CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213004Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114552

MEETING MINUTES

RedHill Biopharma Ltd.
Attention: Reza Fathi, PhD
Senior Vice President, Research and Development
260 Forest Avenue
Oradell, NJ 07649-1307

Dear Dr. Fathi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RHB-105 Fixed Dose Combination Capsule (amoxicillin (250 mg), omeprazole (10 mg) and rifabutin (12.5 mg)).

We also refer to the meeting between representatives of your firm and the FDA on March 18, 2019. The purpose of the Pre-NDA meeting was to discuss the data obtained from the completed Phase 3 study and the proposed submission of a 505(b)(2) NDA for the treatment of *Helicobacter pylori* infection.

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 Jacquelyn Rosenberger, PharmD, Regulatory Project Manager, at (301) 796-9179.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Preliminary Comments
Sponsor's Request for Clarification of Preliminary Comments

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:	March 18, 2019, 9:00 AM – 10:00 AM, EDT
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	IND 114552
Product Name:	RHB-105 Fixed Dose Combination Capsule (amoxicillin (250 mg), omeprazole (10 mg) and rifabutin (12.5 mg))
Indication:	Treatment of *Helicobacter pylori* (*H. pylori*) infection
Sponsor/Applicant Name:	RedHill Biopharma Ltd.
Meeting Chair:	Sumathi Nambiar, MD, MPH
Meeting Recorder:	Jacquelyn Rosenberger, PharmD

FDA ATTENDEES – Division of Anti-Infective Products

Sumathi Nambiar, MD, MPH	Director
Joseph Toerner, MD, MPH	Deputy Director for Safety
Dmitri Iarikov, MD, PhD	Deputy Director
Yuliya Yasinskaya, MD	Clinical Team Leader
Elizabeth O'Shaughnessy, MD	Clinical Reviewer
Zhixia (Grace) Yan, PhD	Clinical Pharmacology Team Leader
Abhay Joshi, PhD	Clinical Pharmacology Reviewer
Terry Miller, PhD	Pharmacology/Toxicology Team Leader
Madisa Macon, PhD	Pharmacology/Toxicology Reviewer
Avery Goodwin, PhD	Clinical Microbiology Team Leader
Lynette Berkeley, PhD, MT (ASCP)	Clinical Microbiology Reviewer
Daphne Lin, PhD	Deputy Director, Division of Biometrics IV
Jie Cong, PhD	Statistical Reviewer
Jiao Yang, PhD	Product Quality Reviewer
Yong Wang, PhD	Product Quality Team Leader (Acting)
Erika Englund, PhD	Product Quality Team Leader (Acting)
George Lunn, PhD	Product Quality Reviewer
Carmen DeBellas, PharmD	Chief, Regulatory Project Management Staff
Jacquelyn Rosenberger, PharmD	Regulatory Project Manager
Lilian Adeojo	Student, Office of Clinical Pharmacology

EASTERN RESEARCH GROUP ATTENDEES

Kuang-Heng Hsiao	Independent Assessor
Sraavya Polisetti	Independent Assessor

SPONSOR ATTENDEES – RedHill Biopharma Ltd. (unless otherwise noted)

Dror Ben Asher	Chief Executive Officer
Ira Kalfus, MD	Medical Director
Reza Fathi, PhD	Senior Vice President, Research & Development
Gilead Raday, MSc	Chief Operating Officer
Rick Scruggs	Chief Operating Officer
David Graham, MD	Professor of Medicine, Lead Investigator, Molecular Virology and Microbiology Veterans Affairs Medical Center, Baylor, Houston
(b) (4)	
Danielle Abramson, PhD	Vice President, Intellectual Property & Research
Aida Bibliowicz, MSc, MBA	Project Manager RHB-105 VP Clinical Operations
Patricia Anderson, MSc	Vice President Regulatory Affairs

BACKGROUND

On December 14, 2018, RedHill Biopharma Ltd. (Sponsor) sent a request to the Division for a Pre-NDA meeting to discuss the data obtained from the completed Phase 3 study, RHB-105-02 and the proposed 505(b)(2) NDA submission for the treatment of *H. pylori* infection. The Division granted the meeting request on December 27, 2018. The Division sent preliminary comments (appended) to the Sponsor on March 12, 2019. The Sponsor responded on March 15, 2019, with requests for clarification (appended) to be discussed at the meeting.

DISCUSSION

- After introductions, the Sponsor gave a brief overview of RHB-105.
- The Sponsor asked if the Division agreed that the information provided by the Sponsor prior to the meeting in response to the preliminary comments supports the bridging strategy for RHB-105. The Division replied that, in addition to the omeprazole PK data from the comparative BA study, literature evidence for clinical safety at the proposed omeprazole dose of 120 mg/day or higher would be helpful. The Sponsor asked if the two-week therapy bridging to chronic therapy would be a review issue and not a filing issue. The Division confirmed that it would be a review issue.
- The Division asked if the PK information for RHB-105 at steady state is available. The Sponsor stated that they used a sparse sampling approach and took a single PK sample

for each subject at the end of the 14-day treatment with the sample timing depending on a subject's return to the clinic. The Sponsor further explained that the available PK data indicate the omeprazole exposure was similar to that seen in the BA study. The Division noted that information regarding omeprazole exposure with doses that are similar or higher than the proposed dose would be helpful. The Sponsor asked if literature publications would be acceptable. The Division replied that it is acceptable. The Sponsor stated that clinical experience with double the labeled 40 mg daily dose of omeprazole has been described, and that the omeprazole exposure from RHB-105 would be comparable to omeprazole dose of 80 mg/day due to the induction effect of rifabutin on omeprazole metabolism.

- Regarding clinical question 3, the Sponsor stated that based on their investigations, they believe the 7 subjects in the comparator (no rifabutin) group who had plasma levels of rifabutin at visit 3 do not impact the overall results of the trial, RHB-105-02. The results of their investigation will be submitted in the NDA. The Sponsor asked if the Division agrees with this approach. The Division replied that from a clinical pharmacology perspective, the approach appears reasonable. The Division informed the Sponsor that they will conduct their own analysis based on the data provided. The Division asked if the Sponsor investigated the bioanalytical site. The Sponsor replied that during sample processing, a pipette or pipette tips used during the batching of samples might have been compromised; however, they do not believe it occurred at the bioanalytical site. The Division asked the Sponsor to clearly outline each of the processes / steps for these blood samples as it will be critical during the review of the NDA.
- The Sponsor noted their intention to update the White Paper that was originally submitted in May 2012 and add more information on *H. pylori* management. The Division responded that an updated White Paper with pertinent published literature was acceptable.
- The Sponsor asked if it was acceptable to submit an updated White Paper describing the contributions of amoxicillin and omeprazole to the combination in Module 5 of the NDA and a summary in Section 2.7.3. The Division replied that this is acceptable.
- Regarding question 9, the Sponsor stated they would like to submit the in-use stability data within 30 days of the NDA submission. The Division noted that they would need to discuss internally, as the NDA should be complete at the time of submission.
- The Sponsor asked whether a Risk Evaluation and Mitigation Strategy (REMS) would be anticipated. The Division replied that it was premature to comment on a REMS, but that they do not anticipate that a REMS program would be necessary.
- The Division asked if the Sponsor had plans to request a CMC dedicated Pre-NDA meeting. The Sponsor replied they had no plans to request one. The Division recommended that the Sponsor request a CMC dedicated meeting to come to agreement on CMC issues, including the stability data package.
- The Division asked when the Sponsor was planning on submitting the NDA. The Sponsor responded that it will likely be in a few months.

Post-Meeting Comments:

1. The proposal to submit the in-use stability data within 30 days of the NDA submission is acceptable.
2. The following question was received 2/25/2019, and the Division agreed to provide a response as a post-meeting comment. Please refer to the FDA response below.

