Product Quality Reviewer, ONDP, OPQ
5. Steven Frisbee, Ph.D., Product Quality Reviewer, OPF, OPQ
6. Elsbeth Chikhale, Ph.D., Biopharmaceutics Team Lead, ONDP, OPQ
7. Terry Miller, MD, Team Lead, Division of Anti-infective Product (DAIP), Office of New Drugs (OND)
8. Owen McMaster, Ph.D., Pharmacotoxicologist Reviewer, DAIP, OND
9. Raymond Veronneau, Pharmacy Intern, ONDP, OPQ
10. Lori Yeterian, Pharmacy Intern, ONDP, OPQ
11. LCDR Luz E Rivera, Psy.D., Team Lead (Acting), Office of Program and Regulatory Operations (OPRO), OPQ

SPONSOR ATTENDEES

1. Stephen Hermitage, Director, API Chemistry
2. Andrew Kennedy, Scientific Leader, API Chemistry
3. Carl Heatherington, Senior Investigator, API Analytical Sciences and Development
4. Fiona King, Scientific Leader, Global Spectroscopy
5. Terry Ernest, Scientific Leader, Drug Product Design and Development
6. Neil Mortimer, Director, Product Analysis UK

7. Satty Sahota, Senior Investigator, Product Analysis UK
8. Sue Holmes, Director, Global CMC Regulatory Affairs- Agent
9. Audrey Scott, Director, Global CMC Regulatory Affairs
10. Richard Ward, Medicine and Process Delivery Leader
11. Jim Harvey, Director, Computational Toxicology
12. Hanu Ramachandrani, Senior Director, Technical Product Development (Medicines for Malaria Venture)

1.0 BACKGROUND

The purpose of meeting is to discuss acceptability of CMC items specific to Tafenoquine Tablets NDA.

2.0 DISCUSSION

Question 1: Does Drug Substance:

Question 1: Does the Agency agree with and/or have any comments on, the proposed control strategy and supporting data packages for mutagenic impurities (b) (4) in the drug substance?

FDA Response to Question 1: No, we do not agree with your control strategy for the following reasons:

1. For a treatment duration of less than 1 month (120 mcg/d intake limit) and a 300 mg/d dose, your control strategy should consider 400 mcg/g as the acceptable total daily intake (TDI) for the combined total mutagenic impurities. Your current strategy relies on consideration of individual mutagenic impurities, where the combined mutagenic impurity limit currently exceeds the acceptable (TDI) recommended by ICH M7. For more information, please refer to Section 7.4 “Acceptable Intakes for Multiple Mutagenic Impurities” in the ICH M7 guidance. We recommend you reassess your control strategy considering the acceptable TDI for combined total mutagenic impurities.
2. Based on the data presented in the meeting package, we do not consider (b) (4) impurity per ICH M7 and therefore do not agree with your control strategy for (b) (4). The structure of (b) (4) is highly analogous to (b) (4) which you have confirmed is Ames positive. Either provide data indicating that GSK (b) (4) is non-mutagenic or perform a formal spike/purge study to demonstrate this impurity will be appropriately controlled in the drug substance.

Discussion: The Agency explained that the origin of the proposal to control total mutagenic impurities in the drug substance (specified and unspecified) at the 120 mcg TDI is based on ICH

M7, Table 3. Following further discussion, the Sponsor agreed that the final drug substance control strategy would be designed to keep total mutagenic impurities at or below this threshold (120 mcg/day). The Agency agreed with the Sponsor that (b) (4) would not be considered under this TDI given that it represents a lower risk for mutagenicity based on ICH M7, (b) (4). The Sponsor indicated that non-clinical data is available to support the fact that (b) (4) is non-genotoxic; this data will be provided to the Agency to justify control of (b) (4) as a normal impurity.

Question 2: Does the Agency agree that the data provided in the briefing document fully supports GSK's proposal for a bicolour description acceptance criterion to be applied to tafenoquine succinate, and/or have any comments on this proposal?

FDA Response to Question 2: Yes, we agree.

Discussion: No further discussion required

II. Drug Product

Question 3: Does the Agency agree with, and/or have any comments regarding, the proposed dissolution acceptance criterion based on the in vivo human PK data results from the SIL study?

FDA Response to Question 3: Provided the PK of the intermediate aged drug product (test treatment of the SIL PK Study) is confirmed to be comparable to the PK of the relevant clinical trial batch(es), we agree that the *in vitro* dissolution profile of the intermediate aged drug product can be considered in the setting of the QC dissolution acceptance criterion for the routine QC of the proposed commercial tafenoquine tablets at batch release and during stability testing. Note that in general, we set the acceptance criterion based on a Q of (b) (4) % at the appropriate time point. Note also that FDA makes the final decision on the dissolution acceptance criterion(a) during the NDA review when all clinical and stability data are available for review. Therefore, until such time we recommend that you continue to collect complete *in vitro* dissolution profile data (e.g. 10, 15, 20, 30, 40 etc. minutes) at batch release and during stability testing.

Discussion: No further discussion required

III. General

Question 4: Does the Agency agree with the proposal for submission of batch records in the NDA?

FDA Response to Question 4: Yes, we agree.

Discussion: No further discussion required

Question 5: Can the Agency confirm that samples will be requested for this application (given them breakthrough therapy designation), and if so does the Agency agree that the proposed samples are considered suitable?

FDA Response to Question 5: This is acceptable.

Discussion: No further discussion required

ADDITIONAL COMMENTS:

1. We recommend including a separate counterion test for succinate in the drug substance specification.
2. Provide a justification for not testing the drug substance and drug product for morp hic form.
3. The following comments apply to the drug product:
 - a. Provide tests for (b) (4) microbiological quality by USP <61> and <62> in the drug product specification.
 - b. You are proposing (b) (4) in manufacturing. Please confirm that suitable particle size distribution specifications will be established for both the drug substance and for key excipients, or provide justification for not doing so.
 - c. Confirm that the long-term drug product stability conditions (b) (4)
 - d. Please refer to your proposal for the submission of the drug product stability data discussed at the October 3, 2014 meeting. Please provide your current proposal and details of the stability data package to be submitted in the NDA.

Discussion:

- 1) For point 3. A: Regarding (b) (4) test, please provide justification in the NDA for not including this test in the drug product specification.
- 2) For 3. C: Storage condition is 25°
- 3) For 3. D: The sponsor confirmed that 12-months long-term stability data from three registration stability batches will be included in the NDA at the time of submission. The Agency recommended submission of the stability protocol to the IND

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/s/

BALAJEE SHANMUGAM
06/14/2017



IND 101471

MEETING MINUTES

Glaxo Group Limited, England d/b/a GlaxoSmithKline
Attention: Sherry Watson
Director, CMC Pre-Approval, Global Regulatory Affairs
5 Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Watson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tafenoquine tablets, 150 mg.

We also refer to the meeting between representatives of your firm and the FDA on October 3, 2014. The purpose of the meeting was to discuss the CMC aspects of the development program for tafenoquine tablets, 150 mg.

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 questions, call me, at 240-402-3815.

