CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214900Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 107521

MEETING MINUTES

SCYNEXIS, Inc.
Attention: Glen D. Park, PharmD, MSJ
Executive Director, Regulatory Affairs and Quality Assurance
1 Evertrust Plaza
13th Floor
Jersey City, NJ 07302

Dear Dr. Park:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ibrexafungerp (SCY-078) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on June 26, 2020. The purpose of the meeting was to discuss the content and format of a New Drug Application (NDA) for the use of ibrexafungerp to treat 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 Alison Rodgers, Regulatory Project Manager, at 301-796-0797.

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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 26, 2020, 12:00 – 1:00 PM
Meeting Location: Teleconference

Application Number: IND 107521
Product Name: Ibrexafungerp (SCY-078) tablets
Indication: Treatment of vulvovaginal candidiasis
Sponsor Name: SCYNEXIS, Inc.
Regulatory Pathway: 505(b)(1)

Meeting Chair: Sumathi Nambiar, MD, MPH
Meeting Recorder: Alison Rodgers

FDA ATTENDEES

Division of Anti-Infectives

Philip Colangelo, PhD, PharmD	Clinical Pharmacology Team Leader
Maureen Dillon-Parker, MS, RAC	Chief, Regulatory Project Management Staff
Cheryl Dixon, PhD	Statistics Reviewer
Avery Goodwin, PhD	Clinical Microbiology Team Leader
Karen Higgins, ScD	Statistics Team Leader
Dmitri Iarikov, MD, PhD	Deputy Director
Xianbin Li, PhD	Statistics Reviewer
Dorota Matecka, PhD	Product Quality Team Leader
Terry Miller, PhD	Nonclinical Team Leader
Jason Moore, PhD	Clinical Pharmacology Reviewer
Shrimant Mishra, MD, MPH	Medical Officer
Sumathi Nambiar, MD, MPH	Director
Alison Rodgers	Regulatory Project Manager
Jacquelyn Rosenberger, PharmD, RAC	Regulatory Project Manager
Simone Shurland, PhD	Clinical Microbiology Reviewer
Edward Weinstein, MD, PhD	Clinical Team Leader
James Wild, PhD	Nonclinical Reviewer

SPONSOR ATTENDEES

SCYNEXIS, Inc.

David Angulo, MD	Chief Medical Officer
Nkechi Azie, MD	Vice President, Clinical Development
Colleen Johnson, MS, DABT	Pharmacology/Toxicology Consultant
Rajeshwar Motheram, PhD	Vice President, Product Development

Glen Park, PharmD, MSJ	Executive Director, Regulatory Affairs
Mark Taglietti, MD	Chief Executive Officer

Consultants

(b) (4)

[redacted]

BACKGROUND

On April 22, 2020, SCYNEXIS, Inc., submitted a request for a Pre-NDA meeting to discuss the format and content of a New Drug Application for the use of ibrexafungerp to treat vulvovaginal candidiasis (VVC). The meeting was granted on May 4, 2020, and the briefing package was received on May 27, 2020. The Division sent preliminary responses to the Sponsor on June 19, 2020 [appended].

On June 25, 2020, the Sponsor communicated that they planned to discuss Questions 7, 6, 1, 12, 13, and 15 (in this order) during the meeting. These questions are relisted below followed by the discussion at the meeting.

DISCUSSION

Question 7

SCYNEXIS proposes to present the efficacy data from two pivotal studies in women with VVC with supportive information from a Phase 2 dose-ranging study (see draft Integrated Summary of Efficacy Statistical Analysis Plan, Appendix 3). The primary presentation of efficacy in the NDA will be side by side as well as pooled presentations of the two pivotal studies. Information on subgroup analyses will be generated from a pooled dataset of efficacy measures.

Does the Division agree with the proposal for the integrated presentation of efficacy data?

FDA Response: *The primary analysis should utilize individual trial results; subgroup and sensitivity analyses may use pooled data. Any comparative efficacy analyses with pooled data should be based on the placebo-controlled Phase 3 trials; it is not necessary to include the Phase 2 Study 204 in pooled analyses.*

For analyses comparing the proportion of subjects, it is recommended that the odds ratio be presented along with the difference in proportions and corresponding 95% confidence interval.

In the preliminary summary of the Phase 3 Study 306 results, clinical cure rates are higher in Bulgaria than in the US; also, a lower reported treatment-emergent adverse event rate was reported in Bulgaria as compared to the US. These observed

differences between the US and Bulgaria should be discussed in the report of Study 306 and may need to be accounted for in the pooled analyses.