   Question: Does FDA accept (b) (4) ?

   (b) (4)

ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue Meeting Minutes	FDA	April 17, 2019

ADDITIONAL APPLICATION INFORMATION (not discussed at the meeting)

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along

with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

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

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not

applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

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

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

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

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

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

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

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

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

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

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

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

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114552

MEETING PRELIMINARY COMMENTS

RedHill Biopharma Ltd.
Attention: Reza Fathi, PhD
Senior Vice President, Research and Development
260 Forest Avenue
Oradell, NJ 07649

Dear Dr. Fathi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RHB-105 Fixed Dose Combination Capsule (amoxicillin (250 mg), omeprazole (10 mg) and rifabutin (12.5 mg)).

We also refer to your December 14, 2018, correspondence, received December 14, 2018, requesting a meeting to discuss the data obtained from the phase 3 study completed and the proposed submission an NDA for the treatment of *H. pylori* infection via the 505(b)(2) route.

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, call Jacquelyn Rosenberger, PharmD, Regulatory Project Manager at (301) 796-9179.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, PharmD, RPh
Chief, Regulatory Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	March 18, 2019, 9:00 AM – 10:00 AM, EDT
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	IND 114552
Product Name:	RHB-105 Fixed Dose Combination Capsule (amoxicillin (250 mg), omeprazole (10 mg) and rifabutin (12.5 mg))
Indication:	Treatment of *H. pylori* infection
Sponsor Name:	RedHill Biopharma Ltd.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 18, 2019, between RedHill Biopharma Ltd. and the Division of Anti-Infective Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

Preliminary Questions:

1. Does the Division agree that the results of the comparative BA study RHB-P2-418 establish a bridge to the approved labeling of the LD(s) for the purposes of reliance upon the preclinical, clinical safety and clinical pharmacology?

FDA Response: *A BA study is acceptable for the purposes of bridging to the LDs. However, the results from the comparative BA study RHB-P2-418 do not support the proposed PK bridging strategy for the omeprazole component, for which the proposed daily dose is 2 to 3 times higher than the approved dose for the corresponding LD, Prilosec (omeprazole) capsules. Study RHB-P2-418 only evaluated 3 doses of RHB-105 under fasted condition. We acknowledge that food intake and potential induction effect of rifabutin are expected to decrease omeprazole exposure over chronic dosing of RHB-105. Therefore, a thorough review of omeprazole PK data from all PK studies would be needed to determine whether adequate PK bridging is established for omeprazole.*

2. RedHill proposes to include the narrative of the integrated analyses in Module 2 while the ISS and ISE in Module 5.3.5.3 will include the integrated outputs and datasets. Is this acceptable to the agency?

   FDA Response: *Your plan is acceptable if the information fits within the space limitations of the Summary of Clinical Efficacy and Summary of Clinical Safety, and the relevant integrated outputs and datasets in Module 5, section 5.3.5.3 are cross-linked in Module 2. Note that our primary assessment of efficacy will come from the individual trials rather than any pooled analyses. We recommend that you provide a discussion with references regarding the added contribution of omeprazole and amoxicillin to the regimen in section 2.7.3 and in the ISE.*

   Although similar information has been submitted previously, please include 1) your rationale for the exclusion of Asian subjects from the clinical trials and 2) the available evidence that eradication of H. pylori in patients with functional dyspepsia is a surrogate for the clinical endpoints of resolution of clinical symptoms and prevention of the development of peptic ulcer disease. A comprehensive review of the information based upon literature, or other clinical data, that support the use of eradication of H. pylori as a surrogate for these endpoints should be included in the NDA.

3. Clinical Question 1: Does the Division agree that the safety and efficacy of TALICIA as demonstrated in the two studies (RHB-105-01 and RHB-105-02) together with the completed biopharmaceutics study (Comparative Bioavailability Study RHB-P2-418) and Food Effect Study ISI-P3-560, support NDA submission via the 505(b)(2) route of TALICIA for the proposed indication of the treatment of *H. pylori* infection in adults?

   FDA Response: *We agree.*

4. In the ISE, the following strategy was taken, given the difference in designs of the two studies. The individual protocols of each study included different definitions as to what primary analysis set should be used for the primary analysis. While in Study RHB-105-01 the primary analysis set is mITT, the FAS definition was used for RHB-105-02. The ISE analyses will be performed using the FAS, mITT and PP analysis sets.

For the efficacy endpoint, subjects with negative test results will be considered treatment successes and subjects with positive test results will be considered treatment failures. Subjects with indeterminate, not assessable or missing results will also be considered treatment failures. In case of repeat results, the last measurement will be taken. A descriptive statistics analysis presenting the proportion of treatment success associated with 95% confidence interval (CI) in each treatment group (individual study and pooled) will be provided. The SAP for the ISE has been attached in Appendix 11.3.

Clinical Question 2: Does the agency agree with this strategy? (See Appendix 11.3 SAP for ISE)

FDA Response: *We will use the ITT population as the primary analysis population.*

5. RedHill has identified several (7) subjects in the active comparator (no rifabutin) in Study RHB-105-02 group that have plasma levels of rifabutin at visit 3. We have verified randomization codes and are confirming clinical trial material ingredients, re-assaying the patient samples, as well as conducting a GCP audit of involved sites. The results of these enquiries will be submitted to the NDA. We have performed a sensitivity analysis excluding those patients in the active comparator group with rifabutin and H. pylori eradication was successfully met by the RHB-105 arm (84% vs. 58%) with a p value of <0.0001. These results confirm the results demonstrated in the ITT analysis.

   Clinical Question 3: Is this approach acceptable to the agency?

   FDA Response: *We are unable to comment on your proposed approach due to the limited information provided. Please address the following:*
   - *Did these 7 subjects come from different sites?*
   - *Were their rifabutin levels comparable to the test subjects?*
   - *Did all subjects randomized to rifabutin have detectable rifabutin levels?*
   - *Were all control subjects checked for rifabutin plasma levels?*
   - *Clarify how the blinded study drugs were packaged and distributed to patients.*

6. Given that for TALICIA, omeprazole concentrations do not appear to be greater in patients with impaired CYP2C19 function, does the Agency agree that TALICIA can be administered to patients with all CYP2C19 phenotypes, including Asian patients?

   FDA Response: *It is premature to answer this question given the limited information provided in the meeting package. Please include all relevant data on patients' baseline CYP2C19 genotypes, PK, efficacy, and safety in the NDA. The final decision on whether RHB-105 can be given to patients with all CYP2C19 phenotypes, including Asian patients will be made during the NDA review.*

7. Given that in the pivotal efficacy trial RHB-105-02, TALICIA was recommended to be administered with food, largely to mitigate the risk of gastrointestinal upset associated

with amoxicillin and rifabutin, does the Agency agree that TALICIA should be administered with food?

FDA Response: *We are in general agreement about administering RHB-105 with food. However, the final decision on this issue will be made during the NDA review.*

8. In view of the (1) excellent safety and tolerability profile in our studies (See Appendix 11.2 ISS Safety Tables) (2) the extensive post-marketing experience with TALICIA's active components and (3) the relatively brief dosing regimen of 14 days, RedHill believes that a standard post-marketing pharmacovigilance strategy is appropriate. Does the agency agree?

   FDA Response: *Your rationale for a standard postmarketing pharmacovigilance strategy is noted. A final decision about the adequacy of your proposal will be made during the NDA review*

9. Proposal 1: Bottles of 84-count.
   A complete treatment cycle of TALICIA comprises 168 capsules, which would be packaged in two 84-count bottles placed in a single box. The proposed commercial 84-count bottles would be proportionally smaller than the 100-count bottles currently placed on stability in order to retain the same or decreased headspace. The proposed bottle will be made of the same materials and resins and will have the same diameter opening and same cap as the larger bottle. The protective properties are unchanged; therefore, RedHill proposes to use the stability data generated for the 100- count bottles to support the shelf life of the 84-count bottles.

