CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215888Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 111675

MEETING MINUTES

Mycovia Pharmaceuticals, Inc.
Attention: Thorsten Degenhardt, PhD
Chief Operating Officer
4505 Emperor Blvd., Suite 300
Durham, NC 27703

Dear Dr. Degenhardt:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for oteseconazole capsules, 150 mg (VT-1161).

We also refer to the teleconference between representatives of your firm and the FDA on November 4, 2020. The purpose of the meeting was to discuss the chemistry, manufacturing, and controls (CMC), nonclinical and clinical data to be submitted in support of a New Drug Application for oteseconazole.

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, Senior Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B

Meeting Category: Pre-NDA

Meeting Date and Time: November 4, 2020, 2:00 PM to 3:00 PM EST

Meeting Location: Teleconference

Application Number: IND 111675

Product Name: Oteseconazole capsules, 150 mg

Indication: [redacted] (b) (4)

Sponsor Name: Mycovia Pharmaceuticals, Inc.

Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Sumathi Nambiar, MD, MPH

Meeting Recorder: Gregory DiBernardo

FDA ATTENDEES

Sumathi Nambiar, MD, MPH	Director
Dmitri Iarikov, MD, PhD	Deputy Director
Abimbola Adebowale, PhD	Associate Director for Labeling
Thomas Smith, MD	Clinical Team Leader
Caroline Jjingo, MD, MPH	Clinical Reviewer
Avery Goodwin, PhD	Clinical Microbiology Team Leader
Lynette Berkeley, PhD, MT (ASCP)	Clinical Microbiology Reviewer
Terry Miller, PhD	Pharmacology/Toxicology Team Leader
Owen McMaster, PhD	Pharmacology/Toxicology Reviewer
Maureen Dillon-Parker, MS, RAC	Chief, Project Management Staff
Carmen DeBellas, RPh, PharmD	Chief, Project Management Staff
Gregory DiBernardo	Senior Regulatory Project Manager
Philip Colangelo, PharmD, PhD	Clinical Pharmacology Team Leader
Henrietta Abodakpi, PhD	Clinical Pharmacology Reviewer

Cheryl Dixon, PhD	Biostatistics Reviewer
Dorota Matecka, PhD	Product Quality Team Leader
Molly Lee, PhD	Product Quality Reviewer
Elsbeth Chikhale, PhD	Biopharmaceutics Team Leader
Kevin Wei, PhD	Biopharmaceutics Reviewer
Christine Falabella, PhD	Process and Facilities Reviewer

SPONSOR ATTENDEES

Mycovia Pharmaceuticals Inc.

Stephen Brand, PhD	Chief Development Officer
Thorsten Degenhardt, PhD	Chief Operating Officer
Erik K. Pacyniak, PhD, DABT	Principal Scientist, Nonclinical Safety Assessment
David Wirth, PhD	Director, Process Chemistry
Mark Coffin, PhD	Senior Director, Pharmaceutical Development and Management
Rachel Gee	Vice President, Project Management and Regulatory Affairs
Jocelyn Jennings, MS, RAC	Senior Director, Regulatory Affairs and Quality Assurance
Sarah Katherine Elmore	Regulatory Coordinator
(b) (4)	Consultant: (b) (4)
(b) (4)	CMC Regulatory Consultant: (b) (4)

1.0 BACKGROUND

Mycovia Pharmaceuticals, Inc. (Mycovia) submitted a meeting request on August 25, 2020, for a type B, Pre-NDA meeting to discuss the CMC, nonclinical and clinical data to be submitted in support of an NDA (b) (4) FDA granted a November 4, 2020, teleconference. Mycovia submitted their meeting package on October 1, 2020. Preliminary meeting comments to the questions outlined in the meeting package were issued to Mycovia on October 30, 2020, and are noted as FDA Response. On November 3, 2020, Mycovia informed FDA, via email communication, that they accepted FDA responses to questions 1-5, 7-8, 10, 14, 16, 18, and 21. Mycovia provided a slide presentation to aid in the discussion of question 11 (attached). A record of the discussion at the meeting is provided below under Meeting Discussion.

2.0 DISCUSSION

Question 1: Does FDA agree that items discussed at the CMC EOP 2 (Type B) Meeting held June 12, 2018 and included in the July 5, 2018 meeting minutes have been adequately addressed for NDA submission?

FDA Response:
It appears that items previously discussed at the CMC EoP2 meeting have been adequately addressed for NDA submission. Final determination will be made based on review of the information submitted in the NDA.

Mycovia acknowledged, no further discussion was needed.

Drug Substance Specifications

Question 2: Does FDA agree to the proposed drug substance release and stability specifications? Specifically, the tests proposed for release and stability of NDA registration and stability batches and commercial drug substance. See Section 15.1.1.1 and Table 4 for the proposed specifications and Table 6 for batch analyses data.

FDA Response:
The proposed drug substance release and stability specifications appear reasonable.

Mycovia acknowledged, no further discussion was needed.

Question 3: Does FDA agree to the approach for establishment of impurity specifications and evaluation of potential impurities in the drug substance? See Section 15.1.1.2 and Table 5.

FDA Response:
Yes, the approach for establishment of impurity specifications and evaluation of potential impurities in the drug substance is reasonable.

Mycovia acknowledged, no further discussion was needed.

Drug Substance Comparability

Question 4: Does FDA agree with the bridging evaluation performed to support transfer of the drug substance manufacturing process used during Phase 2/3 to the planned NDA commercial drug substance manufacturing process?

FDA Response:
We agree with the bridging evaluation performed to support transfer of the drug substance manufacturing process used during Phase 2/3 to the planned NDA commercial drug substance manufacturing process.

Mycovia acknowledged, no further discussion was needed.

Drug Product Specifications

Question 5: Does FDA agree to the proposed drug product release and stability specifications? Specifically, the tests proposed for release and stability of NDA registration and stability batches and commercial drug product. See Section 15.1.2.1 and Table 7 for the proposed specifications and Table 8 for batch analyses data. Please note that the dissolution method and specification will be updated based upon FDA's feedback on the newly proposed dissolution method and specification. Reference is made to Appendix A for a detailed discussion of the new dissolution method and specification.

FDA Response:
In general, the proposed drug product specification for release and stability appears reasonable. We recommend that you include a test (b) (4) *with a proposed acceptance criterion to be used for release and on stability. Alternatively, you may provide in the NDA, justification based on sufficient data from representative batches for* (b) (4) *testing. Final determination regarding the proposed drug product specification (tests, analytical procedures and acceptance criteria) for release and stability will be made during the NDA review.*

Mycovia acknowledged, no further discussion was needed.

Drug Product Dissolution Development Report

Question 6: Does FDA agree that the newly proposed Tier 1 and Tier 2 dissolution methods are appropriately discriminating and can be used for release and stability testing of drug product? Reference is made to Section 15.1.2.2 for a summary of the proposed methods, and to Appendix A for additional details to support approval of the methods.

FDA Response:
We acknowledge that in the meeting package you provided responses to FDA preliminary comments dated August 7, 2020, to your submitted dissolution method development dated May 1, 2017 (Seq. 0072). You also submitted additional data/information to support a newly proposed dissolution method. We recommend that the dissolution method development report for the newly proposed dissolution method be submitted separately under an IND amendment to allow sufficient time for our review of the acceptability of the new method. In the cover letter for the IND amendment, clearly state that a review from the Division of Biopharmaceutics is requested. Note that it takes approximately 3 months for FDA to provide feedback.

Meeting Discussion:
Mycovia stated they understood that FDA would need more time to review the newly proposed dissolution method and that a dissolution method development report should be submitted. Mycovia plans to submit the full dissolution method development report to the IND within a month.

Mycovia asked if FDA had any comments on their plan to use a two-step dissolution approach. FDA stated that the surfactant use may not be ideal and the newly proposed dissolution method needs to be further examined. FDA emphasized that in the dissolution method development report, Mycovia needs to submit information regarding the age of the drug product and capsules being used in manufacturing. Fresh capsules should be used, and dissolution data at each time point (including the early stage) should be collected. FDA stated that they would need more time to review and will provide additional comments to Mycovia.