Please note that in the Clinical Studies section of the proposed label, the two Phase 3 studies should be presented separately rather than as pooled efficacy results.

Meeting comments:

- The Sponsor stated that they would provide the information requested by the Division in its response to question 7. The Sponsor explained that they have tried to determine the reasons for the higher cure rate in Bulgaria versus the United States (US) and have not been able to identify any particular factor to explain the difference in the cure rate.
- The Division noted that the differences between Bulgaria and the US would be examined during the review of the NDA.
- The Division requested that the Sponsor present differences in proportions and associated confidence intervals and not just odds ratios in their analysis. The Sponsor agreed.

Question 6

A single clinical dataset of microbiology data in CDISC (SDTM and ADaM) format will be presented for clinical studies enrolling women with VVC (see draft Microbiology Dataset in Appendix 2).

Does the Division agree that the format of the microbiology dataset is appropriate for review?

FDA Response: *The proposed fields/variables for the dataset appear acceptable. It is recommended that the absolute values for the minimum inhibitory concentrations (MICs) and/or zone diameters for the different antimicrobial agents against tested isolates should be provided as part of the dataset. In addition, information on the visit at which the isolate was detected (baseline, end of treatment, TOC), as well as the population (ITT, mITT, CE, ME) and clinical and mycological responses for individual patients by isolate should be provided. We may have additional requests when the NDA is submitted for review.*

Meeting comments:

- The Sponsor stated the information for the microbiology datasets will include the ITT, mITT, per protocol and safety populations. The clinically evaluable (CE) and microbiologically evaluable (ME) populations will not be included. In addition, the Sponsor will combine the ADSL and ADEFF datasets (ADaM format) to create the microbiology dataset. A reviewer's guide will be provided for the datasets. The Division agreed with the proposal.
- The Sponsor queried whether the microbiology dataset could combine clinical and microbiological responses pooled from the corresponding analysis datasets. The Division agreed.

Question 1

A tabulated summary of toxicity studies to support the NDA is provided in Appendix 1.

Does the Division agree that the toxicology program is sufficient to support the VVC indication?

FDA Response: *In addition to the five nonclinical toxicology studies described in Appendix 1 of the Meeting Briefing Document, and the other nonclinical studies submitted to IND 107521 (e.g., safety pharmacology, pharmacokinetic studies, repeated-dose studies in rats and dogs, a genotoxicity battery, a male and female fertility study in rats, embryo-fetal studies in rats and rabbits, and a pre-postnatal study in rats), an in vitro plasma-protein binding study with plasma from test species and humans is recommended to support an ibrexafungerp NDA for VVC. This recommendation is consistent with the ICH M3(R2) Guidance[1]. Plan to submit final study reports for all the nonclinical studies submitted to IND 107521 in your NDA. The adequacy of the submitted nonclinical data to support your NDA for VVC will be based on evaluation of complete results in final study reports.*

Meeting comments:

- The Sponsor stated that the NDA will contain final study reports for all nonclinical studies including in vitro plasma binding studies conducted to support the VVC indication. The Sponsor noted that the final report for the rabbit in vitro plasma-binding study may not be ready for submission with the NDA and asked if the Division would accept submission of this report within 30 days of NDA submission. The Division agreed and clarified that it had located another in vitro plasma-protein binding study in the studies submitted to IND 107521.

Question 12

SCYNEXIS proposes to submit CDISC (SDTM and ADaM) format datasets for the submitted Phase 1, 2 and 3 studies as described in Appendix 5.

Does the Division agree that the proposed structure and content of electronic dataset satisfy requirements for substantial review?

FDA Response: *The submission of SDTM and ADaM datasets is acceptable.*

Meeting comments:

- The Sponsor inquired about the need for a pre-submission meeting. The Division responded that a pre-submission meeting would not be needed and suggested that the Sponsor submit a sample dataset to confirm compatibility with the review tools used by the Division during the review.

[1] ICH Guidance for Industry: M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. https://www.fda.gov/media/71542/download

Question 13

Can the Division confirm whether there is an expectation that the NDA will be reviewed by the Antimicrobial Drugs Advisory Committee?

FDA Response: *It is premature to decide whether an Advisory Committee meeting will be needed. A decision will be made during the review of the application.*

Meeting comments:

- The Sponsor asked if the Division could comment on its thinking regarding the potential for an Advisory Committee (AC) meeting. The Division responded that it cannot say with certainty until the NDA is submitted, but at this time the likelihood of convening an AC meeting is small. However, the Division reserved the option and noted that on occasion a decision to discuss an application at an AC meeting has been made a few months into the review process if an issue is identified that needs input from external experts.