Sincerely,

{See appended electronic signature page}

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of New Drug Quality Assessment
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: EOP2

Meeting Date and Time: October 3, 2014, 11:00 – 12:00 pm, EST
Meeting Location: Teleconference
Application Number: IND 101471
Product Name: Tafenoquine tablets, 150 mg
Indication: The treatment and relapse prevention (radical cure) of *Plasmodium vivax* malaria
Sponsor/Applicant Name: GlaxoSmithKline (GSK)

Meeting Chair: Dorota Matecka, Ph.D.
Meeting Recorder: Navdeep Bhandari, Pharm.D.

FDA ATTENDEES

Dorota Matecka, Ph.D.	CMC Lead
Rajiv Agarwal, Ph.D.	Chemistry Reviewer
John Alexander, M.D.	Medical Team Leader
Elizabeth O'Shaughnessy, M.D.	Medical Officer
Navdeep Bhandari, Pharm.D.	Regulatory Health Project Manager
Okpo Eradiri, Ph.D.	ONDQA- Biopharmaceutics Reviewer
Gregory DiBernardo	Regulatory Health Project Manager

SPONSOR ATTENDEES

Sherry Watson, Director	Global CMC Regulatory Affairs
Stephen Hermitage	Manager, Global API Chemistry
Martyn Voyle	Director, Global API Chemistry
Carl Heatherington	Senior Investigator, Analytical Development
Terry Ernest, Manager	Global Formulation Development
Satty Sahota, Senior Investigator	Analytical Development
William Martin	Head Primary NPI Centre of Excellence
Alan Parr, Director	Exploratory Development Sciences
Wiweka Kaszubska	Head of Product Development, Medicines for Malaria Venture

1.0 BACKGROUND

A Type B meeting briefing package was submitted July 3, 2014, for an October 3, 2014, CMC meeting for tafenoquine tablets 150 mg.

2.0 DISCUSSION

This meeting's focus was to discuss the CMC aspects of the development program for tafenoquine tablets, 150 mg.

The Agency sent preliminary responses on September 30, 2014 to the Sponsor. The Sponsor provided additional clarifications on October 2, 2014 (see attached) and asked to focus the meeting discussion on Questions 1 and 2 under drug substance and Questions 1, 2, and 4 under drug product.

Prior to beginning the discussion of the Questions, the Sponsor asked for clarification regarding breakthrough therapy submissions. Specifically, the Sponsor asked the Agency what the best way was to facilitate rapid scheduling of future meetings to expedite NDA submission, aligned with breakthrough therapy designation for tafenoquine succinate. The Agency advised the Sponsor to send submissions to the normal channels in addition to sending electronic copies to the appropriate Project Manager. The Agency further stated that since tafenoquine was granted breakthrough designation, the Agency goal would be to respond within the timelines of a Type B meeting. In addition, some of the meeting requests could be handled via a written response within similar timelines.

3.0 QUESTIONS

Drug Substance

1. GSK proposes the following materials as the registered starting materials for the manufacture of drug substance. Does the Agency have any comments on GSK's proposal?

[REDACTED] (b) (4)

Agency Response:

Based on the overall information provided in the background package, [REDACTED] (b) (4)
[REDACTED] We
recommend that as development continues, specifications for potential impurities for the

(b) (4)



Please note that the adequacy of the proposed specifications for each of the starting materials will be assessed during the NDA review based on the overall data submitted.

Sponsor Clarification Provided on October 2, 2014:

GSK acknowledges FDA's feedback concerning the proposed starting materials. GSK will update the IND to include acceptance criteria for (b) (4) in the specification for (b) (4) in the specification for (b) (4) which will be applied to future clinical manufacture. GSK is currently in Phase III studies with tafenoquine succinate and have addressed the risk associated with these compounds:

(b) (4)

Meeting Discussion: *The Agency acknowledged this additional information and requested that the Sponsor provide all supportive data and information in upcoming IND amendments and in the NDA under justification of specifications.*

2. At the previous End of Phase 2 meeting, the Agency requested that a change control protocol be developed to minimize the potentially adverse effects of changes in supplier or in the method of manufacture of (b) (4). GSK believes that the justification provided for (b) (4) in combination with GSK's change management process, will allow for changes in supplier or in the method of manufacture to be managed under GSK's pharmaceutical quality system. Does the Agency agree?

Agency Response:

The approach seems reasonable with the addition of the recommended monitoring of potential impurities during development as outlined in the response to Question 1, above. Tests for these potential impurities should be included in your change control protocol to provide additional assurance that any future changes do not adversely impact the quality of the drug substance.

Sponsor Clarification Provided on October 2, 2014:

GSK acknowledges that the Agency deems our approach to changes in supplier or in the method of manufacture being managed under our pharmaceutical quality system as reasonable but wishes to confirm our interpretation of the response. GSK will develop a protocol for change control to include consideration of, and testing for, the potential impurities discussed in Question 1. GSK will operate this protocol within our pharmaceutical quality system as described in Section 3.7 of the End of Phase II briefing package, and therefore we will not provide a protocol to describe this specific change control in the NDA. Notwithstanding, GSK acknowledges that any notifiable changes in supplier or method of manufacture following approval of the NDA will remain subject to regulatory update as required by post-approval regulations.

Meeting Discussion: *The Agency agreed that the protocol for change control will be managed internally and recommended that the Sponsor provide an overall summary of the change control strategy to the NDA. The Sponsor agreed with this recommendation.*

3. GSK consider that the proposed stability protocols are appropriate to support the NDA. Does the Agency have any comments on GSK's proposed approach?

Agency Response:

You have proposed to submit a minimum of 12 months data on three batches of the drug substance manufactured at the proposed commercial scale at the proposed commercial manufacturing site. The three primary stability batches will be tested at long term [REDACTED] (b) (4) conditions, while one batch will be tested at stress conditions. The above proposal is acceptable. Note that per ICH Q1A(R2) guidance, the primary stability batches should be manufactured by the same synthetic route as commercial batches and using a method of manufacture and procedure that simulates the final process to be used for commercial batches. The scope of the proposed stability testing as outlined in the background package also appears reasonable; however, the decision on the final acceptance criteria and any additional tests will be made during the NDA review upon the review of overall information submitted, e.g., control strategies, results of spiking and purging studies to assess the controls for genotoxic impurities, stability of the crystal form, etc.

Meeting Discussion: *This topic was not discussed at the meeting.*

Drug Product

1. GSK proposes to use a Stable Isotope Label (SIL) study to: (i) confirm equivalence between tablets manufactured at the proposed commercial site (Zebulon, US) and those manufactured by [REDACTED] (b) (4) used in Phase III clinical studies; and (ii) assess the impact of particle size distribution of tafenoquine on systemic drug exposure. Does the Agency agree that GSK's preliminary study design will adequately address these two objectives?

Agency Response:

The preliminary study design summarized in the briefing document seems reasonable. However, since your proposed dosage form is immediate-release, a bioequivalence study is not required provided that the manufacturing process and equipment are similar; please clarify why you believe a BE study is necessary. In order to bridge the product

batches manufactured at the two sites, perform Case B comparative dissolution testing on the drug product batches to demonstrate similarity (e.g. using f2 testing) in drug release profiles. In addition, investigate the dissolution characteristics of your dosage form as a function of particle size distribution.