   CMC Question 1. Does the Agency agree with this proposal?

   FDA Response: *The proposal to provide the drug product in 2 bottles with 84 capsules each appears reasonable. You should provide information to show that the two container-closure systems have comparable protective properties, e.g., similar water vapor permeation rates. Additionally, an in-use study should be carried out to show that bottles that have been opened, i.e., bottles from which the* (b) (4) *seal has been removed (but where the screw cap is still used) will continue to provide protection for the capsules that remain in the bottle. This should cover at least 14 days in case the patient opens both bottles at the start of treatment.*

10. (b) (4)

(b) (4)

11. CMC Question 3. Will the Agency accept new stability data during the review period and if yes, what would be the latest time prior to the PDUFA date that this new data would be accepted?

FDA Response: *Provided that at the time of NDA submission, per the Q1A(R2) recommendation, at least 12 months of long-term and 6-months accelerated stability data for 3 batches of which at least 2 are at pilot scale are included, we would be willing to accept additional stability data not later than 30 days after the NDA is submitted.*

Additional Comments:
To facilitate the review, we recommend that you include the following in the NDA:

General Study Information

- *Please provide a statement of Good Clinical Practice for each Phase 2 and Phase 3 study used to support the NDA. If this information is in the Clinical Study Report (CSR), please provide the section and page number with a hyperlink to the CSR.*
- *Please submit a rationale for assuming the applicability of foreign data, if any, in the submission to the U.S. population in your NDA.*
- *Please provide the summary of the information regarding Financial Certifications and Disclosures in a tabular format if possible. A sample table is provided to be modified as you wish.*

Study No. *(incl. eCTD link for CSR)*	***Study Title***	***Sponsor***	***Name of Principal investigator, Name of Sub-investigators.*** *(include eCTD link to relevant forms and disclosures for each study/ investigator)*	***Financial Disclosure Obtained*** *(Indicate Yes or No)*

Tables and Datasets

- *A table of normal ranges for laboratory tests in the clinical study report for each trial. Include a link to these tables along with a X times upper/lower limit of normal for each laboratory value included in case narratives. Flag out of range laboratory values in the laboratory datasets.*

- *An electronic submission of a site level dataset to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the NDA review process. Please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" for the structure and format of this dataset (available at the following link: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf).*
- *Separate tables for patients with discontinuations of drug, discontinuations from the study, and withdrawal from the study for any reason, along with study ID, subject ID, demographics, study arm, study day of discontinuation of drug or from study, or withdrawal, reason for this disposition, and adverse event (if present).*
- *An interactive table or dataset that contains all subjects that were unblinded. The table or dataset should include the unique subject ID, the treatment received, who was requesting unblinding, date of unblinding, and the reason for unblinding.*
- *An interactive table detailing all the tables and figures featured in the main clinical efficacy and the safety sections of the NDA. The table should contain the following*:

    a. *Title of the table or figure in the NDA*
    b. *A page number hyperlinked to the location of the table or figure*
    c. *A hyperlink to the SAS code (and/or macros) used to create the table or figure*
    d. *Names of the datasets used to create the table or figure (hyperlinks are useful but not necessary).*
    e. *For derived (analysis) datasets used to conduct your analyses, you should indicate the tabulation datasets from which the information was derived.*

- *An interactive table that contains a list of all subjects for whom you submitted a CRF, narrative, or adjudication package(s).*
- *An algorithm which clearly explains how findings from all primary and secondary analyses were produced (e.g. dataset, variable names and programming steps used). This will minimize potential discrepancies between FDA reviewers' and Applicant's analyses.*

The FDA study data technical conformance guide can be located at: https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM624939.pdf

Meeting Minutes and Other Documents

- *A tabulated summary of changes for each protocol version along with the date of implementation, and the number of subjects enrolled at the time.*
- *A tabulated summary of meetings with FDA during the development program of RHB105 along with the meeting minutes of each; ensure that these are bookmarked.*
- *All meeting minutes of all groups with any responsibility for the management of the trial, e.g., Executive Committee, Clinical Endpoint Committee, Steering Committee*

and DSMB. Please include agendas and all data/slides presented. Please indicate if the meeting was opened or closed. For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.

- *All newsletters and other communications to investigational sites and national coordinators from the group(s) responsible for the conduct of your trial. Please bookmark the newsletters by date.*

505(b)(2) REGULATORY PATHWAY

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

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

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

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

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such

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

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

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

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

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

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

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

/s/

CARMEN L DEBELLAS
03/12/2019 09:27:32 AM

RedHills Pre- Meeting Clarification Request and Response

Meeting Type: B
Meeting Category: Pre-NDA
Meeting Date and Time: March 18, 2019, 9:00 AM – 10:00 AM, EDT
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number: IND 114552
Product Name: RHB-105 Fixed Dose Combination Capsule (rifabutin (12.5 mg), amoxicillin (250 mg), and omeprazole (10 mg) as omeprazole magnesium (10.3 mg))
Indication: Treatment of *H. pylori* infection in adults
Sponsor Name: RedHill Biopharma Ltd.

Regulatory Questions

1. Does the Division agree that the results of the comparative BA study RHB-P2-418 establish a bridge to the approved labeling of the LD(s) for the purposes of reliance upon the preclinical, clinical safety and clinical pharmacology?

FDA Response: A BA study is acceptable for the purposes of bridging to the LDs. However, the results from the comparative BA study RHB-P2-418 do not support the proposed PK bridging strategy for the omeprazole component, for which the proposed daily dose is 2 to 3 times higher than the approved dose for the corresponding LD, Prilosec (omeprazole) capsules. Study RHB-P2-418 only evaluated 3 doses of RHB-105 under fasted condition. We acknowledge that food intake and potential induction effect of rifabutin are expected to decrease omeprazole exposure over chronic dosing of RHB-105. Therefore, a thorough review of omeprazole PK data from all PK studies would be needed to determine whether adequate PK bridging is established for omeprazole.

RedHill Response:

This 505(b)(2) NDA relies on the Food and Drug Administration's (FDA) previous findings of safety and efficacy for the individual active ingredients in Talicia, consisting of the approved Listed Drug (LD) for rifabutin (Mycobutin®; NDA 050689), amoxicillin (Amoxil®; NDA 050459), and omeprazole (Prilosec®; NDA 019810), a bridging comparative bioavailability study (RHB-P2-418), a food effect study (RHB-105-12) and clinical studies with Talicia demonstrating safety and efficacy in support of the treatment of *H. pylori* infection in adults and published literature related to omeprazole.

LD Label for Prilosec RedHill acknowledges that the proposed Talicia (RHB-105) regimen, which entails administering 40 mg omeprazole (as 4 capsules each containing 10.3 mg of omeprazole magnesium), is higher than the listed drug (LD) dose for the indication of *Helicobacter pylori* (*H. pylori*) treatment. However, the LD label also includes an indication for the treatment of pathological hypersecretory conditions recommending much higher omeprazole daily doses than for the treatment of *H. pylori* (Prilosec PI Section 2.1). While a recommended

starting dose is 60 mg once daily, this dose is to be adjusted to the patient's needs and doses up to 120 mg three times a day have been administered. The label further states that treatment duration is as long as clinically indicated with some patients having been treated continuously for more than five years. In contrast, Talicia is administered for 14 days. RedHill is seeking to clarify the Agency's position on bridging to the safety data associated with higher omeprazole doses associated with indications other than *H. pylori* eradication. To support the discussion, RedHill is providing herein a summary of the available pharmacokinetic (PK) data to support bridging to doses at or above 120 mg per day of the LD.