Question 15

SCYNEXIS has submitted a request to amend an Agreed Initial PSP to defer inclusion of adolescent females in the original NDA (IND 107521, Sequence 0165). We were not able to recruit adolescents into the pivotal studies as originally planned. The amended PSP is proposed to provide PK data for adolescent females and extrapolation of efficacy and safety from adult women based on a modelling and simulation study. The conduct of the PK study is delayed due to the COVID-19 pandemic. If the pandemic resolves and the results of the analyses are available within 1 month of acceptance of NDA filing, we propose to submit the results.

Does the Division agree to review the pediatric report if submitted within 1 month of the filing date without extension of the PDUFA date?

FDA Response: *As noted in our response to your proposed amended iPSP, we do not believe that a dedicated PK study in adolescents is necessary. Efficacy may be extrapolated from the adult population to adolescents given the expected similar dosing, PK, and disease characteristics. The need for postmarketing safety studies will depend on the review of safety findings in adult patients. If the PK study is completed, these data can be submitted to the NDA for review as proposed.*

Meeting comments:

- The Sponsor acknowledged the Division's recommendation to extrapolate efficacy from the adult population to adolescents and asked if they need to take any additional action regarding the iPSP. The Division responded that the agreed iPSP is acceptable and remains in place. The Division stated that the Sponsor may submit the data from the pharmacokinetic (PK) study in adolescents during the NDA review. The Sponsor stated that they will initiate the study soon and anticipates that the study could be completed by the end of first

quarter 2021, but there is some uncertainty due to the COVID-19 pandemic. The Sponsor stated that they would provide the data from the study to the Division as soon as possible but requested confirmation that the study would not be needed for NDA submission. The Division confirmed that it would not be needed for NDA submission. The Sponsor stated that they will contact the Division before submitting the study results to determine whether the Division will be able to review during the review cycle.

(b) (4)

The Sponsor noted that it is difficult to enroll adolescents in a VVC study.

Additional meeting comments:

- The Division confirmed that it will accept the Sponsor's proposal for late submission of 12-month stability data on one batch 30 days after NDA submission and stability data for the other two batches 60 days after NDA submission as well as the rabbit in vitro plasma binding study submitted within 30 days of NDA submission.
- The Division reminded the Sponsor that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities. The Sponsor acknowledged this.
- The Sponsor stated that they plan to submit the NDA by the end of September 2020.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The NDA will be a 'Program' application and therefore the content of a complete application was discussed.

- The Division agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
  - 12-month stability data on one batch
  - Rabbit in vitro plasma binding study report
- The Division agreed that the following minor application component may be submitted within 60 calendar days after the submission of the original application:
  - 12-month stability data on two other 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 - NONCLINICAL
NDA NUMBER: LATE COMPONENT - QUALITY

ACTION ITEMS

- The Sponsor may submit the data from the pharmacokinetic (PK) study in adolescents during the NDA review.
- The Sponsor may wish to submit a sample dataset to confirm compatibility with the review tools used by the Division prior to the NDA submission.
- The Division will issue meeting minutes within 30 days.

ATTACHMENT

- The Sponsor's questions and the Division's responses [June 19, 2020].

IND 107521

MEETING PRELIMINARY COMMENTS

SCYNEXIS, Inc.
Attention: Glen D. Park, PharmD, MSJ
Executive Director, Regulatory Affairs and Quality Assurance
1 Evertrust Plaza
13th Floor
Jersey City, NJ 07302

Dear Dr. Park:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ibrexafungerp (SCY-078) tablets.

We also refer to your April 22, 2020 correspondence, received April 22, 2020, requesting a meeting to discuss the content and format of a New Drug Application for the use of ibrexafungerp to treat vulvovaginal candidiasis.

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at 301-796-0797.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker, MS, RAC
Chief, Regulatory Project Management Staff
Anti-Infectives Group 2
Division of Regulatory Operations for
Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 26, 2020, 12:00 – 1:00 PM
Meeting Location: Teleconference

Application Number: IND 107521
Product Name: Ibrexafungerp (SCY-078) tablets
Indication: Treatment of vulvovaginal candidiasis
Sponsor Name: SCYNEXIS, Inc.
Regulatory Pathway: 505(b)(1)

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 26, 2020, 12:00 - 1:00 PM, between SCYNEXIS, Inc., and the Division of Anti-Infectives. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND
On April 22, 2020, SCYNEXIS, Inc., submitted a request for a Pre-NDA meeting to discuss the format and content of a New Drug Application for the use of ibrexafungerp to treat vulvovaginal candidiasis (VVC). The meeting was granted on May 4, 2020, and the briefing package was received on May 27, 2020.