Note that FDA has no experience with SIL studies in bioequivalence determination; we may therefore have additional questions regarding the use of the SIL approach in BE assessment, should you decide to conduct a BE study to support the bridging.

Sponsor Clarification Provided on October 2, 2014:

GSK would like to clarify our position on the two components of the SIL study.

Bioequivalence of Group A vs Group B (as defined in Section 6.3 of the End of Phase II Briefing Package):

GSK agree that it may be possible to perform comparative dissolution testing on the drug product batches to demonstrate similarity (e.g. using f2 testing) in drug release profiles between drug product used in Phase III studies and the commercial product.

GSK consider that the manufacturing process and equipment used to manufacture Phase III supplies and that proposed for commercialisation are similar.

The current dissolution method for Tafenoquine Tablets gives a very rapid release profile and is therefore unsuitable for f2 comparison. Due to challenges faced developing a suitable dissolution method the decision was taken to include product from both sites in the proposed SIL study to demonstrate equivalence in vivo. If GSK proceeds with the SIL study, we will request a meeting with FDA to discuss the protocol prior to initiation of the study.

Development of a dissolution method that may be suitable for f2 comparison is ongoing. GSK would like to discuss the proposed method and its suitability for in vitro comparison of tablets manufactured at the two sites, at a future meeting with the FDA. This is an example of where we would like to engage with FDA as part of the breakthrough therapy designation status.

Comparison of Group C vs B and Group D vs B (as defined in Section 6.3 of the End of Phase 2 Briefing Package):

We consider it appropriate to use the proposed SIL study to collect relative bioavailability information to determine the impact of particle size on PK performance and support a relevant particle size specification. This information may also support our understanding of the dissolution method and the setting of an appropriate dissolution specification.

Meeting Discussion: *The Agency agreed with the clarification provided by GSK. The FDA also agreed to review and provide feedback on the proposed dissolution method and its suitability for the drug product during the IND stage. GSK will submit the proposed dissolution package as an amendment to the IND in 2015, with a planned NDA submission in September 2016.*

2. In the event that minor formulation changes are required to the Phase III formulation prior to commercialization, GSK proposes to use the SIL study to confirm equivalence between Phase III tablets and proposed commercial tablets. Does the Agency have any comments on GSK's proposed approach?

Agency Response:

As stated in our response to Question 1 above, minor manufacturing changes, including minor changes in formulation do not require the conduct of BE studies. Perform Case B comparative dissolution testing between Phase 3 tablets and proposed commercial tablets to confirm similarity. Should you decide to continue with the SIL study, the FDA considers your approach acceptable.

Sponsor Clarification Provided on October 2, 2014:

In line with our response to Drug Product Question 1 (comparison of Group A vs B), if a dissolution method which can allow f2 comparison can be developed, GSK would propose to use this to confirm equivalence, rather than incorporate assessment of the formulation change in the SIL study.

Meeting Discussion: *The Agency agreed with GSK's clarification statement. See Question 1 discussion for additional details.*

3. GSK consider that the proposed stability protocols are appropriate to support the NDA. Does the Agency have any comments on GSK's proposed approach?

Agency Response:

We note that the drug product will be packaged in HDPE bottles (for the US market) and in blisters (for the non-US market). It is also noted that three primary stability batches packaged in the bottle pack will be tested

(b) (4)

One batch of each packaging configuration will be also tested at stress conditions. We recommend the registration stability batches are manufactured using the commercial formulation and the proposed

commercial process. Otherwise, the stability protocol appears appropriate to support the NDA submission.

The scope of the proposed stability testing during this stage of development and at the NDA stage appears reasonable; however, the decision on the final acceptance criteria and any additional tests will be made during the NDA review. We recommend that you provide information on polymorphic stability over shelf life. In the stability program, dissolution data on the registration batches should be provided at all profiling sampling time points; dissolution data at only the proposed specification time points are insufficient.

Please be aware that if a decision is made to package drug product in blisters for commercial distribution, the blister packs would need to comply with the child-resistant packaging requirements per 16 CFR 1700.14(a)(10). Refer to the US Consumer Product Safety Commission website (<http://www.cpsc.gov/en/Regulations-Laws--Standards/Statutes/Poison-Prevention-Packaging-Act/>) for more information.

Meeting Discussion: *This topic was not discussed at the meeting.*

4. GSK would like to explore the opportunity to submit six months stability data (three production scale batches from the commercial manufacturing site) and supplement with additional stability data during review of the NDA. Would such an approach for this particular product be acceptable?

Agency Response:

For a breakthrough therapy designated product, it is acceptable to submit six months stability data (for three production scale batches from the commercial manufacturing site) in the initial NDA submission, and supplement with additional stability data during review of the NDA. We recommend that you use the commercial formulation, the proposed commercial process and the commercial packaging.

Sponsor Clarification Provided on October 2, 2014:

GSK acknowledges FDA's response but would like to confirm that the shelf-life to be assigned can be based on the additional data submitted during review.

Meeting Discussion: *The Agency confirmed that the shelf life would be assigned based on the review of the totality of stability data.*

The following comments were provided by the Sponsor via email on October 2, 2014.

GSK would like to thank FDA for their helpful preliminary feedback. Further information is provided below to facilitate appropriate further discussion. However GSK does envisage needing to request further advice during development (for example as indicated in response to Drug Product Question 1). As requested in the End of Phase II briefing package, GSK would like to discuss with FDA the best way to facilitate rapid scheduling of future meetings to expedite NDA submission, aligned with breakthrough therapy designation for tafenoquine succinate.

Drug Substance

Question 1:

GSK acknowledges FDA's feedback concerning the proposed starting materials. GSK will update the IND to include acceptance criteria for (b) (4) in the specification for (b) (4) the specification for (b) (4) which will be applied to future clinical manufacture. GSK is currently in Phase III studies with tafenoquine succinate and have addressed the risk associated with these compounds:

(b) (4)

Question 2:

GSK acknowledges that the Agency deems our approach to changes in supplier or in the method of manufacture being managed under our pharmaceutical quality system as reasonable but wishes to confirm our interpretation of the response. GSK will develop a protocol for change control to include consideration of, and testing for, the potential impurities discussed in Question 1. GSK will operate this protocol within our pharmaceutical quality system as described in Section 3.7 of the End of Phase II briefing package, and therefore we will not provide a protocol to describe this specific change control in the NDA. Notwithstanding, GSK acknowledges that any notifiable changes in supplier or method of manufacture following approval of the NDA will remain subject to regulatory update as required by post-approval regulations.

Question 3:

GSK agrees and no discussion is required.

Drug Product

Question 1:

GSK would like to clarify our position on the two components of the SIL study.

Bioequivalence of Group A vs Group B (as defined in Section 6.3 of the End of Phase II Briefing Package):

The following comments were provided by the Sponsor via email on October 2, 2014.