Mycovia stated they were still working on the completion of the 12-month long-term stability data on the planned registration batched. Mycovia asked if FDA could agree to providing feedback on the full dissolution method development report within 3 months of the receipt of these reports. FDA stated that they would try to meet this timeline but could not commit to a specific date for completing the review until the full report is submitted.

Drug Product Comparability

Question 7: Does FDA agree that the bridging evaluation of the formulation and manufacturing process used for Phase 3 clinical batches, NDA registration stability batches, and the proposed commercial formulation and manufacturing process/scale is acceptable and that further comparability evaluations and a bioequivalence study are not required to support the changes?

FDA Response:
Your bridging approach appears reasonable. The acceptability of the information and data to support the bridging between the drug product used for Phase 3 clinical batches, NDA registration stability batches, and the proposed commercial drug product will be determined during review of the NDA. Submit all detailed supportive information in your NDA for review.

Mycovia acknowledged, no further discussion was needed.

Drug Product Executed Batch Records

Question 8: Does FDA agree to the selection of executed drug product batch records selected for submission in the NDA?

FDA Response:
The proposal to provide executed drug product batch records for Phase 3 Clinical (Batch #ZWVG) and 1 Registration (Batch #CDGCK) in the NDA submission is reasonable; however, during the NDA review, additional batch records from drug product batches mentioned in IND submissions (e.g., Seq. 0077) or the NDA submission may be requested for further assessment and should be available if requested.

Mycovia acknowledged, no further discussion was needed.

Drug Product Stability

Question 9: Does FDA agree that additional drug product stability data may be submitted to the NDA during the NDA review period? Does FDA agree that Mycovia can amend the NDA within 75 days of the NDA submission file date and that the amendment will not result in an extension of the PDUFA date?

FDA Response:
In general, the NDA should include at least 12 months long-term and 6 months accelerated stability data for three primary stability batches at the time of NDA submission, as recommended in ICH Q1A (R2). Any additional stability data for these batches may be submitted within 30 days of the initial NDA submission. Your proposal for the stability data package submission is unclear. Based on the information provided in the meeting background package, it appears that 12-month long-term stability data should be available at the planned NDA submission time (April 2021) since the three registration drug product batches were manufactured in December 2019. Please explain and clarify the type and amount of stability data that you intend to include in the initial NDA submission.

Meeting Discussion:
Mycovia stated they plan to submit the NDA in April 2021 and expect to receive the 12-month long-term stability data for the 3 registration batches in April 2021. Mycovia explained that the availability of the 12-month stability data was dependent on the contract manufacturing organization and in the event a delay was encountered in receiving or processing the data, requested that FDA agree to the 12-month long term data being submitted within 30 days of the initial NDA submission. Mycovia further explained the initial NDA submission would include the 6-month accelerated and 9-month long-term stability data from three representative batches, and stress conditions data. Only the additional 12-month long-term stability data update for three representative batches would be delayed and submitted within 30 days of the initial NDA submission. FDA noted that Mycovia's plan was acceptable and agreed to the late submission.

Question 10: Mycovia believes that the results of the nonclinical studies conducted with oteseconazole are adequate to support the submission of an NDA for oteseconazole. Does FDA agree that the completed nonclinical development program adequately supports the marketing registration of oteseconazole for [redacted] (b) (4) RVVC [redacted] (b) (4) [redacted] (b) (4)?

FDA Response:
The package appears adequate to support the submission of the NDA, but it would be premature to comment on the adequacy to support marketing registration without reviewing the final study reports and a better understanding of the exophthalmos, opacity and other eye abnormalities observed in the pre- and postnatal study. Please submit the final study reports for all completed studies to the IND. Please also submit any draft reports for the studies which showed ocular findings; pdf format is acceptable for submission to the IND.

Mycovia acknowledged, no further discussion was needed.

Pre and Postnatal Development Study

Question 11: In the recently completed Pre- and Postnatal Development study in rats (study number 1234001) (report in preparation), preliminary data (see Section 15.2.2) indicate an increased incidence of abnormal findings in the eyes of the offspring of dams treated with 7.5 mg/kg/day of oteseconazole from Gestation Day 6 through parturition and until Lactation Day 20. To better understand the nature and significance of these eye findings, a targeted study to evaluate potential effects on postnatal ocular development in rat offspring following maternal oral administration of oteseconazole during pregnancy and lactation is ongoing. Mycovia believes the eye findings observed at 7.5 mg/kg/day will be described in the package insert in Section 8 and would not be considered an approval issue. Does FDA agree?

FDA Response:
The eye findings will likely be described in the package insert. It would be premature to comment on the significance of these findings until we are able to review the final study data. The final study report of the targeted study to evaluate postnatal ocular development may help to better characterize the risk to the offspring of patients who are treated with oteseconazole.

Meeting Discussion:
Mycovia directed FDA to the slide deck and explained their rationale and plan to characterize the findings from the pre- and postnatal development (PPN) studies. They hypothesize that the oteseconazole-induced effects on rat hemostasis and inflammation were responsible for the mortality, and eye findings observed in the rat pups and that the effects are rat and strain dependent.

Mycovia believed this because the incidence and severity of the findings were highest in CRL SD rats and there were no similar findings in other species. FDA noted that they appreciate Mycovia's intent to further characterize these eye findings and mortality. FDA agreed with Mycovia's plan to evaluate multiple rat strains to complete the investigation of the mortality and eye findings. FDA stated they would review draft reports of the completed PPN studies when they become available. FDA noted they would consult FDA ophthalmology experts and would work to address any additional questions from Mycovia. FDA stated that it would be important to have historical controls for the strains in the PPN studies. FDA also stated they were willing to provide input on the study protocol for the multi-strain PPN study before the study was initiated. Mycovia stated the study was planned for December 2020, and asked if FDA could provide input. FDA agreed to provide input but noted that protocol review typically takes 4-6 weeks and asked Mycovia to consider this timeline when submitting the request.

2-Year Rat Carcinogenicity Study

Question 12: In the recently completed oral 2-year carcinogenicity study in rats (study number 2130-018; report in preparation), treatment-related neoplastic findings were observed in the thyroid gland (follicular cell adenomas and carcinomas), liver (hepatocellular adenomas and carcinomas), testes (Leydig cell adenomas), and uterus (granular cell tumor). Mycovia believes the development of tumors in rats following chronic treatment with a nongenotoxic compound are secondary to hepatic microsomal enzyme induction (thyroid and liver tumors) and increased concentrations of circulating luteinizing hormone (Leydig cell tumors). See details on this study in Section 15.2.3. Accordingly, the mechanism for induction of thyroid, liver, testes and uterus tumors in the rat is considered to be a species-specific effect and does not represent a risk to humans. Does FDA agree?

FDA Response:
It would be premature to conclude that the tumors in the thyroid, liver, testes and uterus in the rat constituted a species-specific effect and do not represent a risk to humans. The data will be reviewed by the Executive Carcinogenicity Assessment Committee upon submission to the Agency and the human relevance of these findings will be discussed at that time.

Meeting Discussion:
Mycovia inquired if the final mouse and audited draft rat carcinogenicity study reports could be submitted to the IND for FDA Executive Carcinogenicity Assessment Committee (ECAC) review prior to the NDA submission. FDA stated that if the material is submitted in the coming months they should be able to obtain ECAC input prior to the NDA submission. FDA stated that they could not comment on any positive carcinogenicity findings at this time since they have not seen any data.