The Division's preliminary responses to the questions listed in the May 27, 2020 briefing package are provided below in preparation for the June 26, 2020 meeting.

DISCUSSION

A. NONCLINICAL

Question 1

A tabulated summary of toxicity studies to support the NDA is provided in Appendix 1.

Does the Division agree that the toxicology program is sufficient to support the VVC indication?

FDA Response: *In addition to the five nonclinical toxicology studies described in Appendix 1 of the Meeting Briefing Document, and the other nonclinical studies submitted to IND 107521 (e.g., safety pharmacology, pharmacokinetic studies, repeated-dose studies in rats and dogs, a genotoxicity battery, a male and female fertility study in rats, embryo-fetal studies in rats and rabbits, and a pre-postnatal study in rats), an in vitro plasma-protein binding study with plasma from test species and humans is recommended to support an ibrexafungerp NDA for VVC. This recommendation is consistent with the ICH M3(R2) Guidance[1]. Plan to submit final study reports for all the nonclinical studies submitted to IND 107521 in your NDA. The adequacy of the submitted nonclinical data to support your NDA for VVC will be based on evaluation of complete results in final study reports.*

B. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

Question 2

(b) (4)

However, SCYNEXIS proposes that the results of this study are not essential for approval and labeling of ibrexafungerp for the treatment of VVC, a drug "intended for single-dose administration" with a "wide therapeutic range," (b) (4) The proposed dose regimen for treatment of VVC is 600 mg, administered as two 300 mg doses 12 hours apart. While not strictly a single dose, we consider the regimen consistent with the guidance on single doses. Additionally, ibrexafungerp has a wide therapeutic range with daily doses of 800 mg for 4 weeks being generally well tolerated.

Does the Division agree that the results of a study in patients with mild to moderate hepatic impairment are not required for the indication of single day treatment of VVC?

FDA Response: *We agree with your proposal to not submit a hepatic impairment study for the acute VVC indication. The labeling language regarding hepatic impairment will be determined following review of the NDA.* (b) (4)

Question 3

SCYNEXIS has completed the drug-drug interaction studies as proposed in the Clinical Pharmacology Request for Advice, to which FDA responded in writing September 16, 2019. In

[1] ICH Guidance for Industry: M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. https://www.fda.gov/media/71542/download

principle, the FDA agreed that the previously conducted and proposed drug-drug interaction (DDI) studies will be adequate for the acute VVC NDA submission. Clinical drug-drug interaction studies with ketoconazole, diltiazem, rosiglitazone, tacrolimus, pravastatin, dabigatran, and pantoprazole have been completed. An in vitro study of ritonavir in human hepatic microsomes has been completed.

Does the Division agree that the drug-drug interaction studies meet the requirements for submission of the VVC NDA?

FDA Response: *Based on the drug-drug interaction (DDI) information that you have provided in the pre-NDA package, we agree that the DDI studies you have conducted are acceptable for submission of the NDA for treatment of acute VVC.*

Question 4

SCYNEXIS has completed a study (SCY-078-116) to evaluate the absorption, distribution, metabolism and excretion (ADME) of oral [^{14}C]-ibrexafungerp. A single 300 mg dose of [^{14}C]-ibrexafungerp as an oral solution was administered to six subjects. During the study, blood samples for determination of ibrexafungerp concentrations in the plasma and metabolite profiling were collected. In addition, urine and fecal samples were collected for mass balance determination and metabolic profiling of ibrexafungerp. There was a mix up of two fecal samples between two specific subjects at one of the collection intervals that could not be uniquely attributed to each of the two subjects. The mean mass balance recovery in the remaining 4 subjects was 89.58%; mean recovery in all 6 subjects was >90.71%.

The results of the mass balance determination show that after administration of [^{14}C]-ibrexafungerp, the total mean recovery (urine + feces) is approximately 89.58% (N=4). The mean radioactivity excreted in the urine was approximately 1.04% in the post-collection period, up to 216 hours post-dose. Most of the radioactivity in the urine was recovered in the first 48 hours following administration. In the feces, the mean radioactivity excreted was approximately 88.38% in the post-collection period, up to 384 hours post-dose. Most of the radioactivity in the feces was recovered within 144 hours. The mean mass balance recovery for all 6 subjects was 90.71%.