GSK agree that it may be possible to perform comparative dissolution testing on the drug product batches to demonstrate similarity (e.g. using f2 testing) in drug release profiles between drug product used in Phase III studies and the commercial product.

GSK consider that the manufacturing process and equipment used to manufacture Phase III supplies and that proposed for commercialisation are similar.

The current dissolution method for Tafenoquine Tablets gives a very rapid release profile and is therefore unsuitable for f2 comparison. Due to challenges faced developing a suitable dissolution method the decision was taken to include product from both sites in the proposed SIL study to demonstrate equivalence in vivo. If GSK proceeds with the SIL study, we will request a meeting with FDA to discuss the protocol prior to initiation of the study.

Development of a dissolution method that may be suitable for f2 comparison is ongoing. GSK would like to discuss the proposed method and its suitability for in vitro comparison of tablets manufactured at the two sites, at a future meeting with the FDA. This is an example of where we would like to engage with FDA as part of the breakthrough therapy designation status.

Comparison of Group C vs B and Group D vs B (as defined in Section 6.3 of the End of Phase 2 Briefing Package):

We consider it appropriate to use the proposed SIL study to collect relative bioavailability information to determine the impact of particle size on PK performance and support a relevant particle size specification. This information may also support our understanding of the dissolution method and the setting of an appropriate dissolution specification.

Question 2:

In line with our response to Drug Product Question 1 (comparison of Group A vs B), if a dissolution method which can allow f2 comparison can be developed, GSK would propose to use this to confirm equivalence, rather than incorporate assessment of the formulation change in the SIL study.

Question 3:

GSK agrees and no discussion is required.

Question 4:

GSK acknowledges FDA's response but would like to confirm that the shelf-life to be assigned can be based on the additional data submitted during review.

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/s/

DOROTA M MATECKA
11/03/2014

CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Anti-Infective Products
December 9, 2013

Summary Box

1. IND Number: 101,471
2. Company name: Glaxo Group Limited, England - GlaxoSmithKline
3. Drug name: Tafenoquine (SB-252263)
4. Indication: The treatment and relapse prevention (radical cure) of *Plasmodium vivax* malaria.
5. Tafenoquine is an antimalarial drug, intended to be used with chloroquine to treat and prevent relapse of *Plasmodium vivax* malaria which is a serious and occasionally life-threatening infection.
6. The objectives of the clinical development program are to determine the safety and efficacy of Tafenoquine as a combination treatment with a blood schizonticidal drug to achieve radical cure of *P. vivax* malaria. Tafenoquine is administered as single oral dose tablet. Preliminary clinical evidence indicates that tafenoquine 300mg, as a single-dose treatment co-administered with chloroquine, prevents *P. vivax* infection relapse. The clinical evidence suggests that tafenoquine may demonstrate a significant benefit over primaquine, the existing therapy for radical cure (anti-relapse efficacy) of *P. vivax* malaria, by offering improved compliance leading to improvement in serious outcomes and representing a significant help in the ability of healthcare providers to give directly observed treatment to patients. The current standard of care, primaquine, requires 7-14 days of administration to achieve high rates of radical cure.

1. Brief description of the drug

Tafenoquine is an 8-aminoquinoline drug. Tafenoquine possesses activity against all stages of the *Plasmodium vivax* lifecycle, including the dormant liver stage, hypnozoite. Tafenoquine is a synthetic analogue of primaquine, also an 8-aminoquinoline drug. Primaquine is the only approved drug which has activity against the liver stage, hypnozoite. The mechanisms of action of tafenoquine and of the currently approved drugs for treatment of *P. vivax* malaria (chloroquine followed by primaquine) are not established. Tafenoquine has slow clearance of blood stage therefore co-administration with another faster acting blood schizonticide (initially chloroquine) will be required for treatment of *P. vivax* malaria as this combination targets both blood and liver stages of infection.

All members of the 8-aminoquinoline drugs and aminoquinolines in general, induce hemolysis in subjects with G-6-PD deficiency. Other safety concerns include QT prolongation and effects on the eye, corneal deposits, retinal toxicity and visual field abnormalities. Ocular side-effects usually occur with long term use over several months for example, in patients with rheumatologic diseases taking hydroxychloroquine.

Tafenoquine was granted an orphan-drug designation for the treatment of malaria by the FDA on January 15, 2013.

2. Brief description of the disease and intended population

There are five known species of *Plasmodium spp.* that cause disease in humans, *P. falciparum*, *P. vivax*, *P. knowlesi*, *P. ovale*, and *P. malariae*. *P. falciparum* causes the most severe and life-threatening disease. Of the non-falciparum species, *P. vivax* has the greatest geographic range and burden of disease, and worldwide estimates of *P. vivax* infections range between 130 and 390 million (~50% cases of malaria). *P. vivax* is seen in the US in returning travelers, for example, in 2011, the CDC reported that *P. falciparum* and *P. vivax* comprised the majority of infections and were identified, respectively, in 64% and 28% of 1,490 infected persons with a reported species.¹ The World Health Organization (WHO) has recently announced the development of a global strategy for vivax malaria to control and eliminate this relapsing form of malaria. Among the WHO specific objectives is the review of the drugs and treatment regimens for radical cure of *P. vivax*.

P. vivax has a complex lifecycle which includes a dormant liver stage; the hypnozoite. The activation of hypnozoites in the liver leads to the re-appearance of clinical symptoms of malaria (relapse) normally for up to several months after the initial infection. Relapse of malaria may occur in the setting of infection due to *P. vivax* or *P. ovale* infection, since the life-cycle of these two species includes hypnozoites, a quiescent stage in the liver. Patients get relapsing malaria which drives further episodes of illness and hampers elimination efforts. Chloroquine or mefloquine (used for chloroquine-resistant strains) are commonly used for treatment of the blood (erythrocytic) forms for non-falciparum malaria species such as *P. vivax*. None of these drugs have activity against hypnozoites in the liver.

Vivax malaria is a serious infection. Common symptoms and signs of malaria may include fever, chills, malaise, fatigue, shortness of breath, diaphoresis, headache, cough, nausea, vomiting, abdominal pain, diarrhea, arthralgias, and myalgias. Physical findings may include tachycardia, jaundice, splenomegaly and/or hepatomegaly. Recent evidence suggests that the severity of disease that can be caused by *P. vivax* has been underestimated.² The mortality rate for *P. vivax* infection is generally low, although one report of 36 cases from Indonesian New Guinea (Papua) noted a death rate of 25 percent.³ Splenic rupture is a rare complication of acute *P. vivax* malaria and approximately 150 cases have been described.^{4,5} Other severe and less common manifestations of *P. vivax* malaria include, acute respiratory

¹ <http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6205a1.htm>

² Kochar DK, Saxena V, Singh N, Kochar SK, Kumar SV, Das A. Plasmodium vivax malaria. Emerg Infect Dis. 2005;11(1):132

³ Barcus MJ, Basri H, Picarima H, Manyakori C, Sekartuti , Elyazar I, Bangs MJ, Maguire JD, Baird JK. Demographic risk factors for severe and fatal vivax and falciparum malaria among hospital admissions in northeastern Indonesian Papua. Am J Trop Med Hyg. 2007;77(5):984

⁴ Gockel HR, Heidemann J, Lorenz D, Gockel I. Spontaneous splenic rupture, in tertian malaria. Infection. 2006;34(1):43.

distress syndrome, profound anemia, disseminated intravascular coagulation, renal failure, shock and cerebral malaria.^{6,7,8} Vivax malaria was associated with increased morbidity and mortality in early infancy⁹ in Indonesian New Guinea (Papua) and carried an elevated risk of miscarriage in the first trimester in women with acute vivax malaria in Thailand.⁸

3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

The following endpoints are considered by the sponsor as supporting the breakthrough therapy designation. The relapse-free efficacy at six months post-dosing was the primary endpoint the sponsor used in the completed phase 2 trial and it is proposed for use in future phase 3 trials. Subjects for whom initial clearance of parasitemia is confirmed (parasite numbers fall below the limit of detection in a blood smear and remain undetectable at the second blood smear collected 6-12 hours later) and who do not present with *P. vivax* asexual stage parasites within six months will be considered treatment successes.