Proposed Indication

Question 13: Does FDA agree with the proposed integrated effectiveness analysis plan (See Appendix B) (b) (4)

FDA Response:
(b) (4)

Therefore, we have the following comments with respect to (b) (4) *your proposed indications:*

(b) (4)

Please also note the following:

(b) (4)

For the reasons cited above, the data obtained from Study 006 and Studies 011, 012 017 would be most supportive of (b) (4) *recurrent vulvovaginal candidiasis* (b) (4) (b) (4) *indication. As designed, your clinical development program does not appear to provide sufficient evidence to support* (b) (4) (b) (4) *indications.*

Meeting Discussion:

Mycovia asked why FDA did not agree (b) (4)

(b) (4)

POST MEETING NOTE:

Regarding an indication (b) (4) *the Division continues to have concerns* (b) (4) (b) (4) *If Mycovia wishes to seek this indication, this will be evaluated during the NDA review.*

(b) (4)

Mycovia also inquired about obtaining an indication (b) (4)
The FDA responded that it was premature to discuss the indications at this time and it would best be addressed during the NDA review.

Dosing Regimen

Question 14: Based on the Phase 3 studies CL-011 and CL-012 together with the non-inferiority efficacy data generated in the Phase 3 CL-017 study, does FDA consider a 2-day loading dose regimen (600 mg Day 1, 450 mg Day 2), followed by 11 weekly doses acceptable to treat subjects with RVVC?

FDA Response:
We will defer commenting on the acceptability of the data generated to support the proposed dosing regimen for RVVC until we have had the opportunity to review the NDA.

Mycovia acknowledged, no further discussion was needed.

Question 15: (b) (4)

FDA Response:
We refer you to our response to Question 13.

Meeting Discussion:
Please see Meeting Discussion for Question 13 for discussion of studies CL-017 and CL-004.

Pregnancy Claims

Question 16: In the absence of new data indicating to the contrary, does FDA agree with the label claim, (b) (4)

(b) (4)

?

FDA Response:
We cannot commit to including such a statement in labeling at this time considering that there are several women for whom the status of their pregnancy outcomes is unknown. There are also outstanding nonclinical reproductive toxicology data that need to be reviewed by the Agency.

Mycovia acknowledged, no further discussion was needed.

Hepatic and Renal Studies

Question 17: Enrollment into the hepatic and renal impairment PK studies (studies CL-019 and CL-020 respectively) is taking significantly longer due to challenges associated with the ongoing COVID-19 pandemic for these at-risk populations. Due to the recruitment and enrollment issues related to the continuing COVID-19 pandemic, would FDA agree to waiving these studies for approval of oteseconazole?

FDA Response:
We do not agree with waiving the hepatic and renal impairment PK studies. If the NDA is approved, these studies will need to be conducted postmarketing.

Meeting Discussion:
Mycovia inquired if FDA would accept a reduced number of subjects for both the hepatic and renal impairment PK studies because of the challenges with enrollment related to the COVID-19 pandemic. Mycovia outlined their efforts to enroll such subjects, noting that after 6 months, they have enrolled only two. Although FDA stated that if the NDA is apporved, these PK studies could be done postmarketing, Mycovia still had concerns that enrollment of a sufficient number of subjects with hepatic and renal impairment could not be accomplished and/or would take too long. FDA stated that they understood the circumstances imposed by the pandemic and requested Mycovia submit a proposal to the IND that outlines the reduced number of subjects with renal and hepatic impairment for each study protocol, and a justification on how this dataset could still provide meaningful data. FDA noted they would consider a reduction from 8 to 6 subjects (i.e., per each renal or hepatic impairment group) for these studies.

Regarding submission of renal and hepatic study reports at the 120-day safety update time period, FDA stated that this would not provide adequate time for review. FDA stated that if the study reports were not available for the initial NDA submission and the application is approved, Mycovia could submit the study reports postmarketing.

TQT Study

Question 18: Enrollment into CL-018 (TQT study) is taking significantly longer due to challenges associated with the ongoing COVID-19 pandemic. Given the continuing impact of the pandemic, if enrollment continues to be a challenge at the time Mycovia plans to submit the NDA, would FDA agree to accepting the final report for the TQT study at the time the 120-day safety report is due and that the amendment will not result in an extension of the PDUFA date?

FDA Response:
Submission of the final report for the TQT study at the time that the 120-day safety is due is acceptable.

Mycovia acknowledged, no further discussion was needed.

NDA Safety Analysis

Question 19: Does FDA agree with the proposed integrated analysis plan for pooling safety data from the oteseconazole clinical program for the NDA?

FDA Response:
Your proposed pooling of safety data in the ISS appears acceptable. There appears to be an error in Table 2-1 on p. 8 of the ISS Statistical Analysis Plan. Please clarify that Study VMT-VT-1161-CL-004 will not be included in the Phase 2/3 RVVC patient pool.

Please note that we request that all laboratory values be reported using standard US conventional units, including but not limited to the following examples:

- *Albumin: g/dL*
- *Bilirubin (total, direct, indirect): mg/dL*
- *Blood urea nitrogen (serum): mg/dL*
- *Electrolytes (e.g., chloride, potassium, sodium): mEq/L*
- *Calcium: mg/dL*
- *Cholesterol/triglycerides: mg/dL*
- *Glucose: mg/dL*
- *Hemoglobin: g/dL*
- *Serum creatinine: mg/dL*
- *We note that alkaline phosphatase, AST, ALT, and creatine kinase are reported by U/L in both the US and abroad*

When conducting your safety analyses, please also include Grade 2 (moderate) severity treatment-emergent adverse events by treatment group, in addition to the Grade 3 (severe) or Grade 4 (life-threatening) treatment-emergent adverse events that you plan to present, as stated on page 26 of 54 of your ISS SAP.

Meeting Discussion:
Mycovia stated that Study CL-004 would not be included in the Phase 2/3 RVVC patient pool, but would be included in the Phase 2 non-RVVC patient pool in the integrated safety analysis. Mycovia confirmed that laboratory values would be reported using US conventional units. FDA agreed.

Mycovia asked FDA why they requested that Grade 2 treatment emergent adverse events (AEs) be included in the safety analysis. FDA responded that including Grade 2 AEs, as found in the DAIDS toxicity grading scale, would be helpful in the analysis of laboratory data, particularly in the evaluation of hepatic toxicity. FDA agreed to Mycovia's plan to present Grade 3 and 4 AEs in a primary safety analysis and to present a separate analysis of Grade 2, 3, and 4 AEs.

Population PK

Question 20: In the EOP2 meeting package submitted to FDA on July 12, 2017 Mycovia discussed the results of our PK model to predict the half-life of oteseconazole. Mycovia has decided not to expand the PK modeling with the data from our Phase 3 studies since it will not provide new information relevant for the NDA. Does FDA agree that results from expanded PK modeling is not required to support our NDA?

FDA Response:
We do not agree. We recommend that you expand the PK modeling to include PK and other relevant patient data (e.g., demographic, laboratory, efficacy and safety) from your Phase 3 studies.

Meeting Discussion:
Mycovia asked for clarification on what additional information would be gained by adding the Phase 3 PK data to the population PK analysis. FDA stated that in addition to establishing the half-life estimation, the population PK analysis would also help understand PK covariate and exposure relationships for the purpose of efficacy and safety determinations. FDA noted that currently, the only study that was included in the analysis for RVVC patient data was Study 006 and the additional patient data from the Phase 3 data would further enrich the initial analysis. Mycovia stated that the benefit of including Phase 3 PK data into the population PK model would be minimal and would only delay submission of the NDA. FDA recommended Mycovia submit their rationale for not incorporating Phase 3 data into the population PK model.

Regulatory

Question 21: Does FDA agree that an Advisory Committee Meeting is not needed for oteseconazole?

FDA Response:
At this time, we cannot comment on the need for an advisory committee meeting. A preliminary decision on the need for an advisory committee meeting will be communicated to you in the NDA filing letter.

Mycovia acknowledged, no further discussion was needed.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed and a number of agreements were reached for late submission as captured below.

- 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.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

  - *FDA agreed to accept the final report for the TQT study at the time the 120-day safety report is due and that the amendment will not result in an extension of the PDUFA date.*
  - *FDA agreed to the submission of 12-month long term data for three representative drug product stability batches within 30 days of the initial NDA submission. Mycovia confirmed the initial NDA submission would include stress conditions data, and the 6-month accelerated, and 9-month long-term data from three representative drug product batches.*

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

NDA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY
NDA NUMBER: LATE COMPONENT - QUALITY

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*.[1] 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 FDA.gov.[2]

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[3] and Pregnancy and Lactation Labeling Final Rule[4] 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.