The plasma and fecal samples in the study have been evaluated for metabolites. The only major peak in the profile identified belongs to the parent ibrexafungerp that is about 38% of the total drug related entities. Several other fractions are observed that are less than 10%. There is one peak identified in the profile that is slightly above 10% and in the chromatographic method it appears to be near the organic gradient with a broad shoulder appearance, indicating there are two entities eluting at the same time at this peak. Further characterization of this peak is in progress.

Does the Division agree that the ADME study of ibrexafungerp as described is adequate for VVC NDA?

FDA Response: *Based on the information and results described for the ADME Study SCY-078-116, we agree that this study is adequate for submission of the NDA for treatment of acute VVC.*

C. MICROBIOLOGY

Question 5

SCYNEXIS proposes to present surveillance data with >2200 isolates tested between 2003 and 2018 and 750 isolates from VVC clinical efficacy studies (see Section 9.13 Microbiology).

Does the Division agree this information represents a sufficient range of clinically relevant fungi to allow an assessment of the potential clinical efficacy of the antifungal drug for the intended indication?

FDA Response: *We agree that the clinical microbiology information on the clinically relevant fungi and the studies conducted appear acceptable for submission of the NDA.*

Question 6

A single clinical dataset of microbiology data in CDISC (SDTM and ADaM) format will be presented for clinical studies enrolling women with VVC (see draft Microbiology Dataset in Appendix 2).

Does the Division agree that the format of the microbiology dataset is appropriate for review?

FDA Response: *The proposed fields/variables for the dataset appear acceptable. It is recommended that the absolute values for the minimum inhibitory concentrations (MICs) and/or zone diameters for the different antimicrobial agents against tested isolates should be provided as part of the dataset. In addition, information on the visit at which the isolate was detected (baseline, end of treatment, TOC), as well as the population (ITT, mITT, CE, ME) and clinical and mycological responses for individual patients by isolate should be provided. We may have additional requests when the NDA is submitted for review.*

D. CLINICAL

Question 7

SCYNEXIS proposes to present the efficacy data from two pivotal studies in women with VVC with supportive information from a Phase 2 dose-ranging study (see draft Integrated Summary of Efficacy Statistical Analysis Plan, Appendix 3). The primary presentation of efficacy in the NDA will be side by side as well as pooled presentations of the two pivotal studies. Information on subgroup analyses will be generated from a pooled dataset of efficacy measures.

Does the Division agree with the proposal for the integrated presentation of efficacy data?

FDA Response: *The primary analysis should utilize individual trial results; subgroup and sensitivity analyses may use pooled data. Any comparative efficacy analyses with pooled data should be based on the placebo-controlled Phase 3 trials; it is not necessary to include the Phase 2 Study 204 in pooled analyses.*

For analyses comparing the proportion of subjects, it is recommended that the odds ratio be presented along with the difference in proportions and corresponding 95% confidence interval.

In the preliminary summary of the Phase 3 Study 306 results, clinical cure rates are higher in Bulgaria than in the US; also, a lower reported treatment-emergent adverse event rate was reported in Bulgaria as compared to the US. These observed differences between the US and Bulgaria should be discussed in the report of Study 306 and may need to be accounted for in the pooled analyses.

Please note that in the Clinical Studies section of the proposed label, the two Phase 3 studies should be presented separately rather than as pooled efficacy results.

Question 8

SCYNEXIS proposes to present safety data based on populations of subjects / patients exposed to ibrexafungerp tablet (see draft Integrated Summary of Safety Statistical Analysis Plan, Appendix 4). The primary presentation of safety will be pooled data of women with VVC randomized to treatment with the target dose regimen 300 mg administered 12 hours apart on one day (Studies SCY-078-204, SCY-078-303 and SCY-078-306).

Does the Division agree that the proposed primary safety analysis will be acceptable for describing the safety of ibrexafungerp in women with VVC in the label?

FDA Response: *Pooled safety analyses should include the two phase 3 placebo-controlled studies (studies 303 and 306). Safety results from other studies (phase 1 and 2) can be presented separately.*

Question 9

The safety database of ibrexafungerp includes >1200 total exposures to ibrexafungerp: ~375 healthy subjects; ~770 women with VVC at all doses and ~575 treated with 600 mg dose of ibrexafungerp in Phase 2 and 3 studies; and ~100 women in an ongoing study of recurrent VVC. (b) (4)

Does the Division agree that the safety database at the time of NDA submission will be sufficient to support substantive review of the safety of ibrexafungerp in the treatment of VVC?