Study RHB-P2-418 Comparative Bioavailability

The comparative bioavailability study (RHB-P2-418) was intended to characterize the bioavailability of omeprazole from the proposed Talicia regimen to an equivalent daily dose of omeprazole from the LD.

TABLE 1: RHB-P2-418 Summary of Main Study Results: Omeprazole

Parameter	RHB-105 tid		Myocobutin qd + Amoxicillin tid +Prilosec tid	
	Mean	C.V. (%)	Mean	C.V. (%)
C_{max} (ng/mL)	1280.92	40.5	1294.99	27.5
T_{max} (hours)*	2.00	105.3	12.00	55.4
AUC_{0-24} (ng·h/mL)	7161.15	49.3	10128.37	36.0
$AUC_{0-\infty}$ (ng·h/mL)	7718.73	46.1	10964.00	33.8
$T_{1/2}$ (hours)	1.49	19.6	2.10	72.1

Parameter	Geometric LS Means		Ratio (%)	90% Confidence Limits	
	RHB-105 tid	Myocobutin qd + Amoxicillin tid +Prilosec tid		Lower	Upper
C_{max} (ng/mL)	1174.85	1243.98	94.44	77.28	115.41
AUC_{0-24h} (ng·h/mL)	6344.13	9478.27	66.93	57.57	77.82
$AUC_{0-\infty}$ (ng·h/mL)	7143.42	10395.80	68.71	59.39	79.50

* Median is presented

Abbreviations: C.V. = Coefficient of Variation; tid= three times a day; qd= four times a day

Source:Study RHB-P2-418 CSR, Tables 14 and 15

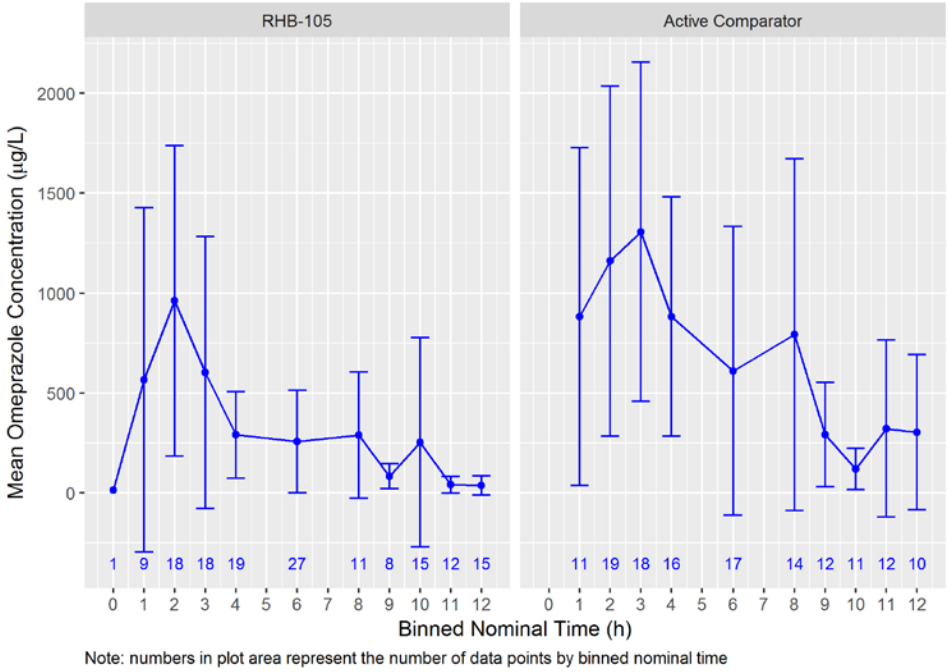
When administered as Talicia, omeprazole achieved on average slightly lower peak exposure (Geometric Ratio 94.4 and 90% CI 77.3-115.4), however the AUC over 24 hours was approximately 68.7% (90% CI59.4-79.5) of the LD administered at equal divided doses. Therefore, under similar meal conditions to Study RHB-P2-418 study, Talicia can be expected to deliver the equivalent of approximately 80 mg of the LD. In RHB-P2-418, the dosing conditions were not strictly fasted with fasting periods of 10 hours pre-first dose, 3.5-4.5 hours post first dose and 3.5-4.5 hours pre- and post-dosing for the subsequent doses.

While not steady-state conditions, the exposure of the LD during the treatment of hyper-secretory conditions at doses at or above 120 mg per day can be expected to be at least as high as what was observed in Study RHB-P2-418 (i.e. geometric least square mean of approximately 10,395 ng•hr/mL).

RHB-105-02 Pivotal Study

In the pivotal efficacy and safety trial RHB-105-02, sparse PK samples were drawn for each Talicia component at the end of a two-week course (Visit 3). Omeprazole plasma concentrations were binned into time after the last dose to facilitate data summarization. Summary concentrations at Visit 3 for omeprazole following Talicia or active comparator administration are presented in Figure 1.

Figure 1 Summary Plots of Plasma Omeprazole Concentrations at Visit 3 Following RHB-105 or Active Comparator Administration



Data source: Clinical Study Report for RHB-105-02 Pharmacokinetic Report

Mean omeprazole levels following RHB-105 or active comparator administration peaked around 2 and 3 hours post-dose, respectively. Peak and overall omeprazole levels appeared to be lower following RHB-105 administration, relative to the profile observed following active comparator administration, and consistent with the short half-life for omeprazole, substantially lower up to 12 hours after the last dose. On average, concentrations appeared to be relatively lower in the Talicia-treated patients, potentially due to an inductive effect of rifabutin on the clearance of omeprazole.

Study RHB-105-02 vs Study RHB-P2-418

Table 2 summarizes the binned concentrations which provide for a numerical peak exposure comparison between Study RHB-105-02 and Study RHB-P2-418.

TABLE 2 Summary of Plasma Omeprazole Concentrations at Visit 3 Following RHB-105 Administration

Stats	Binned Nominal Time After Dose (h)										
	Concentration (ng/mL)										
	0	1	2	3	4	6	8	9	10	11	12
N	1	9	18	18	19	27	11	8	15	12	15
Mean	14.95	565.991	961.963	601.921	290.322	256.866	289.951	83.386	253.033	41.228	37.053
SD	NC	861.777	777.193	680.106	215.636	257.114	316.086	62.873	522.629	41.816	48.032
CV%	NC	152.3	80.8	113	74.3	100.1	109	75.4	206.5	101.4	129.6
Median	14.95	73.99	873.245	370.93	304.02	159.3	155.55	82.355	108.13	21.475	14.24
Min	14.95	4.28	8.29	17.36	4.86	2.99	10.64	8.85	3.36	2.57	2
Max	14.95	2037.89	3438.46	2595.45	782.67	910.4	1049.23	167.85	2041.04	138.44	144.09

NC = Not calculated; The number of concentrations with TAD>12h comprised 7.3% of the total number of concentrations; these were not presented in this table. Units presented in this table are in µg/L which is equivalent to ng/mL for cross-study comparisons.

Source Data: Data source: Clinical Study Report for RHB-105-02 Pharmacokinetic Report

When administered in RHB-105-02, omeprazole concentrations following Talicia reached a mean peak of approximately 962 ng/mL (CV% 80.8%, N=18) at 2 hours after the last dose compared to a Cmax of approximately 1,281 ng/mL for Talicia in RHB-P2-418. These results suggest, that under clinical conditions prescribed by the protocol, where Talicia was to be administered with food, peak exposure is somewhat reduced compared to fasted conditions in

Study RHB-P2-418. When considering a peak-to-AUC ratio based on that observed for the mean RHB-P2-418 data (Cmax of 1,281 ng/mL ÷ AUC_{0-24h} 7161.15 ng•hr/mL = 0.179), the mean peak of 962 ng/mL observed in RHB-105-02 is estimated to be associated with an AUC_{0-24h} of approximately 5,374 ng•hr/mL, which is approximately half of the AUC_{0-24h} associated with the LD in RHB-P2-418 following 120 mg over 24 hours and approximately 60% higher than the reported AUCs in adults found in the Prilosec label (see Table 7).