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- 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*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

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

- Description of all trials to be included in the ISS. Please provide a tabular listing

of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[5]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[6]

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*

[5] http://www.fda.gov/ectd
[6] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

Submissions, and the associated conformance guide, *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*.[7]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Mycovia to submit:

- the final mouse and audited draft rat carcinogenicity study reports to the IND for ECAC review prior to the NDA submission;
- a detailed noninferiority justification to the IND for FDA review and input; and
- the updated Dissolution Method Development report for oteseconazole capsule.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue Meeting Minutes	FDA	December 4, 2020
Submit Meeting Slides to IND file	Sponsor	Within 1 month of teleconference

6.0 HANDOUT

- Mycovia November 3, 2020, Meeting Slides

5 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

[7] https://www.fda.gov/media/85061/download

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
12/02/2020 06:33:51 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111675

MEETING MINUTES

Mycovia Pharmaceuticals, Inc.
Attention: Thorsten Degenhardt, Ph.D.
Vice President
4505 Emperor Boulevard
Suite 300
Durham, NC 27703

Dear Dr. Degenhardt:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VT-1161 (oteseconazole).

We also refer to the meeting between representatives of your firm and the FDA on June 12, 2018. The purpose of the meeting was to discuss Chemistry, Manufacturing, and Controls.

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, please contact Anh-Thy Ly, Regulatory Business Process Manager at (240) 402-1001.

Sincerely,

{See appended electronic signature page}

Balajee Shanmugam, Ph.D.
Branch Chief, Branch III
Division of New Drug Product I
Office of New Drug 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:	End of Phase 2
Meeting Date and Time:	June 12, 2018, 1:00PM-2:00PM Eastern Standard Time
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	111675
Product Name:	VT-1161
Indication:	Treatment of recurrent vulvovaginal candidiasis
Sponsor/Applicant Name:	Mycovia Pharmaceuticals, Inc.
Meeting Chair:	Balajee Shanmugam, Ph.D.
Meeting Recorder:	Anh-Thy Ly, Pharm.D.

FDA ATTENDEES

Elsbeth G Chikhale, Ph.D.	Biopharmaceutics Quality Assessment Lead, ONDP, OPQ
Balajee Shanmugam, Ph.D.	Branch Chief, ONDP, OPQ
Raymond Frankewich, Ph.D.	Drug Substance Reviewer, ONDP, OPQ
Sateesh Sathigari, Ph.D.	Process Reviewer, Office of Process and Facilities, OPQ
Owen G McMaster, Ph.D.	Pharmacology/Toxicology Reviewer, Division of Anti-Infective Products (DAIP)
Terry Miller, Ph.D.	Pharmacology/Toxicology Team Leader, DAIP
Anh-Thy Ly, Pharm.D.	Regulatory Business Process Manager, OPQ

SPONSOR ATTENDEES

Stephen Brand, Ph.D.	Vice President of Clinical Development
Rachel Gee	Director of Project Management and Regulatory Affairs
Thorsten Degenhardt, Ph.D.	Vice President of Project Management
Mark Davis Coffin, Ph.D.	Senior Director of Pharmaceutical Development
David Wirth, Ph.D.	Director of Process Chemistry

1.0 BACKGROUND

On March 29, 2018 Mycovia Pharmaceuticals, Inc. submitted a Type B End of Phase 2 meeting request to discuss Chemistry, Manufacturing, and Controls for VT-1161. The FDA Office of Pharmaceutical Quality granted a Face to Face meeting on April 13, 2018.

VT-1161, also called lanosterol demethylase or sterol 14α demethylase, is a selective inhibitor of fungal CYP51. The proposed indication for VT-1161 is [redacted]

FDA sent Preliminary Comments to Mycovia Pharmaceuticals, Inc. on June 5, 2018.

2. DISCUSSION

Question 1: *Does the Division agree that the starting materials selected and their proposed specifications are acceptable to support registration and commercial batches of VT-1161 API?*

FDA Response to Question 1: Yes, we agree that the proposed compounds [redacted] are acceptable as starting materials to produce Phase 3 clinical, registration, and commercial-scale batches of VT-1161 API. We recommend that you continue to monitor potential carry-through of the starting materials and their impurities to VT-1161 as the process is scaled up and as additional suppliers are qualified. In addition, we recommend that you establish the [redacted] impurity as a specified impurity in the specification [redacted] and not just as an unspecified impurity.

Discussion 1:
Mycovia Pharmaceuticals, Inc. agrees with the FDA's recommendation. Mycovia will track the limit of the [redacted] impurity [redacted] and move forward with the plan.

Question 2: *Does the Division agree with the proposed PGI control strategy for VT-1161?*

FDA Response to Question 2: In general, we agree. We recommend that you attempt to isolate the [redacted] impurity and perform a spike-and-purge study using it, since this was [redacted] for which it appears no purge evaluation was performed.

Discussion 2:
Mycovia provided background information regarding the significant number of PGI investigations and indicated that [redacted] is available but it has not been possible to develop an analytical procedure capable of detecting it thus far. Mycovia plans to follow up the work on PGI to demonstrate that the impurity is controlled. Alternatively, the FDA recommended that Mycovia provide justification why it cannot be done. Additionally, the FDA recommended Mycovia provide a case on purge of related compound and perform a spike and purge study if possible. Mycovia accepts FDA's recommendation to submit a justification if they are unable to do so but plans to continue to explore methods and provide justification.

Question 3: *Does the Division agree with the specifications used for VT-1161 API Phase 3 batches and proposed changes for API registration and commercial batches?*

FDA Response to Question 3: Yes, we agree. We do recommend that you retain the limit (b) (4) since Q3D ICH Guidance recommends that (b) (4) should be controlled at (b) (4) ppm or less in oral dosage forms (b) (4) In addition, clarification should be provided for the (b) (4)-ppm limit (b) (4) since it is not listed in Q3C ICH Guidance. It is acknowledged that both (b) (4) are listed (b) (4)

Discussion 3:
Mycovia accepts the FDA's recommendation regarding the specification (b) (4)
The FDA recommends that Mycovia establish a limit (b) (4) and provide justification for the proposed limit. Mycovia agrees with the FDA and will provide justification on how the limit was set in the NDA.

Question 4: *Does the Division agree with the proposed drug substance stability program?*

FDA Response to Question 4: Yes, we agree.

Discussion 4: Mycovia acknowledged the FDA preliminary response and no further discussion was requested during the meeting.

Question 5: *Does the Division agree with the proposed plans for the development of a discriminating dissolution method, development of an enzymatic method for assessment of cross-linking of the gelatin capsule shells, and the establishment of an appropriate specification for assessing product performance?*

FDA Response to Question 5: Yes, we agree with your proposed plans. Please refer to the Additional Biopharmaceutics Comments, for the dissolution information/data to be submitted in your NDA regarding the development and validation of an optimal, discriminating dissolution method and setting of the dissolution acceptance criterion. It is noted that the currently proposed use of surfactant in the dissolution medium and the selection of a high paddle rotation speed (*Apparatus 2, 75 rpm*) should be fully justified with supporting data. It is also noted that based on the information provided in your meeting package, your proposed acceptance criterion of Q= (b) (4)% at 45 minutes is not appropriate and we recommend that a tighter dissolution acceptance criterion be set for the evaluation of the Phase 3 clinical batches.