FDA Response: *Yes, this is acceptable.*

Question 10

The proposed Integrated Summary of Efficacy (ISE) will be composed of pooled subjects treated with the target dose regimen in Study SCY-078-204 and the two Phase 3 studies (SCY-078-303 and SCY-078-306). The Integrated Summary of Safety (ISS) will be composed of all Phase 1 studies and Phase 2 and 3 studies. The combined summaries are expected to be less than 400 pages total. Therefore, SCYNEXIS proposes to cross-reference the Integrated

Summaries of Efficacy (ISE) and Safety (ISS) from Module 5.3.5.3 to Modules 2.7.3 and 2.7.4, respectively. Module 5 will contain the respective Statistical Analysis Plans; the supporting pooled tables, listings and figures; and the pooled datasets in CDISC format.

Does the Division agree that, given the relatively limited content of the summaries, cross-referencing the Module 5.3.5.3 Integrated Efficacy and Safety Summaries to Modules 2.7.3 and 2.7.4 is appropriate?

FDA Response: *This is acceptable.*

Question 11

The ISS will include completed clinical trials as described above. For ongoing studies, all of which will involve either Phase 2 and 3 studies with different dosing regimens (invasive fungal infections and recurrent VVC prevention) than that proposed for treatment of VVC, SCYNEXIS proposes a safety data cutoff date of 60 days before the NDA submission and 60 days before the 120 day safety update due date for ongoing studies. Further, we propose that the safety reporting for these studies will include deaths, serious adverse events, and withdrawals due to adverse events from the ongoing studies, which will not be pooled with the VVC safety database.

Does the Division agree to the proposed content and safety data cutoff dates for ongoing studies for the original NDA submission and the 120 day safety update submission?

FDA Response: *Yes, this is acceptable.*

E. ELECTRONIC DATASETS

Question 12

SCYNEXIS proposes to submit CDISC (SDTM and ADaM) format datasets for the submitted Phase 1, 2 and 3 studies as described in Appendix 5.

Does the Division agree that the proposed structure and content of electronic dataset satisfy requirements for substantial review?

FDA Response: *The submission of SDTM and ADaM datasets is acceptable.*

F. REGULATORY

Question 13

Can the Division confirm whether there is an expectation that the NDA will be reviewed by the Antimicrobial Drugs Advisory Committee?

FDA Response: *It is premature to decide whether an Advisory Committee meeting will be needed. A decision will be made during the review of the application.*

Question 14

Can the Division confirm whether a Risk Evaluations and Management Strategy will be required in the original NDA submission?

FDA Response: *A determination regarding the need for REMS will be made during the review of the application.*

G. PEDIATRIC DEVELOPMENT PLAN

Question 15

SCYNEXIS has submitted a request to amend an Agreed Initial PSP to defer inclusion of adolescent females in the original NDA (IND 107521, Sequence 0165). We were not able to recruit adolescents into the pivotal studies as originally planned. The amended PSP is proposed to provide PK data for adolescent females and extrapolation of efficacy and safety from adult women based on a modelling and simulation study. The conduct of the PK study is delayed due to the COVID-19 pandemic. If the pandemic resolves and the results of the analyses are available within 1 month of acceptance of NDA filing, we propose to submit the results.

Does the Division agree to review the pediatric report if submitted within 1 month of the filing date without extension of the PDUFA date?

FDA Response: *As noted in our response to your proposed amended iPSP, we do not believe that a dedicated PK study in adolescents is necessary. Efficacy may be extrapolated from the adult population to adolescents given the expected similar dosing, PK, and disease characteristics. The need for postmarketing safety studies will depend on the review of safety findings in adult patients. If the PK study is completed, these data can be submitted to the NDA for review as proposed.*

Additional Clinical Pharmacology Comments:

1. *Submit the following information regarding the population PK, exposure-response, and PK/PD datasets in the NDA:*
   - *The PK and PK/PD analysis/parameter datasets in .xpt format for Phase 1 to Phase 3 studies (data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets; the flag for exclusion should be clearly explained in the define.pdf file);*
   - *The NONMEM control streams of the base and final models for population PK analyses;*
   - *The codes (R, SAS, etc.) for PK/PD analyses;*
   - *The output files for the final population PK and PK/PD models if applicable; the standard model diagnostic plots, tables with parameter estimates, and a description of the clinical application of modeling results;*
   - *Include a USUBJID (unique subject ID) column to all the population PK and PK/PD datasets so that we can relate these datasets to the corresponding clinical analysis datasets.*