Food Effect Study RHB-105-12

A summary of the effect of a high-fat, high caloric meal on omeprazole exposure following Talicia administration is presented in Table 3.

TABLE 3 Summary of Plasma Omeprazole Pharmacokinetic Parameters – Treatment-1 (RHB-105 Fed) vs Treament-2 (RHB-105 Fast)

Parameter	Treatment-1 (RHB-105 Fed) (n=18)[b]		Treatment-2 (RHB-105 Fast) (n=18)[c]	
	Mean	C.V. (%)	Mean	C.V. (%)
C_{max} (ng/mL)	86.38	84.7	983.18	61.4
T_{max} (hours)[a]	4.25	(2.50-6.00)	1.25	(0.75-1.77)
AUC_{0-T} (ng·h/mL)	292.74	87.4	1686.87	82.6
$AUC_{0-\infty}$ (ng·h/mL)	316.81	83.8	1693.47	82.6
$T_{1/2,Z}$ (hours)	1.34	28.9	1.06	28.3

Parameter	Geometric LS Means		Ratio (%)	90% Confidence Limits	
	Treatment-1 (RHB-105 Fed) (n=18) [d, e]	Treatment-2 (RHB-105 Fast) (n=18) [d, e]		Lower	Upper
C_{max} (µg/mL)	62.59	817.53	7.66	5.62	10.43
AUC_{0-T} (µg·h/mL)	220.46	1252.41	17.60	14.67	21.12
$AUC_{0-\infty}$ (µg·h/mL)	218.75	1258.05	17.39	14.43	20.95

[a] Median and range are presented,[b] n=16 for $AUC_{0-\infty}$ and $T_{1/2,z,}$ [c] n=17 for AUC_{0-T}, $AUC_{0-\infty}$, % and $T_{1/2,z,}$ [d] n=17 for $AUC_{0-T,}$ [e] n=15 for $AUC_{0-\infty}$

Source: RHB-105-12 CSR Appendix 16.2.6.1.2.1, Section 14.2.2, Tables 11 and 12

Following a high-fat, high caloric mean, the systemic exposure of omeprazole was reduced by 82%.

Given that the LD labeling recommends significantly higher doses than what is currently proposed for Talicia, when indicated in the treatment of hyper-secretory conditions for treatment

durations longer than five years in some cases; Talicia is indicated for short-term treatment (i.e. two-weeks); Omeprazole systemic exposure during Talicia treatment at 40 mg q8h is anticipated to fall substantially below the anticipated exposure of the LD in the treatment of hypersecretory condition.

In summary, the proposed Talicia regimen is intended to deliver 40 mg of omeprazole (as 41.2 mg omeprazole magnesium) every 8 hours which is within the labeled doses for Prilosec in the treatment of hypersecretory conditions. Omeprazole peak exposure (Cmax) was similar and systemic exposure (AUC) was approximately 30% lower when Talicia was administered as 4 capsules containing 10 mg of omeprazole (as 10.3 mg omeprazole magnesium), compared to Prilosec 40 mg administered, both administered every 8 hours for three consecutive doses (reference RHB-P2-418). As evidenced by summary concentration data obtained from Study RHB-105-02, after repeated doses, with the concurrent exposure to rifabutin, omeprazole exposure from Talicia administration is expected to fall well below that of Prilosec doses in label reported to be safe in the treatment of hypersecretory conditions. Moreover, Talicia is indicated for short-term treatment, whereas, omeprazole (as omeprazole magnesium) delayed-release capsules was well tolerated in high dose level treatment of hypersecretory conditions for prolonged periods (> 5 years in some patients).

RedHill believes that taken together, the above data support the proposed bridging strategy for the omeprazole component in Talicia. Does the agency agree?

2. RedHill proposes to include the narrative of the integrated analyses in Module 2 while the ISS and ISE in Module 5.3.5.3 will include the integrated outputs and datasets. Is this acceptable to the agency?

FDA Response: Your plan is acceptable if the information fits within the space limitations of the Summary of Clinical Efficacy and Summary of Clinical Safety, and the relevant integrated outputs and datasets in Module 5, section 5.3.5.3 are cross-linked in Module 2. Note that our primary assessment of efficacy will come from the individual trials rather than any pooled analyses. We recommend that you provide a discussion with references regarding the added contribution of omeprazole and amoxicillin to the regimen in section 2.7.3 and in the ISE.

Although similar information has been submitted previously, please include 1) your rationale for the exclusion of Asian subjects from the clinical trials and 2) the available evidence that eradication of H. pylori in patients with functional dyspepsia is a surrogate for the clinical endpoints of resolution of clinical symptoms and prevention of the development of peptic ulcer disease. A comprehensive review of the information based upon literature, or other clinical data, that support the use of eradication of H. pylori as a surrogate for these endpoints should be included in the NDA.

RedHill Response by Comment:

2.1 A discussion with references regarding the added contribution of omeprazole and amoxicillin to the regimen in section 2.7.3 and in the ISE.

As requested, we have assembled a White Paper discussing the contribution of both amoxicillin and omeprazole to Talicia to Module 5 with a summary in section 2.7.3. Is this acceptable to the Agency?

2.2 Rationale for the exclusion of Asian subjects from the clinical trials

Upon FDA correspondence in an email dated July 5, 2017, a decision was made to exclude Asian population as even with stratification it might create bias in the study due to CYP2C19 interactions and prevalence of poor metabolizer status in the Asian population. At that time there was no information available on the impact of cyp genotype and interaction with Talicia.

2.3 Available evidence that eradication of *H. pylori* in patients with functional dyspepsia is a surrogate for the clinical endpoints of resolution of clinical symptoms and prevention of the development of peptic ulcer disease and a comprehensive review of the information based upon literature, or other clinical data, that support the use of eradication of *H. pylori* as a surrogate for these endpoints should be included in the NDA.

It is our intention to update the previously submitted White Paper: Association between *H. pylori* Infection and Clinical Sequelae and Role of *H. pylori* Eradication in Mitigation or Prevention of Outcomes, initially submitted to FDA in June 2012 and further clarified in email correspondence with FDA July 11, 2013- July 17, 2013, and Study May Proceed letter February 11, 2014 (Reference ID: 3452188), with the recent Kyoto, Houston and Maastrich consensus documents and submit the updated White Paper in module 5 with a summary of this White Paper added in the Clinical Overview.

H. pylori is a major human pathogen that causes chronic gastric inflammation and structural damage along with changes in gastric function in all infected patients. While some infected individuals remain asymptomatic throughout life, the progressive nature of the damage often results in development of atrophic gastritis and a number of clinically important sequelae, including peptic ulcers and gastric cancer, the second most common cancer in the world and a wholly preventable disease.

Talicia is being developed for the treatment of *H. pylori* infection distinct from functional dyspepsia. As discussed in the previously submitted White Paper, the eradication of *H. pylori* is not a surrogate for symptomatic relief of functional dyspepsia. Rather, treatment of *H. pylori* infection with Talicia which has been designated by FDA as a Qualified Infectious Disease Product, treats the infection itself. Although *H. pylori* eradication may not resolve the clinical problem of dyspepsia in patients, successful *H. pylori* eradication therapy will reduce significantly the long-term risk of developing either peptic ulcer or gastric cancer (Lee et al. 2016).