Discussion 5:
The FDA stated that it is common to have tier 1 and 2 dissolution testing for capsules that might have problems with cross linking.
Mycovia explained their justification of the paddle rotation speed and the impact it has on dissolution. The FDA recommends that Mycovia provides a dissolution development

report per the Additional Biopharmaceutics Comments noted below, in order for the FDA to review and provide feedback. The FDA noted that the acceptance criterion will only be finalized during review of the NDA and recommends that Mycovia collects full profile dissolution data from the registration batches prior to the NDA submission.
Mycovia stated the registration batches were set on Q= (b) (4)% 45 minutes based on the limited number of batches. The FDA commented that the dissolution method has not been agreed upon at this point and that generally the dissolution acceptance criterion is expected to be set at Q= (b) (4)%. The FDA also recommended collecting a full dissolution profile on clinical batches. Mycovia agreed to collect full profile dissolution data and set the acceptance criterion accordingly in the NDA.

Question 6: *Does the Division agree with the proposal to use dissolution testing to demonstrate comparability between development, clinical, registration, and commercial batches of VT-1161 capsules?*

FDA Response to Question 6: We do not have sufficient information to agree with your proposal. Please provide a detailed comparison of the VT-1161 capsules used in the clinical studies and the proposed commercial product and include qualitative and quantitative composition, and differences in the manufacturing site, process and equipment. Note that the information needed (*in vitro dissolution testing or in vivo BA/BE*) to support the bridging between the development, clinical, registration, and commercial drug product, would depend on the level of change regarding formulation, process, equipment, and/or manufacturing site.

Discussion 6:
Mycovia stated that they plan to perform bridging of the information during scale up at different manufacturing site using the same equipment. The FDA stated that the proposal is reasonable, however, it will depend on the level of changes.

Question 7: *Does the Division agree with the stability protocol, product specification, and duration of stability data that will be included in the NDA to support product registration?*

FDA Response to Question 7:

We agree with your proposed stability protocol. In addition, we recommend that you perform appropriate studies to demonstrate the package integrity and suitability (moisture permeation, open dish study if the drug substance is hygroscopic, etc.). Your proposal to include in the NDA stability data on three registration batches after storage for 12 months under long term storage condition and 6 months under accelerated storage conditions follows ICH recommendations and, therefore, is considered acceptable.

In general, we concur with the proposed tests in the finished drug product specification. However, the product specification, including the proposed acceptance criteria, is a review issue and will be evaluated during the NDA review. Please include a limit (b) (4) in the proposed specification based on the batch analysis test results. Also, we recommend

that related substances (impurities and/or degradation products) are listed per ICH format, i.e., specified, (identified and unidentified), unspecified and total impurities/degradation products. Note that the proposed limits for impurities/degradation products should be adequately qualified as per ICH Q3B Guidance.

Regarding the dissolution test, the proposed acceptance criterion is not appropriate and we recommend that you collect complete dissolution profile data (15, 20, 30, 45, and 60 minutes) at initial and long term stability at 25°C/60% RH storage conditions.

Discussion 7: Mycovia acknowledged the FDA preliminary response and no further discussion was requested during the meeting.

Question 8: *Does the Division agree with the use of* (b) (4) *in the event the final commercial image is not defined prior to manufacture of the registration batches?*

FDA Response to Question 8: We do not have sufficient information to evaluate your proposal. Note both Phase 3 and registration batches should be representative of the commercial drug product formulation, which includes components and composition of the hard gelatin capsule shell and the marking ink. The capsule appearance for the registration batches may differ from the 'to be marketed' drug product but the hard gelatin capsule shell formulation and ink composition should be the same as planned for the commercial drug product or additional studies may be needed.

Discussion 8:
In response to Mycovia's question on possibly using (b) (4) for batches to test, the FDA stated that the capsules planned to be used in Phase should be the same (such as composition, size, shape and other attributes) as the to-be marketed product. The FDA recommends using capsules from the same manufacture but a different color instead of changing manufacture or else it may need bridging. Mycovia acknowledged the concern with using (b) (4) and accepts the FDA's recommendation. Mycovia will continue to work on this issue and update the FDA at the Pre-NDA meeting.

Question 9: *Does the Division agree with the plans for manufacture of the registration and initial commercial batches of VT-1161 capsules?*

FDA Response to Question 9:

Registration Batches:

We agree with your plan for manufacturing the 2 out of 3 registration batches of at least (b) (4)% of the anticipated commercial batch size. You have stated (b) (4)

(b) (4) is manufactured (b) (4) This approach appears acceptable provided that (b) (4) should include adequate testing to demonstrate (b) (4)

Production Batches:

You have stated that production batches of the drug product will be manufactured with the equipment's of the same design and principle. You have also stated that the commercial batch size will not exceed (b) (4) the registration batch size. This is acceptable. However, for the commercial scale, the proposed (b) (4) scale up size (b) (4) (b) (4) when compared to the registration batch (b) (4) size (b) (4) Hence, discuss the scale up approach and provide a justification in the NDA with supporting development data (b) (4)

The (b) (4) production batch will be manufactured (b) (4)

Discussion 9:

Mycovia expressed concerns (b) (4) The FDA recommended Mycovia to explain the plan for scale up and provide justification in the NDA. Mycovia asked if the FDA will consider (b) (4) (b) (4) The FDA stated that the plan can be considered but will require adequate justification. Mycovia stated they will explore the size options they have for the lots.

Additional Biopharmaceutics Comments:

We have the following recommendations regarding the dissolution information/data that should be provided in the NDA submission.

1) ***Dissolution Method:*** *Provide the dissolution method development and validation report. The report should include the following information.*

   a. *Solubility data for the drug substance over the physiologic pH range.*
   b. *Detailed description of the dissolution test parameters (i.e., equipment/apparatus, type and volume of media, agitation/rotation speed, pH, temperature, etc.). Include a narrative of why these parameters were selected and how the test conditions were optimized (e.g., sink conditions, stability considerations). If applicable, the type and the amount of surfactant added to the dissolution medium, and/or the use of strength dependent dissolution methods should be justified. The dissolution–time profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3*

consecutive time-points) is reached; initial sampling time points typically include 10, 15, 20, 30, 45, 60, 90 and 120 min. At least twelve samples should be used per testing variable.

c. *A list of the critical material attributes (CMA) and critical process parameters (CPP) affecting dissolution.*
d. *Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test (variant) products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). If available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent to the reference (target) product. Provide f_2 (profile similarity) values between target and aberrant products/conditions.*
e. *Summary figures and tables showing mean and %RSD cumulative amount of drug released at each sampling timepoint, and if applicable, f_2 values.*
f. *Validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).*

2) ***Dissolution Acceptance Criterion****: For the selection of the dissolution acceptance criterion for the proposed drug product, the following points should be considered.*

a. *In setting the dissolution acceptance criterion of the product, use the dissolution profile data of the pivotal PK and clinical batches (n = 12) at the initial time of manufacture and during long-term storage for the duration of the trial(s). In addition, the dissolution profiles of the registration batches at initial and long-term stability at 25°C/60% RH storage conditions should be considered.*
b. *The selected sampling time point for the dissolution acceptance criterion should be where Q= (b) (4) % drug dissolution occurs.*
c. *Include in the dissolution report, a detailed justification of the selection of the proposed dissolution acceptance criterion.*

3) Supporting Data: *The following detailed experimental data should be submitted to support the dissolution method development and setting of acceptance criterion:*

a) *As much individual vessel data as possible in the narrative portion of the report, particularly regarding investigation of selection of equipment, media, agitation speed, etc.*
b) *Analysis datasets in ". xpt" format, and their define files. The dataset should contain individual vessel data for all sampling timepoints.*
c) *Batch release and stability dissolution data presented graphically. The plot(s) of individual vessel data for the clinical and stability batches should include data at release, time zero stability time point, and over the duration of stability testing under long-term storage conditions.*

If you would like the FDA to evaluate the acceptability of the proposed dissolution method before the NDA submission, please submit the complete dissolution method development report with complete data to the IND as an IND Amendment, and in the cover letter for the IND Amendment

clearly state that a review from the Division of Biopharmaceutics is requested. Please note that, while acceptability of the dissolution method can be determined during the IND or NDA stage, evaluation of the dissolution acceptance criterion will be performed during the NDA review stage. Until the dissolution acceptance criterion is accepted by the FDA, we recommend that you collect complete dissolution profile data (individual, mean, SD, figures, 10, 15, 20, 30, 45 minutes, etc.) for the pivotal clinical and registration batches of the proposed drug product at batch release and during the stability studies.