2. *We recommend the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be*

consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at https://go.usa.gov/xn4qB). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

3. *We recommend you submit all pharmacokinetic (PK) and/or pharmacodynamic (PD) bioanalytical method validation reports and bioanalytical study reports for PK and/or PD assessments used in clinical studies. In addition, we recommend you submit tables summarizing the bioanalytical methods and the life-cycle information using the templates available in the 'Bioanalytical Methods Templates' Technical Specifications Document (https://go.usa.gov/xVsdJ) and submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1.*

Additional Important Application Information

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our May 4, 2020, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

Information on the Program is available at FDA.gov.[2]

In addition, we note that a chemistry pre-submission meeting is scheduled for June 25, 2020. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

PRESCRIBING INFORMATION

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

[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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[5] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[6]. Submit all related manufacturing and testing facilities in eCTD

[5] https://www.fda.gov/media/84223/download
[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* 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]

[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/

MAUREEN P DILLON PARKER
06/19/2020 09:09:05 PM

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
07/16/2020 05:59:38 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107521

MEETING MINUTES

SCYNEXIS, Inc.
Attention: Glen D. Park, PharmD, MSJ
Executive Director, Regulatory Affairs and Quality Assurance
101 Hudson Street, Suite 3610
Jersey City, NJ 07302

Dear Dr. Park:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SCY-078 Tablet.

We also refer to the meeting between representatives of your firm and the FDA on September 21, 2018. The purpose of the meeting was to discuss your development program for the treatment of vulvovaginal candidiasis and prevention 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 Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

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:	September 21, 2018, 10:00 AM – 11:00 AM
Meeting Location:	10903 New Hampshire Avenue, Silver Spring, MD 20903 Building 22, Room 1415
Application Number:	IND 107521
Product Name:	SCY-078 (ibrexafungerp) tablets
Indication:	Treatment of vulvovaginal candidiasis (VVC) and prevention of recurrent vulvovaginal candidiasis (rVVC)
Sponsor/Applicant Name:	Scynexis, Inc.
Meeting Chair:	Sumathi Nambiar, MD, MPH
Meeting Recorder:	Alison Rodgers

FDA ATTENDEES

Division of Anti-Infective Products

Philip Colangelo, PharmD, PhD, Clinical Pharmacology Team Leader
Maureen Dillon-Parker, MS, Chief, Regulatory Project Management Staff
Cheryl Dixon, PhD, Statistics Reviewer
Erika Englund, PhD, Acting Chemistry, Manufacturing and Controls Team Leader
Avery Goodwin, PhD, Acting Clinical Microbiology Team Leader
Karen Higgins, ScD, Statistics Team Leader
Terry Miller, PhD, Pharmacology and Toxicology Team Leader
Jason Moore, PhD, Clinical Pharmacology Reviewer
Shrimant Mishra, MD, Medical Officer
Sumathi Nambiar, MD, MPH, Director
Alison Rodgers, Regulatory Project Manager
Simone Shurland, PhD, Clinical Microbiology Reviewer
Joseph Toerner, MD, MPH, Deputy Director for Safety
James Wild, PhD, Pharmacology and Toxicology Reviewer
Nan Zheng, PhD, Scientific Lead for QT, Office of Clinical Pharmacology

SPONSOR ATTENDEES

Scynexis, Inc.

David Angulo, MD, Chief Medical Officer

Stephen Barat, PhD, Executive Director, Preclinical Development
Glen Park, PharmD, MSJ, Executive Director, Regulatory Affairs and Quality Assurance

BACKGROUND

On June 21, 2017, a Pre-IND meeting was held to discuss the Sponsor's proposed development program for SCY-078 tablets for the treatment of acute VVC and the prevention of rVVC. On June 7, 2018, the Sponsor submitted a request for an End-of-Phase 2 meeting to further discuss the proposed development program to enable submission of a New Drug Application (NDA) for VVC and a supplemental NDA for rVVC. A briefing package was submitted on August 1, 2018.

The Division sent Preliminary Comments to the Sponsor on September 14, 2018. On September 17, 2018, the Sponsor communicated that they planned to discuss the Division's responses to Questions 1, 5, and 8 at the meeting. At the start of the meeting the Sponsor stated that they did not require discussion of Question 5.

The Sponsor's original questions and the Division's preliminary responses to Questions 1 and 8 are provided below followed by meeting discussion points. The remaining questions and responses are appended.