The following secondary efficacy endpoints will be included in the proposed phase 3 protocols.

- 1) Relapse-free efficacy four months post-dosing
- 2) Time to relapse of malaria
- 3) Parasite Clearance Time — Time in hours from the initiation of therapy until the first of two successive parasite-negative smears are obtained.
- 4) Fever Clearance Time — Time in hours from the initiation of therapy until disappearance of fever for at least 24 hours.

⁵Jiménez BC, Navarro M, Huerga H, López-Vélez R. Spontaneous splenic rupture due to Plasmodium vivax in a traveler: case report and review. J Travel Med. 2007;14(3):188.

⁶Tjitra E, Anstey NM, Sugiarto P, Warikar N, Kenangalem E, Karyana M, Lampah DA, Price RN. Multidrug-resistant Plasmodium vivax associated with severe and fatal malaria: a prospective study in Papua, Indonesia. PLoS Med. 2008;5(6):e128.

⁷Lomar AV, Vidal JE, Lomar FP, Barbas CV, de Matos GJ, Boulos M. Acute respiratory distress syndrome due to vivax malaria: case report and literature review. Braz J Infect Dis. 2005;9(5):425.

⁸McGready R, Lee SJ, Wiladphaingern J, Ashley EA, Rijken MJ, Boel M, Simpson JA, Paw MK, Pimanpanarak M, Mu O, Singhasivanon P, White NJ, Nosten FH. Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: a population-based study. Lancet Infect Dis. 2012;12(5):388.

⁹Poespoprodjo JR, Fobia W, Kenangalem E, Lampah DA, Hasanuddin A, Warikar N, Sugiarto P, Tjitra E, Anstey NM, Price RN. Vivax malaria: a major cause of morbidity in early infancy. RN Clin Infect Dis. 2009;48(12):1704.

The primary and secondary efficacy endpoints described above are accepted by the Division and are described in the FDA *Guidance for Industry Malaria: Developing Drug and Non-vaccine Biological Products for Treatment and Prophylaxis*.¹⁰

The safety endpoints proposed by the sponsor cover the safety concerns of interest with 8-aminoquinoline drugs. Key safety endpoints used by the sponsor include in phase 2 trial and proposed for use in future phase 3 trials include:

- 1) Clinically relevant hemolysis leading to drops in hemoglobin / hematocrit or complications thereof (required transfusions, acute renal failure)
- 2) Changes in methemoglobin
- 3) Ophthalmic safety - incidence of corneal deposits, retinal and visual field abnormalities. Data will be collected at investigator sites appropriately qualified to perform ophthalmological assessments.
- 4) GI tolerability - incidence of abdominal pain, heartburn, diarrhea, constipation, nausea and vomiting
- 5) The incidence and severity of adverse events and abnormal laboratory observations will be presented.

The safety endpoints proposed by the sponsor for phase 3 trials are acceptable to the division.

4. Brief description of available therapy

Relapse of *P. vivax* malaria may be prevented by administering presumptive anti-relapse therapy; primaquine, an oral drug, approved by the FDA in 1952, is the only drug approved for anti-relapse treatment. Primaquine is in clinical use for approximately 60 years and its mechanism of action is not known. Primaquine is used to prevent relapse of *P. vivax* and *P. ovale* malaria by eliminating dormant hypnozoites and it also has activity against the pre-erythrocytic stage and gametocytes of *P. falciparum*. Primaquine is administered as a once a day oral dose for 7 to 14 days. Primaquine also causes hemolysis in patients who are G-6-PD deficient. There are no available treatments that may be used off-label for this indication of radical cure of vivax malaria.

There is a need to provide alternative treatments to manage relapse of vivax malaria other than primaquine which is the only treatment currently widely available..

5. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation

There are no other drugs being studied for the same indication that received breakthrough therapy designation.

6. Description of preliminary clinical evidence

To date, tafenoquine has been studied in > 4000 subjects which included > 574 healthy volunteers. The majority of this exposure was from a malaria chemoprophylaxis program, including single oral dose and repeat oral dose programs (dose range 4 mg - 600 mg up to 6 months) and malaria

¹⁰ <http://www.fda.gov/downloads/Drugs/Guidances/ucm071951.pdf>

challenge studies (in *P. falciparum* malaria). The available clinical data include efficacy data from a recently completed Phase 2b clinical study (TAF112582) for the treatment of vivax malaria in adults and supporting efficacy evidence from two additional clinical studies. Study TAF112582 was multi-center, double-blind, double-dummy, parallel group, randomized, active control, dose -ranging study in adults with vivax malaria comparing chloroquine plus tafenoquine (dose range 50 to 600mg) to the chloroquine control arm and the current standard of care for radical cure, primaquine. The study recruited 329 subjects and 97% of subjects completed the six month follow-up period. Analysis of the primary efficacy endpoint (relapse free efficacy by malarial slide read) showed evidence of efficacy for the tafenoquine 300mg and 600mg doses. The primary endpoint i.e., relapse free efficacy rates at six months post-dose, was statistically significant at 89% and 92% for the TQ 300 mg and 600 mg treatment groups, respectively. Relapse free efficacy rates at six months post-dose were 77% in the primaquine arm and 38% in the chloroquine arm. Results from this trial demonstrated that tafenoquine as a single-dose treatment coadministered with chloroquine prevented *P. vivax* relapse. The 300mg dose of tafenoquine was chosen for further study in phase 3 trials based on these results.