3.0 SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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/

BALAJEE SHANMUGAM
07/05/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111675

MEETING MINUTES

Viamet Pharmaceuticals, Inc.
Attention: Thorsten Degenhardt, Ph.D.
Vice President, Project Management
4505 Emperor Blvd., Suite 300
Durham, NC 27703

Dear Dr. Degenhardt:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VT-1161 capsules.

We also refer to the meeting between representatives of your firm and the FDA on August 18, 2017. The purpose of the End-of-Phase 2 meeting was to discuss the Phase 3 development program for VT-1161 capsules for the treatment of recurrent vulvovaginal candidiasis.

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: B

Meeting Category: End-of-Phase 2

Meeting Date and Time: August 18, 2017, 10:00 AM-11:00 AM

Meeting Location: White Oak Campus, Building 22, Room 1313

Application Number: IND 111675

Product Name: VT-1161 Capsules

Indication: Treatment of recurrent vulvovaginal candidiasis (RVVC)

Sponsor Name: Viamet Pharmaceuticals, Inc.

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
Thomas Smith, M.D.	Clinical Team Leader
Caroline Jjingo, M.D., M.P.H.	Clinical Reviewer
Yuliya Yasinskaya, M.D.	Clinical Team Leader
Edward Weinstein, M.D., Ph.D.	Clinical Reviewer
Shabnam Naseer, M.D.	Clinical Reviewer
Lynette Berkeley, Ph.D., MT (ASCP)	Clinical Microbiology Reviewer
Terry Miller, Ph.D.	Pharmacology/Toxicology Team Leader
Owen 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

John Lazor, Pharm.D.	Director
Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader

Sonia Pahwa, Ph.D.	Clinical Pharmacology Reviewer

Division of Biometrics IV

Cheryl Dixon, Ph.D.	Biostatistics Reviewer

SPONSOR ATTENDEES

Viamet Pharmaceuticals, Inc.

Robert Schotzinger, M.D., Ph.D.	Chief Executive Officer
Amir Tavakkol, Ph.D.	Chief Development Officer
Stephen Brand, Ph.D.	Vice President of Clinical Development
Thorsten Degenhardt, Ph.D.	Vice President of Project Management (PM)
Rachel Childers Gee	Director of PM and Regulatory Affairs
John Jett, Ph.D.	Clinical Development Scientist
Karen Person, M.S.	Clinical Trial Manager
Susan McDaniel, B.S.N., MJ	Clinical Trial Manager

Consultant

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

1.0 BACKGROUND

Viamet Pharmaceuticals, Inc. (Viamet) submitted a meeting request on May 11, 2017, for an End of Phase 2 (EOP2) meeting to discuss the Phase 3 development program for VT-1161 for the treatment of RVVC. FDA granted an August 18, 2017 meeting. Viamet submitted their meeting package on July 12, 2017, and FDA issued preliminary meeting responses to Viamet on August 16, 2017 (appended). Viamet informed FDA via telephone call on August 17, 2017, that they planned to discuss Questions 2, 4, 5, 6, and 7 during the meeting, and confirmed that no further clarifications were needed for all other responses.

2.0 DISCUSSION

Following introductions from both Viamet and FDA the following discussion occurred.

Question 2: Given the lack of genotoxicity of VT-1161 and the lack of pre-neoplastic or neoplastic lesions observed in the rat 26-week toxicology study, does the Division agree that the 26-week carcinogenicity study of VT-1161 in transgenic mice would support the marketing registration of VT-1161 for the treatment of RVVC, and that the full study report from the 104-week carcinogenicity study in rats could be provided post-approval?

FDA Preliminary Meeting Response:
The request to defer the submission of the final study report for the conventional rat carcinogenicity study may be acceptable, but you have not indicated when a draft will be available. Please provide a Gantt chart indicating when you plan to provide the final transgenic study report, the draft 2 year rat report and the final 2 year rat study report.

Meeting Discussion:
Viamet explained that the audited draft report for the 2-year rat carcinogenicity study and the final report for the 26-week transgenic mouse carcinogenicity study would be included in the NDA. The final report for the 2-year rat carcinogenicity study is expected to be available during the NDA review. The FDA indicated this plan was reasonable.

Post-meeting Note: After further internal discussion, FDA requests that Viamet plan to submit the final report for the 2-year rat carcinogenicity study no later than 30 days after the NDA submission. As these studies tend to generate large amounts of data, adequate review time will be required

Question 4: Does the Division agree that, upon receipt of acceptable data from a human radio-labeled mass balance study confirming VT-1161 is minimally excreted in human urine, the requirement to conduct a separate PK study in patients with impaired renal function could be waived?

FDA Preliminary Meeting Response:
We would like to have further discussion with you regarding your proposed plan for radio-labeled mass balance study with respect to your question about waiver of a renal impairment PK study of VT-1161. Even though the drug is minimally excreted in the urine, a reduced design renal impairment study may be required.

Meeting Discussion:
The FDA asked how Viamet planned to conduct the radio-labeled mass balance study given the long half-life of VT-1161.

Viamet explained they were considering a study design to be conducted in two phases:

- The initial phase of the study would be conducted with subjects in an inpatient unit for a defined period of time (e.g., 21-28 days).
- The second phase of the study would be conducted with subjects returning to the clinical site on a periodic basis.

Viamet stated they believed this study design would allow for extrapolation of data between the follow-up visits. FDA asked Viamet to submit a draft protocol for review.

The FDA stated the evaluation of the PK of VT-1161 in subjects with renal impairment would be addressed once the data from the radio-labeled mass balance study was reviewed.

Question 5: Does the Division agree that, pending review of the data generated in the studies outlined above, the proposed late-stage clinical pharmacology development plan would adequately support the marketing registration of VT-1161 for the treatment of RVVC?

FDA Preliminary Meeting Response:
The proposed clinical pharmacology plan appears to adequately support submission of the NDA. Whether the proposed clinical pharmacology development plan would be adequate to support approval of VT-1161 will be determined upon review of the data.

We have following additional comments regarding your proposed clinical pharmacology development plan:

- We recommend that you conduct a study to evaluate the effect of food intake on the bioavailability of VT-1161 with the final to-be-marketed tablet formulation before the initiation of the Phase 3 trials.
- In the proposed Phase 3 trials, include documentation in the Case Report Forms for the time to ingestion of the main meal relative to when VT-1161 was dosed.
- You have provided the concept sheets for Drug-Drug Interaction (DDI) studies in the meeting package; we may provide additional comments once the full protocols are submitted.
- Provide the full protocol for the DDI study with the Gastric pH Modulator, omeprazole, for our review and comment.
- We recommend that you exclude patients with moderate and severe renal and/or hepatic impairment from the proposed Phase 3 trials. Patients with mild renal and/or hepatic impairment may be enrolled.
- Based on in vitro studies, there is a potential for DDI between VT-1161 and CYP2C8 substrates. Therefore, we recommend you exclude subjects taking sensitive CYP2C8 substrates (e.g., repaglinide) from the trials.
- You need to collect a baseline pre-dose blood sample for the determination of VT-1161 concentration.

Meeting Discussion:
Regarding the FDA's preliminary response recommending the evaluation of food effect before Phase 3 trials, Viamet stated that the final formulation for the RVVC indication was a capsule and that a similar capsule formulation was evaluated in fed and fasted cohorts in the single ascending dose study (VMT-VT-1161-CL-001). Viamet noted the following:

- The results of this study demonstrated a positive food effect, so Viamet has instructed study participants in all subsequently conducted clinical studies to take study drug with food.
- Viamet was planning to conduct a comparative bioavailability study with the final capsule formulation before Phase 3, and then would proceed with the formal food effect study in parallel with Phase 3 trials using the capsule drug product from a larger batch of the to-be-marketed formulation.