The recommendation to test and treat those with dyspepsia and *H. pylori* infection has been included in the Kyoto, Houston, Maastricht, American College of Gastroenterology, and Canadian consensuses. (Chey et al. 2017, El-Serag et al. 2018,b Fallone et al. 2016, Malfertheiner et al. 2017, Sugano et al. 2015). The recent Kyoto consensus guideline on gastritis concluded that *H. pylori* gastritis is an infectious disease. As such, *H. pylori* gastritis requires treatment whether or not it is associated with symptoms because it represents a condition that may evolve towards serious complications, including peptic ulcer and gastric neoplasia. The estimated number needed to treat for *H. pylori* to achieve one symptomatic response has been estimated at eight. (Sugano et al. 2015). The symptomatic gain takes at least 6 months to become significant vs. not eradication of *H. pylori.* The diagnosis of functional dyspepsia or *H. pylori* associated gastritis is dependent on the presence of *H. pylori* infection and Talicia is indicated only for patients with diagnosed *H. pylori* infection.

It is reasonable to conclude, given the current body of evidence, that a clinical strategy eradicating *H. pylori* infection in patients presenting with dyspepsia is appropriate and beneficial. In so doing, the risk of ulcers, ulcer recurrence, and more importantly, developing gastric cancer, are significantly reduced. The strong evidence linking *H. pylori* infection with serious and preventable clinical outcomes supports using *H. pylori* eradication in patients presenting with dyspepsia who are infected with *H. pylori* and further supports using *H. pylori* eradication as a surrogate marker for prevention of the long-term infection outcomes.

Does the agency agree?

References:

Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection Am J Gastroenterol. 2017 Feb;112(2):212-239.

El-Serag, Kao j, Kanwal F, Gilger m, LoVecchio F, Moss S, Crowe S, Elfant A, Haas T, Hapke R, Graham D. Houston Consensus Conference on Testing for *Helicobacter pylori* Infection in the United States. Clinical Gastroenterology and Hepatology 2018; 16:992-1002

Fallone C, Chiba N, van Zanten S, Fischbach L, Gisbert J, Hunt R, Jones N, Render C, Leontiadis G, Moayyedi P, Marshall J. The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults. Gastroenterology 2016;151:51–69

Lee YC, Chiang TH, Liou JM, et al. Mass Eradication of *Helicobacter pylori* to prevent gastric cancer: Theoretical and practical considerations. Gut Liver 2016;10:12–26.

Malfertheiner P, Megraud F, O'Morain CA on behalf of the European Helicobacter and Microbiota Study Group and Consensus panel. Management of *Helicobacter pylori* infection—the Maastricht V/Florence consensus report. Gut 2017;66.1:6-30.

Sugano K, Tack J, Kuipers E, Graham D, El-Omar E, Miura S, Haruma K, Asaka M, Uemura N, Malfertheiner P. Kyoto global consensus report on *Helicobacter pylori* gastritis Gut 2015; 64:1353-1367.

3. Clinical Question 1: Does the Division agree that the safety and efficacy of TALICIA as demonstrated in the two studies (RHB-105-01 and RHB-105-02) together with the completed biopharmaceutics study (Comparative Bioavailability Study RHB-P2-418) and Food Effect Study ISI-P3-560, support NDA submission via the 505(b)(2) route of TALICIA for the proposed indication of the treatment of *H. pylori* infection in adults?

FDA Response: *We agree.*

RedHill Response: Thank you.

4. In the ISE, the following strategy was taken, given the difference in designs of the two studies. The individual protocols of each study included different definitions as to what primary analysis set should be used for the primary analysis. While in Study RHB-105-01 the primary analysis set is mITT, the FAS definition was used for RHB-105-02. The ISE analyses will be performed using the FAS, mITT and PP analysis sets.

For the efficacy endpoint, subjects with negative test results will be considered treatment successes and subjects with positive test results will be considered treatment failures.

Subjects with indeterminate, not assessable or missing results will also be considered treatment failures. In case of repeat results, the last measurement will be taken. A descriptive statistics analysis presenting the proportion of treatment success associated with 95% confidence interval (CI) in each treatment group (individual study and pooled) will be provided. The SAP for the ISE has been attached in Appendix 11.3.

Clinical Question 2: Does the agency agree with this strategy? (See Appendix 11.3 SAP for ISE)

FDA Response: *We will use the ITT population as the primary analysis population.*

RedHill Response: We thank the Agency for its response and would like to clarify that FAS in the RHB-105-02 pivotal study SAP is the ITT population.

5. RedHill has identified several (7) subjects in the active comparator (no rifabutin) in Study RHB-105-02 group that have plasma levels of rifabutin at visit 3. We have verified randomization codes and are confirming clinical trial material ingredients, re-assaying the patient samples, as well as conducting a GCP audit of involved sites. The results of these enquiries will be submitted to the NDA. We have performed a sensitivity analysis excluding those patients in the active comparator group with rifabutin and *H. pylori* eradication was successfully met by the RHB-105 arm (84% vs. 58%) with a p value of <0.0001. These results confirm the results demonstrated in the ITT analysis.

Clinical Question 3: Is this approach acceptable to the agency?

FDA Response: We are unable to comment on your proposed approach due to the limited information provided. Please address the following:

- *Did these 7 subjects come from different sites?*
- *Were their rifabutin levels comparable to the test subjects?*
- *Did all subjects randomized to rifabutin have detectable rifabutin levels?*
- *Were all control subjects checked for rifabutin plasma levels?*
- *Clarify how the blinded study drugs were packaged and distributed to patients.*

RedHill Response: Please find below responses to each of the questions posed by the Agency

1. Did these 7 subjects come from different sites?

The seven active comparator treated subjects with quantifiable rifabutin concentrations originated from 6 different clinical sites (one site with 2 subjects).

2. Were their rifabutin levels comparable to the test subjects?

In general, rifabutin levels in the seven active comparator treated subjects were similar in concentrations to those detected in the Talicia treated group. The following Table 1 is a listing of the seven subjects enrolled in the active comparator treatment arm of RHB-105-02 with non-zero/reportable rifabutin concentrations, along with the reported values of the other analytes measured in the trial.

TABLE 1. Listing of Reported Concentrations for Active Comparator Treated Subjects with Quantifiable Rifabutin Plasma Concentrations at Visit 3

SUBJECT	VISIT	TAD	ANALYTE	CONCENTRATION	COMMENT
RHB-105-02-(b) (6)	VISIT 3	5.25	Amoxicillin	3.175	Within plausible range of concentrations for active comparator treated subjects at binned time
			Omeprazole	217.55	
			Rifabutin	6.33	Within range of concentrations for Talicia treated subjects at binned time
			25-O-desacetylrifabutin	0.929	Within range of concentrations for Talicia treated subjects at binned time
RHB-105-02-(b) (6)	VISIT 3	11.16667	Amoxicillin	BLQ	Within plausible range of concentrations for active comparator treated subjects at binned time
			Omeprazole	7.71	
			Rifabutin	2.1	Below range of concentrations for Talicia treated subjects at binned time

SUBJECT	VISIT	TAD	ANALYTE	CONCENTRATION	COMMENT
			25-O-desacetylrifabutin	BLQ	Below range of concentrations for Talicia treated subjects at binned time
RHB-105-02-(b) (6)	VISIT 3	9.383333	Amoxicillin	BLQ	Within plausible range of concentrations for active comparator treated subjects at binned time
			Omeprazole	BLQ	
			Rifabutin	6.23	Below range of concentrations for Talicia treated subjects at binned time
			25-O-desacetylrifabutin	0.563	Below range of concentrations for Talicia treated subjects at binned time
RHB-105-02-(b) (6)	VISIT 3	21.13333	Amoxicillin	0.298	N/A as binning not performed beyond 12 hours TAD
			Omeprazole	65.53	
			Rifabutin	13.84	
			25-O-desacetylrifabutin	1.364	
RHB-105-02-(b) (6)	VISIT 3	5.25	Amoxicillin	11.738	Within plausible range of concentrations for active comparator treated subjects at binned time
			Omeprazole	1007	
			Rifabutin	132.36	Higher than observed range of concentrations at binned time
			25-O-desacetylrifabutin	8.495	Within range of concentrations for Talicia treated subjects at binned time
RHB-105-02-(b) (6)	VISIT 3	0.5	Amoxicillin	16.79	Higher than observed range of concentrations at binned time
			Omeprazole	2264.79	Within plausible range of concentrations for active comparator treated subjects at binned time
			Rifabutin	201.02	Higher than observed range of concentrations at binned time
			25-O-desacetylrifabutin	32.489	Higher than observed range of concentrations at binned time
RHB-105-02-(b) (6)	VISIT 3	3.4	Amoxicillin	16.167	Within plausible range of concentrations for active comparator treated subjects at binned time
			Omeprazole	663.52	