Supporting evidence of efficacy comes from two additional studies, Study SB-252263/047 a proof-of-concept, randomized, open-label, dose-ranging study to investigate the safety and efficacy of tafenoquine in the prevention of relapse of *P. vivax* malaria and Study SB-252263/058 a randomized, active control, double blind, phase 2 study to evaluate the treatment of acute *P. vivax* and the prevention of *P. vivax* relapse in Thailand. In Study SB-252263/047, a total of 124 subjects were enrolled into 9 treatment arms (7 dose regimens of tafenoquine ranging from total doses of 500mg to 3000mg, primaquine, and chloroquine alone). There were a total of three relapses across the tafenoquine arms of 69 patients dosed (4%), 12/17 (71%) in the chloroquine arm and 3/12 (25%) in the primaquine arm. In Study SB-252263/058, subjects received either a tafenoquine dose of 400 mg daily for 3 days (N=46) or the standard regimen of chloroquine + primaquine (15mg x 14 days) (N=24). The tafenoquine monotherapy regimen exhibited slow parasite and fever clearance times relative to the chloroquine + primaquine control. Tafenoquine did not meet the pre-defined efficacy threshold for the treatment of acute vivax malaria in this study, however, tafenoquine achieved 100% relapse-free efficacy for up to 120 days. The chloroquine + primaquine regimen achieved 95% efficacy. This sponsor concluded that subsequently tafenoquine needed to be coadministered with a faster acting blood schizonticide such as chloroquine, which is the basis for the sponsor's current clinical development program.

Overall, tafenoquine has been shown to be effective in the treatment of plasmodial infections *in vitro*, and also in preclinical models *in vivo* and during early phase clinical studies. To date, tafenoquine has shown to be reasonably well-tolerated in clinical studies in more than 4000 subjects under a variety of development programs including malaria chemoprophylaxis, post-exposure prophylaxis in addition to *P. vivax* treatment and relapse prevention studies.

With regard to safety results in the completed clinical studies, the range of hemoglobin decline seen in female heterozygous G6PD deficient subjects dosed with tafenoquine 300 mg was considered a clinically acceptable level of risk in the absence of any clinical signs and few symptoms, and the potential benefit of preventing subsequent malaria relapse. The is limited data available for female heterozygous G6PD subjects with a > 70% enzyme activity level that suggests that with higher G-6-PD enzyme levels, the risk

of hemolysis may be lower. The safety of tafenoquine in G6PD heterozygous deficient females with vivax malaria and 40- 70% G6PD enzyme activity will be investigated in a phase 3 trial, Study TAF116564, the objective being to collect data on safety in this population. A TQT study for tafenoquine was reviewed by FDA, tafenoquine has a dose-dependent effect on QT interval prolongation the proposed clinical dose 300mg did not have a significant effect on QT interval prolongation. Preliminary ophthalmic safety data from the studies in healthy volunteers suggest that one dose of tafenoquine is reasonably safe.

7. Division's recommendation and rationale

- Recommendation: The Division recommends that breakthrough designation be granted for tafenoquine for radical cure of patients with *P. vivax* malaria.
- Rationale: Tafenoquine has been shown to be effective in the treatment of plasmodial infections *in vitro*, and also in preclinical models *in vivo* and during early phase clinical studies. To date, tafenoquine has shown to be well-tolerated in clinical studies in over 4000 subjects under a variety of development programs including malaria chemoprophylaxis, post-exposure prophylaxis in addition to *P. vivax* treatment and relapse prevention studies. Preliminary evidence in patients with *P. vivax* malaria indicates that the tafenoquine could provide a substantial benefit over the current standard of care, primaquine. Tafenoquine has the potential to provide alternative treatment with shorter dosing regimen, which can be administered as a single dose thereby resulting in improved compliance and expected to lead to an improvement in serious outcomes associated with *P. vivax* infection.

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

- The Division met with the sponsor on 11/17/2013 for an end-of-phase 2 meeting to discuss phase 2 study results and the sponsor's proposed phase 3 clinical development program. The Division of Ophthalmology and Transplant Products (DTOP) were consulted regarding ocular safety for tafenoquine and they will review the ocular safety data from the completed clinical studies and will make recommendations, if any, on additional monitoring for phase 3 trials based on their review. Complete protocols for two new multicenter, multinational, phase 3 trials which will be reviewed by the Division and comments will provided to the sponsor. The proposed phase 3 program consists of two studies: TAF112582, the pivotal efficacy study. The primary objective of TAF112582 will be to determine the efficacy of tafenoquine as a radical cure for vivax malaria, relative to a chloroquine control. The second trial, TAF116564 will be evaluate the safety of tafenoquine in G-6-PD heterozygous deficient females with vivax malaria and 40- 70% G-6-PD enzyme activity.

9. References

See references in footnotes.

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/s/

SANDRA J BENTON
12/09/2013

SUMATHI NAMBIAR
12/09/2013



IND 101471

MEETING MINUTES

Glaxo Group Limited, England d/b/a GlaxoSmithKline
Attention: Munir Abdullah, Ph.D.
Director, Regulatory Affairs
5 Moore Drive
Research Triangle Park, NC 27709-3398

Dear Dr. Abdullah:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Tafenoquine (SB-252263) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on November 13, 2013. The purpose of the End-of-Phase 2 meeting was to discuss the data generated for tafenoquine to date and the plans for Phase 3 in support of a New Drug Application.

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: End-of-Phase 2

Meeting Date and Time: November 13, 2013 at 10:00 A.M. to 11:00 A.M.

Meeting Location: White Oak Campus, Building 22, Room 1311

Application Number: IND 101471

Product Name: Tafenoquine (SB-252263) Tablets

Indication: Treatment and relapse prevention (radical cure) of *Plasmodium vivax* malaria

Sponsor Name: Glaxo Group Limited, England d/b/a GlaxoSmithKline

Meeting Chair: Sumathi Nambiar, M.D., M.P.H.

Meeting Recorder: Gregory F. DiBernardo

FDA ATTENDEES (FDA)

Office of Antimicrobial Products

John J. Farley, M.D., M.P.H. Deputy Director

Division of Anti-Infective Products

Sumathi Nambiar, M.D., M.P.H. Director

Katherine A. Laessig, M.D. Deputy Director

John J. Alexander, M.D., M.P.H. Clinical Team Leader

Elizabeth O'Shaughnessy, M.D. Medical Officer

Shukal Bala, Ph.D. Microbiology Reviewer

Wendelyn J. Schmidt, Ph.D. Pharmacology/Toxicology Team Leader

Owen G. McMaster, Ph.D. Pharmacology/Toxicology Reviewer

Maureen P. Dillon-Parker Chief, Project Management Staff

Gregory F. DiBernardo Regulatory Project Manager

Division of Clinical Pharmacology IV

Philip M. Colangelo, Pharm.D., Ph.D. Clinical Pharmacology Team Leader
Zhixia (Grace) Yan, Ph.D. Clinical Pharmacology Reviewer

Division of Biometrics IV

Karen M. Higgins, Sc.D. Biostatistics Team Leader
Lan Zeng, M.S. Biostatistics Reviewer

Division of Transplant and Ophthalmology Products

William M. Boyd, M.D. Medical Officer

SPONSOR ATTENDEES

Glaxo Group Limited, England d/b/a GlaxoSmithKline

Joerg-Peter Kleim, Ph.D. Director, Clin. & Medicines Development Leader
Justin Green, M.D., Ph.D. Director, Clin. Development, Project Physician
Alison Webster, M.D. Vice President, Therapeutic Area Clinical Leader
Lynda Kellam, M.Sc.Dir. Statistics, Programming, Clin. Team Lead
Richard Ansbro Medicines & Process Delivery Leader
Ann Miller, Ph.D. Manager, Clinical Pharmacology
Randal Batenhorst, Pharm.D. Vice President, Global Regulatory Affairs
Munir Abdullah, Ph.D. Director, Regulatory Affairs

Medicines for Malaria Venture (MMV)

Wiweka Kaszubska, Ph.D. Project Sponsor
Timothy Wells, Ph.D. Chief Scientific Officer

(b) (4)

1.0 BACKGROUND

On July 30, 2013, Glaxo Group Limited, England d/b/a GlaxoSmithKline (GSK) requested a type B, End-of-Phase 2 (EOP2) meeting with the Division of Anti-Infective Products (DAIP).. FDA granted a November 13, 2013, meeting. GSK submitted their meeting package to the IND on October 10, 2013. FDA sent GSK Preliminary Meeting Comments on November 8, 2013, in response to GSK's questions outlined in the meeting package.