The FDA acknowledged Viamet's plan but reiterated that Viamet conduct the food effect study prior to the initiation of Phase 3 trials.

Regarding FDA's preliminary comment to document in the Case Report Form the time of study drug administration relative to ingestion of the main meal of the day, Viamet noted the following:

- They are committed to educating subjects and investigators on the importance of dosing VT-1161 within 30 minutes of each subject's largest meal of the day and the importance of being consistent with the meal selected for each dose to optimize compliance.
- Given that the largest meal of the day may vary from subject to subject, Viamet has learned in the previous Phase 2a and Phase 2b studies that overall compliance and adherence to dosing instructions was improved if the subject is given the ability to choose their largest meal for dosing.

The FDA stated they understood Viamet's rationale and agreed with the approach stressing dosing instructions that promote dosing consistency and suggested these instructions be further detailed in the protocol to better aid the investigator.

Regarding FDA's preliminary response for excluding subjects taking sensitive CYP2C8 substrates, Viamet stated that in vitro CYP inhibition and induction data were used as inputs for a mechanistic static model for each CYP isoform. Viamet noted the following:

- The only isoform implicated for potential clinical drug interaction assessment was CYP3A4. A clinical drug interaction study for CYP3A4 was conducted using midazolam as the substrate and showed no clinically relevant inhibition of midazolam metabolism.
- In the mechanistic static model calculations, CYP2C8 did not meet the cutoff for clinical assessment (i.e., AUCR values were 1.01 to 1.03).

The FDA stated the mechanistic static model requires assumptions that may not always be accurate. FDA requested Viamet to provide clarification about the assumptions used in mechanistic static model calculations. FDA stated they would review these data and would decide whether CYP2C8 substrates as acceptable concomitant medications for subjects in future studies.

Clinical and Statistics (Pivotal):
Question 6: Does the Division agree with the Phase 3 trial design as proposed in the submitted protocol, including the level of documentation required for establishing a history of RVVC, and the definition of resolution of acute VVC prior to randomization to VT-1161 or placebo?

FDA Preliminary Meeting Response:
Overall, we find your proposed Phase 3 trial design acceptable. To reduce the likelihood that a patient self-reported episode of acute VVC is not a misdiagnosed case of non-candidal vulvovaginitis, we recommend that at least two of the three reported episodes of acute VVC that are required within a 12 month period for confirmation of a history of RVVC be laboratory confirmed, as was done in the Phase 2b RVVC trial (Inclusion Criterion 1).

Meeting Discussion:
The Sponsor inquired as to whether the Division would find it acceptable if they were to modify the eligibility criterion (Inclusion Criterion 3) requiring documentation of at least one positive confirmatory laboratory test of acute VVC in the 24 months prior to screening. The Division agreed that this would be acceptable. Therefore, as in the Phase 2b RVVC trial, at least two laboratory confirmed episodes of acute VVC (including the episode confirmed at screening) would be required in the past 12 months to establish subject eligibility for the proposed Phase 3 trials.

Question 7: Does the Division agree with the proposed statistical analysis plan for the Phase 3 studies including the proposed primary and secondary endpoints, the definition of the Intent-to-Treat population, and methods for handling missing data?

FDA Preliminary Meeting Response:
The proposed primary and secondary endpoints and proposed analyses, definitions of analysis populations, and method for control of type I error are acceptable. However, the method for handling missing data in the primary analysis, i.e., treating missing data as no event, is not acceptable. The currently proposed Sensitivity Analysis 3 which treats missing data as an event is recommended as the primary analysis. We therefore recommend that all efforts be taken to minimize the amount of missing data and that all subjects be followed through Week 48 as much as possible. The remaining sensitivity analyses proposed are acceptable for assessing the impact of missing data on the results.

Meeting Discussion:
Viamet explained that of the patients who dropped out of the Phase 2b RVVC study, 70% did so due to relocation or other reasons not related to adverse events or tolerability issues. Therefore, they did not consider it to be optimal to treat subjects with missing data as failures. Viamet proposed to handle the missing data for the Phase 3 trials using a multiple imputation approach for the primary analysis. The FDA acknowledged Viamet's proposal and recommended that a revised statistical analysis plan for the Phase 3 trials including this proposal be submitted for review.

3.0 OTHER IMPORTANT MEETING INFORMATION

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.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of

IND applications and marketing applications. The implementation of data standards 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. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

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.

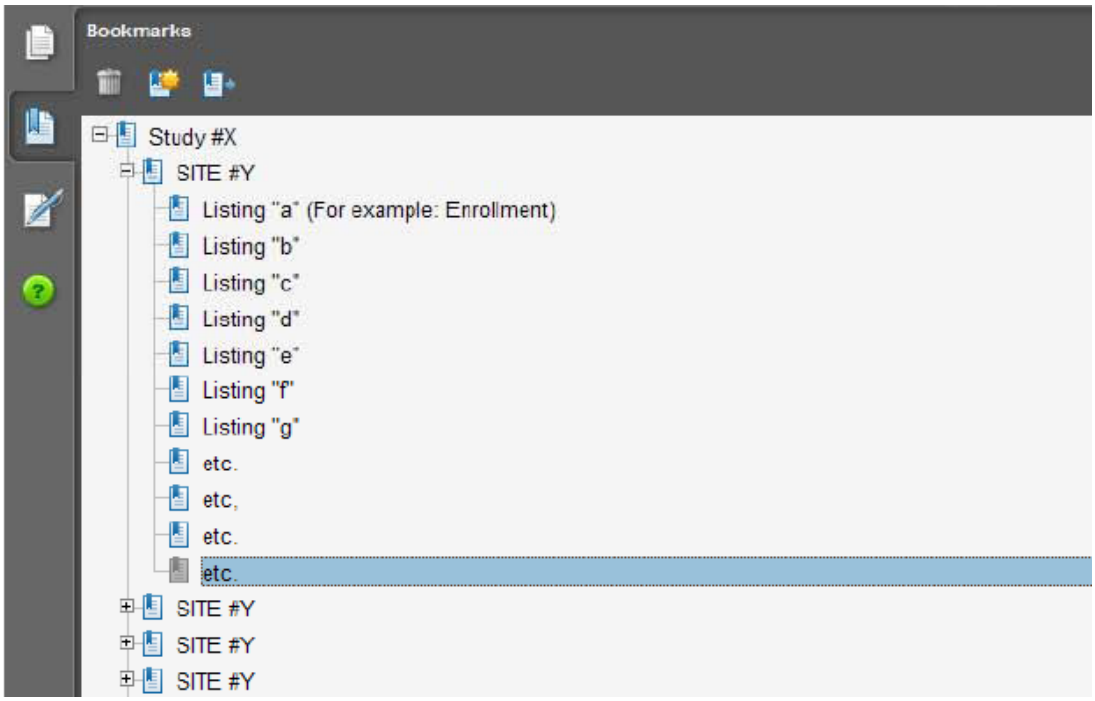
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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.

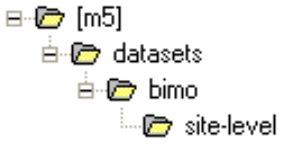
Attachment 1

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 Item[1]	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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue Meeting Minutes	FDA	September 15, 2017

5.0 ATTACHMENT

FDA August 16, 2017, Preliminary Meeting Responses

From:	DiBernardo, Gregory
To:	"Thorsten Degenhardt"
Subject:	FDA Communication: IND 111675-VT-1161-Viamet-FDA Preliminary Meeting Responses for 8/18/17 Meeting
Date:	Wednesday, August 16, 2017 1:23:24 PM
Attachments:	FINAL FDA Preliminary Meeting Response for 08.18.17 Meeting.pdf
Importance:	High

Hello Dr. Degenhardt,

I would like to provide the FDA Preliminary Meeting Responses for the meeting scheduled for August 18, 2017, regarding IND 111675. Please be aware that there will **be no paper/hardcopy communication** to follow this email communication.

Please let me know if after reviewing this material, if you plan to reduce the number of questions for discussion, change the format of the meeting to a teleconference, or cancel the scheduled meeting.