SUBJECT	VISIT	TAD	ANALYTE	CONCENTRATION	COMMENT
			Rifabutin	8.9	Within range of concentrations for Talicia treated subjects at binned time
			25-O-desacetylrifabutin	0.921	Below range of concentrations for Talicia treated subjects at binned time

BLQ: Below the limit of quantitation; TAD: Time after the last dose

No discernable pattern is obvious when comparing the rifabutin and 25-O-desacetyl rifabutin concentrations to those of the respective analyte range of concentrations at common time bins.

A descriptive summary of binned rifabutin and 25-O-desacetylrifabutin concentrations at Visit 3 in the Talicia (RHB-105) treated subjects are summarized below for reference.

TABLE 2. Summary of Plasma Rifabutin Concentrations at Visit 3 Following RHB-105 Administration

Stats	Binned Nominal Time After Dose (h)										
	Concentration (µg/L)										
	0	1	2	3	4	6	8	9	10	11	12
N	1	9	18	19	18	28	15	11	16	19	19
Mean	73.77	53.86	91.36	85.436	79.928	83.834	60.683	66.869	66.751	55.759	59.443
SD	NC	12.587	35.44	36.064	27.575	38.264	39.317	29.162	26.301	29.774	17.731
CV%	NC	23.4	38.8	42.2	34.5	45.6	64.8	43.6	39.4	53.4	29.8
Median	73.77	54.87	90.11	88.83	82.745	83.22	76.96	67.28	72.35	57.15	62.96
Min	73.77	35.41	45.29	2.2	24.93	3.04	2.92	30.03	11.36	7.52	33.05
Max	73.77	70.49	166.81	161.73	124.69	178.65	134.94	112.75	128.37	116.85	93.98

NC: Not calculated; TAD: Time after last dose. The number of concentrations with TAD>12h comprised 15.2% of the total number of concentrations; these were not presented in this table.

TABLE 3. Summary of Plasma 25-O-desacetylrifabutin Concentrations at Visit 3 Following RHB-105 Administration

Stats	Binned Nominal Time After Dose (h)										
	Concentration (µg/L)										
	0	1	2	3	4	6	8	9	10	11	12
N	1	9	18	18	18	28	15	11	16	19	19
Mean	3.478	4.054	6.39	6.26	6.584	5.727	5.54	5.046	4.189	3.867	4.443
SD	NC	1.426	2.575	3.388	3.184	2.77	3.931	3.296	1.875	2.892	1.958
CV%	NC	35.2	40.3	54.1	48.4	48.4	70.9	65.3	44.8	74.8	44.1
Median	3.478	3.876	6.073	5.443	6.005	5.2	5.285	3.904	4.209	3.289	4.647
Min	3.478	2.094	2.79	1.612	2.597	0.356	0.34	1.869	0.956	0.474	1.709
Max	3.478	6.677	10.782	12.664	17.345	10.909	11.184	12.649	7.09	11.874	7.836

NC: Not calculated; TAD: Time after last dose. The number of concentrations with TAD>12h comprised 14.4% of the total number of concentrations; these were not presented in this table.

Similarly, amoxicillin and omeprazole concentrations were largely consistent with the range of values observed in the Talicia and active comparator treated subjects at common binned times.

The likelihood of bioanalytical lab site cross-contamination or bioanalytical carryover is unlikely for the following reasons:

1) For the rifabutin and 25-O-desacetylrifabutin bioanalytical method, the presence or absence of carryover was evaluated prior to the injection of every batch using the injection of a high concentration sample (equivalent to the upper limit of quantitation [ULOQ] concentration) followed by an analyte-free sample, as well as the injection of a LOQ sample (Bioanalytical Report ISI-P0-585 to be provided in the NDA). To start the injection of each batch, carryover must be deemed not significant, i.e. the analyte response of the analyte-free sample must be ≤ 20.0% of the analyte response of the LOQ, and/or IS response must be ≤ 5.0 % of the IS response of the LOQ.
2) Furthermore, carryover was continuously monitored within every batch when applicable, using the results of the analyte-free samples in each batch, which were always injected following a ULQ calibrant, both at the beginning and end of the injection sequence. In all accepted batches, the analyte and IS responses of the analyte-free samples met the interference acceptance criteria described in SOP LAP-1009 (Calibration Curve Preparation and Acceptance Criteria). No significant carryover was observed in all accepted batches, nor was anticipated using this bioanalytical method.
3) Of the seven identified subjects in the active comparator group, samples for Subjects (b) (6) were reassayed for incurred sample reproducibility (ISR). An additional two subjects ((b) (6)) were reassayed in an exploratory fashion upon initial observation of non-zero rifabutin sample in the active comparator treated subjects. The remaining two subjects ((b) (6)) could not be reassayed as their samples were no longer covered by stored sample stability data.

TABLE 4. Reassayed Plasma Rifabutin Concentrations at Visit 3

USUBJID (b) (6)	Analyte	Original Concentration (ng/mL)	ISR or Reassay Concentration (ng/mL)
RHB-105-02-	Rifabutin	6.33	6.14
RHB-105-02-	Rifabutin	6.23	6.13
RHB-105-02-	Rifabutin	13.84	14.10
RHB-105-02-	Rifabutin	2.10	BLQ*
RHB-105-02-	Rifabutin	132.36	127.00 and 132.71*

BLQ: Below the limit of quantitation (2.00 ng/mL)
Subject samples reassayed as part of the investigation were assayed in duplicate

With the exception of one subject ((b) (6)) the ISR and exploratory reassay confirmed the presence of rifabutin in the subject samples. For Subject (b) (6), the original value was close to the lower limit of assay quantitation (LLOQ, i.e. 2.00 ng/mL) and therefore not surprising given the allowable precision and accuracy of the assay at the LLOQ (<20% at the LLOQ).

3. Did all subjects randomized to rifabutin have detectable rifabutin levels?

With respect to subjects randomized to Talicia (with rifabutin), at Visit 3, a total of 17 subjects had rifabutin samples below the LLOQ. One subject had their sample drawn at approximately 661 hours ((b) (6)) after their last dose and therefore values below the LLOQ (BLOQ) are not implausible given the half-life of the drugs in question. However, in all 17 subjects noted here, **all** analytes were reported as BLOQ and therefore indicate no treatment was administered to the subject within the last day (or more) prior to Visit 3. A PK analysis population, which excluded subjects who had no evidence of drug administration where all analytes were BLOQ, was considered in the efficacy and safety analysis.

4. Were all control subjects checked for rifabutin plasma levels?

If by control subjects the Agency is referring to active comparator treated subjects, then yes, this document summarizes all active comparator treated subjects in RHB-105-02 with Visit 3 samples assayed for rifabutin.

5. Clarify how the blinded study drugs were packaged and distributed to subjects.

The required quantity of blinded study drug, Talicia (RHB-105) or active comparator, was encapsulated in opaque capsules to prevent identification at (b) (4). The study drug was packaged in high-density polyethylene bottles with (b) (4) closures. Each of the bottles contained 100 capsules (adequate study drug for approximately 8 days). The study drug was manufactured in accordance with Good Manufacturing Practices guidelines.