The minutes below include GSK's questions in **bold** font, FDA's Preliminary Meeting Responses in normal font, and meeting discussion and additional recommendations in *italics*.

GSK informed FDA via email communication on November 13, 2013, that they would like to focus the meeting discussion to Questions #8, #9, #10, #14, and #18. GSK indicated that they were satisfied with the FDA responses to the other questions.

After introductions, GSK mentioned that since the submission of the meeting package, a breakthrough therapy request had been made for the IND. They then requested that the questions be discussed in the following order #14, #8, #18, #9 and #10.

2.0 DISCUSSION

Question #14:

Does the Division agree that data from 100 subjects on TQ collected in phase 3 is adequate to assess level of ophthalmic risk? That the retinal assessments which were performed in Phase 2b are appropriate to assess retinal safety in phase 3, taking into consideration the environment that the phase 3 studies will be conducted in?

FDA Response:

No. We do not agree that 100 subjects on TQ collected in Phase 3 trials would be adequate to assess the level of ophthalmic risk. One hundred (100) subjects could only be expected to detect adverse events which occurred at a 3% adverse event rate or greater; we believe that the seriousness of potential retinal adverse events warrants additional evaluation. We would recommend that you assess at least 300 subjects to adequately assess the level of ophthalmic risk.

You appear to have some ophthalmic data from previously conducted trials for this IND and in other INDs; this meeting package identifies some of these trials, but appears to utilize multiple identifiers. We request that you identify your completed trials (and other trials for which you would have right to reference for a NDA), and provide the application number, submission dates, and exact locations of the relevant clinical study reports.

Regarding the proposed Phase 3 ophthalmic study parameters: based on the current literature regarding the screening for chloroquine and hydroxychloroquine retinopathy, the Phase 3 trials should evaluate spectral domain ocular coherence tomography and fundus auto fluorescence at month 3 in addition to best corrected distance visual acuity and slit lamp evaluation of the cornea. Retinal photography and Ishihara chart assessment are unlikely to provide additional useful information and are not recommended. Automated central 10 degree perimetry, while it may prove to be a useful tool, is unlikely to be interpretable in the context of your current trials. If the “environment” of the proposed Phase 3 trials prohibits the proper evaluation of the potential ophthalmic adverse events, these ophthalmic evaluations could be performed in normal subjects exposed to the study drug as intended to be prescribed.

Meeting Discussion:

- *GSK requested clarification on why FDA requested 300 subjects. FDA referred to the second paragraph of their response, emphasizing that they had difficulty identifying how many completed studies contained ocular safety information and interpreting how the ocular data was collected. Without adequate information from the prior studies, it was difficult to provide further comments.*

- *FDA expressed concern that 100 patients will not provide adequate data to identify adverse events (AEs) that occur at a low rate.*
- *FDA commented that some of the ophthalmic tests described are no longer routinely recommended for screening as the yield is low. FDA noted that other tests would provide better results. FDA offered to assist with study design, noting that study sites in some countries may not have access to the necessary equipment. FDA also stated that using a different population such as healthy subjects could be considered since the data is being collected for safety.*
- *GSK stated they would provide a summary of all the information collected to date with regard to ocular safety. GSK stated that they will compile and submit the information to their IND. FDA stated that they will review the information and then provide further advice to GSK.*

Question #8:

GSK propose to exclude India from part 2 of Study TAF112582 and from TAF116564 due to the findings of very little relapse in the control arm for the Indian sites in part 1 of TAF112582. Does the Division agree with this approach?

FDA Response:

The low relapse rate in subjects receiving CQ alone for *P. vivax* malaria in Northwestern India is noted. We agree to the exclusion of Northwestern India sites from Phase 3 trials; however, have you considered conducting the trials in other regions of India? Please also indicate which four countries in Asia are included in the Phase 3 trials.

Meeting Discussion:

- *GSK requested clarification on FDA's comment regarding conducting trials in other regions of India. GSK stated that their Phase 2b data from India did not provide good data on chloroquine relapse rates. *P. vivax* malaria is heterogeneous within the Indian subcontinent likely due to long, mosquito-free, dry seasons in some regions. Published literature identifies relapse rates of 0-40%. Epidemiologic data from India are very limited and therefore, selecting a site without the aid of high quality epidemiologic data is difficult. While GSK is proposing to remove India as a site from the Phase 3 program, they see no biological reason why the drug could not be used at the same dose and duration, as there are no expected differences in *P. vivax* infection in India compared to others areas. FDA explained that based on CDC data from 2011, the majority of *P. vivax* cases in the United States are imported cases from India and hence it is preferred that some cases from India be included in their trial. GSK stated that their decision not to include India in the current proposed trials should not be interpreted as a sign that they will not try to obtain information to support the licensure of tafenoquine in India.*
- *FDA inquired if there was any follow-up beyond six months on the 57 patients in the Phase 2 trial from Northwestern India. GSK stated that follow-up data beyond six months was not available.*

- *GSK stated that they plan to target the following regions for the Phase 3 studies: Philippines, Cambodia, and Thailand, with Vietnam potentially being supportive as the transmission rates there are low.*
- *FDA inquired if GSK had considered potential study sites in Bangladesh, Pakistan, or Sri Lanka. GSK stated that they explored potential study sites in these countries. In Bangladesh, there were logistical difficulties and in Pakistan there were issues similar to those observed in India, and there is little malaria in Sri Lanka. Therefore, GSK does not consider these areas as viable study sites.*

Question #18:

It is proposed to submit CDISC compliant datasets only for Studies TAF112582 (DETECTIVE Parts 1 and 2), TAF116564 and TAF110027. These three studies will be the only studies for which data are integrated for the purposes of an ISS or an ISE. All other studies were performed prior to phase 2b and will remain in SDTM/IDSL format. Is this acceptable?

FDA Comment:

Your proposal to include integrated analyses of Studies TAF112582 (DETECTIVE Parts 1 and 2), TAF116564 and TAF110027 in the ISE and ISS is acceptable. The ISS should also include significant safety findings (which can be in a separate section) from the clinical studies completed prior to Phase 2 b.

Meeting Discussion:

GSK stated that they wanted to confirm that conversion of Studies TAF112582 (DETECTIVE Parts 1 and 2), TAF116564 and TAF110027 to CDISC compliant datasets was acceptable and all other studies that were performed prior to Phase 2b will remain in SDTM/IDSL format. FDA agreed that this proposal was acceptable.