Thank you,

Gregory F. DiBernardo
Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products

10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: August 16, 2017

To: Thorsten Degenhardt, Ph.D. Vice President, Project Management	**From:** Gregory F. DiBernardo Regulatory Project Manager
Company: Viamet Pharmaceuticals, Inc.	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	**Fax number:** (301) 796-9882
Phone number: (b) (6)	**Phone number:** (301) 796-4063
E-mail: (b) (6)	

Subject: Preliminary Meeting Comments [IND 111675]

Total no. of pages including cover: 5

Comments:
FDA Preliminary Meeting Responses regarding your July 12, 2017, submission to IND 111675, VT-1161 capsules.

Confirm receipt of this communication at: gregory.dibernardo@fda.hhs.gov

Document to be mailed: ☐ YES ☑ NO

Investigational New Drug Application (IND) Number: 111675

Drug Name: VT-1161Capsules

Re: Preliminary Comments in Preparation for the August 18, 2017, Meeting

This document provides our preliminary responses to the questions outlined in your briefing document submitted July 12, 2017, and additional comments in preparation for the upcoming meeting. We are sharing these in advance of the meeting to promote a collaborative and successful discussion. 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 for the meeting, again please contact the RPM. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions.

Nonclinical:
Question 1: Does the Division agree that the proposed late-stage nonclinical development plan adequately supports the marketing registration of VT-1161 for the treatment of RVVC?

FDA Response:
The studies described in the proposed late stage nonclinical development plan will provide sufficient information to determine if submission of an NDA is appropriate. The adequacy of the data to support approval will be determined once the studies are reviewed by the agency.

Question 2: Given the lack of genotoxicity of VT-1161 and the lack of pre-neoplastic or neoplastic lesions observed in the rat 26-week toxicology study, does the Division agree that the 26-week carcinogenicity study of VT-1161 in transgenic mice would support the marketing registration of VT-1161 for the treatment of RVVC, and that the full study report from the 104-week carcinogenicity study in rats could be provided post-approval?

FDA Response:
The request to defer the submission of the final study report for the conventional rat carcinogenicity study may be acceptable, but you have not indicated when a draft will be available. Please provide a Gantt chart indicating when you plan to provide the final transgenic study report, the draft 2 year rat report and the final 2 year rat study report.

Clinical Pharmacology:
Question 3: Does the Division agree that, upon receipt of acceptable data from human drug-drug interaction studies with sensitive P-gp and BCRP substrates, subjects taking known P-gp or BCRP substrates could be enrolled in Phase 3 studies provided they meet all other enrollment requirements?

FDA Response:
Your proposed plan appears to be appropriate conceptually. However, we are not able to provide a definitive answer until you submit the results and/or study reports for the Drug-Drug Interaction studies with sensitive P-gp and BCRP substrates for our review.

Question 4: Does the Division agree that, upon receipt of acceptable data from a human radio-labeled mass balance study confirming VT-1161 is minimally excreted in human urine, the requirement to conduct a separate PK study in patients with impaired renal function could be waived?

FDA Response:
We would like to have further discussion with you regarding your proposed plan for radio-labeled mass balance study with respect to your question about waiver of a renal impairment PK study of VT-1161. Even though the drug is minimally excreted in the urine, a reduced design renal impairment study may be required.

Question 5: Does the Division agree that, pending review of the data generated in the studies outlined above, the proposed late-stage clinical pharmacology development plan would adequately support the marketing registration of VT-1161 for the treatment of RVVC?

FDA Response:
The proposed clinical pharmacology plan appears to adequately support submission of the NDA. Whether the proposed clinical pharmacology development plan would be adequate to support approval of VT-1161 will be determined upon review of the data.

We have following additional comments regarding your proposed clinical pharmacology development plan:

- We recommend that you conduct a study to evaluate the effect of food intake on the bioavailability of VT-1161 with the final to-be-marketed tablet formulation before the initiation of the Phase 3 trials.
- In the proposed Phase 3 trials, include documentation in the Case Report Forms for the time to ingestion of the main meal relative to when VT-1161 was dosed.
- You have provided the concept sheets for Drug-Drug Interaction (DDI) studies in the meeting package; we may provide additional comments once the full protocols are submitted.
- Provide the full protocol for the DDI study with the Gastric pH Modulator, omeprazole, for our review and comment.
- We recommend that you exclude patients with moderate and severe renal and/or hepatic impairment from the proposed Phase 3 trials. Patients with mild renal and/or hepatic impairment may be enrolled.
- Based on in vitro studies, there is a potential for DDI between VT-1161 and CYP2C8 substrates. Therefore, we recommend you exclude subjects taking sensitive CYP2C8 substrates (e.g., repaglinide) from the trials.
- You need to collect a baseline pre-dose blood sample for the determination of VT-1161 concentration.

Clinical and Statistics (Pivotal):
Question 6: Does the Division agree with the Phase 3 trial design as proposed in the submitted protocol, including the level of documentation required for establishing a history of RVVC, and the definition of resolution of acute VVC prior to randomization to VT-1161 or placebo?

FDA Response:
Overall, we find your proposed Phase 3 trial design acceptable. To reduce the likelihood that a patient self-reported episode of acute VVC is not a misdiagnosed case of non-candidal vulvovaginitis, we recommend that at least two of the three reported episodes of acute VVC that are required within a 12 month period for confirmation of a history of RVVC be laboratory confirmed, as was done in the Phase 2b RVVC trial (Inclusion Criterion 1).

Question 7: Does the Division agree with the proposed statistical analysis plan for the Phase 3 studies including the proposed primary and secondary endpoints, the definition of the Intent-to-Treat population, and methods for handling missing data?

FDA Response:
The proposed primary and secondary endpoints and proposed analyses, definitions of analysis populations, and method for control of type I error are acceptable. However, the method for handling missing data in the primary analysis, i.e., treating missing data as no event, is not acceptable. The currently proposed Sensitivity Analysis 3 which treats missing data as an event is recommended as the primary analysis. We therefore recommend that all efforts be taken to minimize the amount of missing data and that all subjects be followed through Week 48 as much as possible. The remaining sensitivity analyses proposed are acceptable for assessing the impact of missing data on the results.

Clinical and Statistics (Overall):
Question 8: Does the Division agree that a safety database of approximately 1,200 total subjects exposed, with 700 subjects exposed at or above the indicated dose and duration, would adequately assess the safety profile of VT-1161 demonstrated to date given the known long half-life of the agent, and that this safety database is sufficient for marketing registration of VT-1161 for the treatment of RVVC?

FDA Response:
We agree that your proposed safety database is likely sufficient, unless an unforeseen safety signal emerges that would necessitate a larger safety database.

Regulatory Pathway/Submissions:
Question 9: Does the Division agree that the VT-1161 marketing application for the treatment of RVVC would receive Priority Review?

FDA Response:
VT-1161 has QIDP designation for the indication of treatment of RVVC and therefore qualifies for priority review.

Question 10: Based on the results of the Phase 2b RVVC study, does the Division agree that the VT-1161 marketing application for the treatment of RVVC can be submitted for review on a rolling basis (i.e., Rolling Review)?

FDA Response:
Rolling review can be requested for products that receive Fast Track or Breakthrough Therapy (BT) designations. This application has Fast Track designation for the treatment of RVVC and is therefore eligible for rolling review. Please submit a formal request for rolling review inclusive of submission plans.

Question 11: Does the Division accept the proposed Study Data Standardization Plan intended for data submitted in support of the marketing application of VT-1161 for the treatment of RVVC?

FDA Response:
Yes, your plan is acceptable.

Additional FDA Comments:

Clinical:
As this is a multi-national study, please submit all laboratory values obtained in SI units as the appropriate U.S. conversions for all Phase 1, 2, and 3 studies for which laboratory data will be submitted. At present, it appears that the total bilirubin levels from your Phase 2b RVVC study were reported in µmol/L, whereas these values are reported as mg/dL in the US.

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUMATHI NAMBIAR
09/12/2017