Bottles were packed in drug kits containing 2 bottles per kit and identified with a 4-digit number to maintain the blind (b) (4). The study drug was labeled in accordance with US FDA requirements for clinical trial supplies. The packaging company provided the IWRS with an unblinded list of kits for each treatment group: RHB-105 and active comparator. The kit list remained blinded to the sponsor, the CRO personnel and the study site personnel.

Upon first subject screened at any individual site, the IWRS generated a shipment with a pre-determined number of kits to be shipped to the site. The kit numbers were non-sequential. Upon receipt to the site, the study site personnel acknowledge the receipt of the kits through the

system. At visit 1, once a subject was confirmed to meet all inclusion/exclusion criteria, the site personnel randomized the subject through the IWRS system. The system assigned a unique kit number to each subject randomized and study drug kits could not be reassigned to other subjects.

A complete kit was dispensed to the subject on Visit 1 including two bottles of study drug with instructions to take 4 capsules 3 times per day every 8 hours with food. A bottle of 20 tablets of Riboflavin 50mg was also dispensed with instruction of taking one tablet a day.

Subjects were requested to bring study drug to the clinic on Visit 3 for accountability, PK assessment and re-dispensing. If visit 3 was the end of the dosing period, then study accountability and PK assessment were performed at that time.

For each of the seven active comparator treated subjects, one or more Talicia treated subject (including rifabutin) visited the respective sites and a Talicia treated subject preceded each seven aforementioned subjects with rifabutin in active comparator samples.

Conclusion

The investigation suggests rifabutin and metabolite in the clinical samples may have been introduced via a cross-contamination (e.g. via a transfer pipette) at some point during sample processing as 25-O-desacetylrifabutin is not a known impurity of the drug product, bioanalytical carryover was not observed during the LCMS/MS assay and reassay confirmed the original results and drug was packaged and dispensed in accordance with cGMP and drug supply was reconciled for each of the impacted subjects.

We have performed a sensitivity analysis excluding those patients in the active comparator group with rifabutin and *H. pylori* eradication was successful in the RHB-105 arm (n=228) vs active comparator (n=220), 84% vs. 58% with a p value of <0.0001. A statistical analysis of the primary endpoint based on the PK analysis population, defined as subjects in the FAS that have demonstrable presence of any components of investigational drug at Visit 3, or for whom the pk assessment at Visit 3 was performed more than 250 hours after the last dose of randomized study drug before this assessment period, also favored Talicia. This analysis demonstrated the efficacy of the RHB-105 arm (n=207) vs active comparator (n=184), 90% vs 65% with a p value <0.0001. Finally, sensitivity analysis performed in the PK population where, as in the first sensitivity analysis, patients from the active comparator group that have a measurable rifabutin concentration at Visit 3 were excluded from the analysis. This analysis supported the efficacy of the RHB-105 arm (n=207) vs active comparator (n=184), 90% vs 66% with a p value <0.0001. These findings confirm the results demonstrated in the ITT analysis.

6. Given that for TALICIA, omeprazole concentrations do not appear to be greater in patients with impaired CYP2C19 function, does the Agency agree that TALICIA can be administered to patients with all CYP2C19 phenotypes, including Asian patients?

FDA Response: It is premature to answer this question given the limited information provided in the meeting package. Please include all relevant data on patients' baseline CYP2C19 genotypes, PK, efficacy, and safety in the NDA. The final decision on whether RHB-105 can be given to patients with all CYP2C19 phenotypes, including Asian patients will be made during the NDA review.

RedHill Response: We thank the Agency for their response and understand that this will be a review issue.

7. Given that in the pivotal efficacy trial RHB-105-02, TALICIA was recommended to be administered with food, largely to mitigate the risk of gastrointestinal upset associated with amoxicillin and rifabutin, does the Agency agree that TALICIA should be administered with food?

FDA Response: We are in general agreement about administering RHB-105 with food. However, the final decision on this issue will be made during the NDA review.

RedHill Response: RedHill thanks the Agency for its response.

8. In view of the (1) excellent safety and tolerability profile in our studies (See Appendix 11.2 ISS Safety Tables) (2) the extensive post-marketing experience with TALICIA's active components and (3) the relatively brief dosing regimen of 14 days, RedHill believes that a standard post-marketing pharmacovigilance strategy is appropriate. Does the agency agree?

FDA Response: Your rationale for a standard post-marketing pharmacovigilance strategy is noted. A final decision about the adequacy of your proposal will be made during the NDA review

RedHill Response: We understand that this decision will be made during the NDA review.

9. Proposal 1: Bottles of 84-count.

A complete treatment cycle of TALICIA comprises 168 capsules, which would be packaged in two 84-count bottles placed in a single box. The proposed commercial 84- count bottles would be proportionally smaller than the 100-count bottles currently placed on stability in order to retain the same or decreased headspace. The proposed bottle will be made of the same materials and resins and will have the same diameter opening and same cap as the larger bottle. The protective properties are unchanged; therefore, RedHill proposes to use the stability data generated for the 100- count bottles to support the shelf life of the 84-count bottles.

CMC Question 1. Does the Agency agree with this proposal?

FDA Response: The proposal to provide the drug product in 2 bottles with 84 capsules each appears reasonable. You should provide information to show that the two container-closure systems have comparable protective properties, e.g., similar water vapor permeation rates. Additionally, an in-use study should be carried out to show that bottles that have been opened, i.e., bottles from which the (b) (4) *seal has been removed (but where the screw cap is still used) will continue to provide protection for the capsules that remain in the bottle. This should cover at least 14 days in case the patient opens both bottles at the start of treatment.*

RedHill Response: Redhill thanks the Agency for this response and will ensure that the in-use study will be conducted.

10. (b) (4)

(b) (4)

11. CMC Question 3. Will the Agency accept new stability data during the review period and if yes, what would be the latest time prior to the PDUFA date that this new data would be accepted?

FDA Response: Provided that at the time of NDA submission, per the Q1A(R2) recommendation, at least 12 months of long-term and 6-months accelerated stability data for 3 batches of which at least 2 are at pilot scale are included, we would be willing to accept additional stability data not later than 30 days after the NDA is submitted.

RedHill Response: Thank you. The Q1A(R2) recommendation will be followed.

Additional Comments:

To facilitate the review, we recommend that you include the following in the NDA:

RedHill Response: We acknowledge the requests below from the Agency but would ask for some further clarification for two items:

1. An interactive table detailing all the tables and figures featured in the main clinical efficacy and the safety sections of the NDA. The table should contain the following:

a. *Title of the table or figure in the NDA*
b. *A page number hyperlinked to the location of the table or figure*
c. *A hyperlink to the SAS code (and/or macros) used to create the table or figure*
d. *Names of the datasets used to create the table or figure (hyperlinks are useful but not necessary).*
e. *For derived (analysis) datasets used to conduct your analyses, you should indicate the tabulation datasets from which the information was derived.*

Clarification request:
RedHill assumes that such an interactive table should focus on all tables and figures included in ISS and ISE sections. Is this assumption correct? If yes, we propose to include this table as an appendix to the overall note to reviewer to be located in Module 1. Is that acceptable?

2. *An interactive table that contains a list of all subjects for whom you submitted a CRF, narrative, or adjudication package(s) and*

An algorithm which clearly explains how findings from all primary and secondary analyses were produced (e.g. dataset, variable names and programming steps used). This will minimize potential discrepancies between FDA reviewers' and Applicant's analyses.

Clarification request:
RedHill plans to include pertinent analysis datasets supported by the data tabulation data definition (define.xml) files and reviewer's guide documents, for all pivotal studies and ISS/ISE sections supporting this NDA. Does the above fulfill the Agency request?

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

/s/

SUMATHI NAMBIAR
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