Question #9:

At the Type C meeting in March 2010, FDA stated that they would analyze the primary endpoint by imputing treatment failure for subjects with missing data. Will this imputation be performed only for subjects with a missing 6-month assessment or will failure also be imputed for subjects who have missing efficacy assessments at earlier time points (but a valid assessment at 6 months)?

FDA Response:

We agree that the missing as failure imputation be performed only for subjects with a missing 6-month assessment.

Additionally in Table 10 of your briefing document, subjects are censored if they did not have *P. vivax* at baseline, or failed to demonstrate initial parasite clearance, or took a drug with anti-malarial action despite not having malaria parasites, or did not have a 6 month assessment. We can only agree that subjects who did not have *P. vivax* at baseline be censored. Those subjects

who failed to demonstrate initial parasite clearance, or took a drug with anti-malarial action despite not having malaria parasites, or did not have a 6-month assessment should all be considered as failures for the purpose of primary efficacy analysis.

Meeting Discussion:

- *GSK stated that they would like the language in the protocol to stay as currently written, but stated they would perform the analysis for the Phase 3 trial as FDA proposed. GSK stated that the primary analysis will be a survival analysis. The analyses will censor subjects who took antibacterials for the treatment of other conditions (noting that these antibacterials could have antimalarial effects), yet had no malaria (no *P. vivax* present). The sensitivity analysis would impute them as failures.*
- *GSK stated that the reason they preferred their plan is because their analysis is generally how outcomes are described in malaria trials outside of the U.S. and because this is how the data will be described in the literature.*
- *GSK stated that there are antimicrobial drugs with antimalarial activity that are clear and easy to identify, but there are others that are not. GSK stated that the use of beta-lactam antibacterial drugs is preferred should the patients require antibacterial therapy and they have emphasized the use of beta-lactams during the trial. GSK stated that Appendix 4 contains a list of drugs they had identified as having antimalarial activity. GSK stated that investigators in the Phase 3 trial will be encouraged to use drugs that are not on the prohibited list. FDA stated that the concern with patients, who were prescribed other antimicrobial drugs that may have antimalarial activity, was they would still need to be followed to determine if they were failures. GSK stated that this was a problem since very few of these patients continue follow-up care.*
- *FDA stated they had a concern with the protocol (section 4.4.2) regarding early treatment withdrawal, indicating these patients would be followed up only through day 90. GSK stated this was adjusted so that they would be followed through Day 180.*
- *FDA inquired what GSK was doing to address mixed infections. GSK stated they were doing rapid diagnostic tests (RDTs), stating that if a patient was recruited with a mixed infection, the RDT would detect a *P. falciparum* infection. GSK did not see the recruitment of mixed infection patients as an issue in part 1 of the study; they stated that *P. vivax* was the dominant species seen. GSK said that if *P. falciparum* emerged, rescue therapy would be given. These patients would be censored in the WHO analysis and be considered failures in the FDA analysis. The patients would be followed for 6 months.*
- *FDA noted that they had worked with other sponsors when the primary endpoints differed; for example, one for non-U.S. regulators and one for the FDA. FDA suggested that GSK should use this approach. GSK stated they could provide an WHO primary endpoint and a FDA primary endpoint in the protocol, but emphasized that they would not to adjust the alpha level for multiple endpoints. FDA agreed that this was a reasonable approach.*

- *FDA inquired when GSK planned to submit the revised protocol. GSK stated they planned to submit by the end of 2013. GSK does not plan to submit the protocol as a Special Protocol Assessment (SPA).*

Question #10:

Does the Division agree with our interpretation of *P. vivax* PCR data in Phase 2b and proposal for Phase 3 to repeat this methodology with a minimum of three markers also analyzing all baseline samples?

FDA Response:

Based on your past experience in Part 1 of the phase 2 study TAF112582, you propose to perform PCR using 3 markers (msp1F3, MS16, and Pv327) in the phase 3 trial. Please note that the suitability of your proposal cannot be ascertained in the absence of complete details of the performance characteristics of the assays and quality control measures in the laboratory where testing is performed. Also, what is the degree of certainty that a patient is infected with a single clone/strain of *P. vivax* prior to initiation of treatment and at the time of relapse, based on such testing? All details of the methods used for testing, the name of the laboratory where testing is performed, and data supporting the performance characteristics of the assays should be provided at the time of submission of a NDA. Inclusion of corrected cure rates in the labeling will be a review issue. The primary endpoint should be based on blood smear results.

Meeting Discussion:

- *GSK asked for clarification of the following comment, “Inclusion of corrected cure rates in the labeling will be a review issue.” FDA stated that it appeared from the submission that GSK was proposing to differentiate relapse from new infection by PCR. If that was the case, then the Division wanted to remind GSK that PCR was considered an experimental assay. If PCR results were to be used for any regulatory purpose, then details of the methods and performance characteristics of the assay in the laboratory where testing is performed should be made available for review. GSK agreed and stated that it was impossible to differentiate relapse from new infection based on the tests available.*

CLOSING REMARKS

GSK asked if FDA had any updates on their recent [October 2013] request for Breakthrough Therapy Designation. FDA commented that the review of Breakthrough Therapy Designation was ongoing and the final Division recommendation will be discussed with the Medical Policy Council Review Committee prior to the determination (grant or deny) being communicated in letter format to GSK. The determination letter will issue within the 60-day review period.

MEETING SUMMARY

Question #14: Regarding ocular assessments, GSK will provide additional information including information from prior studies, and the submission will be clearly marked for the FDA to review.

Question # 8: GSK acknowledged FDA concerns because of the high numbers of US travelers to India, noting that there is no scientific reason for differences in biology of *P. vivax* infection in India compared to other endemic countries. GSK is evaluating further work in India for registration of tafenoquine in that country. GSK will conduct the proposed Phase 3 trials in four Asian countries (not India) and at sites in S. America and Africa.

Question #18: GSK stated that there were no issues with the CDISC datasets and that the legacy data will be in the ISS but not converted.

Question #9: GSK stated that there would be two primary analysis plans in the protocol, representing two different approaches to the analysis. Separate statistical analyses will be conducted for the WHO and the FDA. A teleconference will be held as necessary to further clarify.

Question #10: PCR data will be provided. GSK will clarify their plans for the use of PCR and will provide details of the experimental method in the laboratory where testing will be performed and data supporting performance characteristics of the assay.

3.0 OTHER IMPORTANT CONSIDERATIONS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized

format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Following the submission of the revised clinical protocol, FDA will provide GSK comments on the ophthalmological safety evaluation, study design, and statistical plan, and, if needed, have a follow-up teleconference.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue Meeting Minutes	FDA	December 13, 2013
Submit a revised clinical protocol	GSK	December 2013
Submit ocular information	GSK	As soon as possible

6.0 ATTACHMENTS AND HANDOUTS

November 8, 2013, FDA Preliminary Meeting Comments.

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/s/

SUMATHI NAMBIAR
12/10/2013