DISCUSSION

Question 1

A tabulated summary of pivotal toxicity studies to support the Phase 3 clinical development and an NDA is provided as Appendix 1. Considering the 20-hour half-life of ibrexafungerp, the dosing regimen of 300 mg BID for one day administered every 4 weeks for recurrent VVC represents a cyclic administration schedule of the same dose regimen used in the acute VVC trials. As such, carcinogenicity studies are not planned for the registration of ibrexafungerp.

Does the Division agree that the toxicology program is sufficient to support the VVC and rVVC indications?

FDA Response:

The nonclinical toxicology studies that have been completed appear to be sufficient in scope to support initiation of Phase 3 trials for the VVC and rVVC indications with the following exceptions:

Study reports for the rat fertility and embryonic development study (Study No.: SCY-TOX-025) and the definitive embryo-fetal studies in rats (Study No.: SCY078-TOX-023) and rabbits (SCY078-TOX-024) will need to be submitted for review before initiating Phase 3 trials.

As recommended in the ICH M3(R2) Guidance[1], if repeated intermittent courses of clinical dosing occur such that the cumulative duration of dosing is > 1 month, nonclinical toxicology studies of 6 months duration may be requested.

A pre-postnatal study in rats will be required to support an NDA for oral ibrexafungerp, which can be conducted concurrently with the phase 3 clinical development trials and submitted in your NDA. Your planned Phase 3 trials should exclude enrollment of pregnant and lactating female patients. Also, women of childbearing potential should be required to practice abstinence or use appropriate contraception to prevent pregnancy.

Nonclinical carcinogenicity studies will not be required for ibrexafungerp unless clinical exposure extends to a cumulative total of 6 months. However, as noted in the ICH S1A Guidance[2], if repeated courses of clinical dosing occur such that a cumulative duration of dosing or exposure extends to 6 months, nonclinical carcinogenicity studies may be requested.

Meeting discussion:

- The Sponsor explained that their Phase 3 studies will utilize six doses of ibrexafungerp during one course of therapy, one dose per week for six weeks. Also, the Sponsor will seek approval for the same course of therapy. Additional courses of therapy are not anticipated. The Sponsor requested confirmation that carcinogenicity studies will not be required for their NDA. The Division agreed that carcinogenicity studies will not be required unless patients require repeated doses of therapy such that the cumulative duration of ibrexafungerp dosing or exposure extends to 6 months or more.

Question 8

SCYNEXIS plans to conduct a single Phase 3 randomized clinical trial of ibrexafungerp in women 12 years of age or older with a diagnosis of recurrent VVC. The draft protocol is summarized in Section 9.14.2 and included in Appendix 5. The proposed trial design will be randomization to one of three treatment arms: ibrexafungerp 300 mg BID for one day every 4 weeks for 6 doses (Day 1 and then Weeks 4, 8, 12, 16 and 20) or placebo every 4 weeks for 6 doses, with an additional 12 weeks of follow-up after the Week 24 TOC visit.

Does the Division agree:

a. **the dose regimen is supported by available nonclinical and clinical information?**

FDA Response: *The dose regimen for rVVC is acceptable.*

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1 *http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf*

2 *http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S1A/Step4/S1A_Guideline.pdf*

b. the intended population is appropriate?

FDA Response: *From a clinical pharmacology perspective, the intended population including the exclusion criteria for concomitant medication usage appears to be acceptable. From a clinical perspective, it might be important to prespecify a plan for evaluation of subjects based on culture negativity following treatment with fluconazole and before the start of study drug administration in this prevention trial.*

Meeting discussion:

- The Sponsor requested clarification regarding the Division's concern about culture negativity following treatment with fluconazole. The Sponsor explained that patients who present with active VVC receive fluconazole. Patients then return two weeks later to determine if their VVC has resolved.
- The Division stated that patient randomization at the time signs and symptoms have cleared is acceptable but stated subjects should also be culture negative at baseline. The Division stated that there may be concerns if there is an imbalance in the number of culture positive subjects at baseline between treatment groups (particularly if there are more on the placebo arm) as interpretation of the primary endpoint for recurrence based on positive culture will then be difficult. The Sponsor stated that there could be a delay in randomization if they need culture information.
- The Division acknowledged that culture results at baseline may not be known at the time of randomization. Therefore, it is best to define a modified intent-to-treat (MITT) population that requires that subjects are culture positive at screening and culture negative at baseline. The Sponsor stated that this would require a different sample size calculation as they expect 10-20% of subjects to be positive but anticipate that most would likely be due to colonization. The Sponsor asked if it is a strong request from the Division to resize the study. The Division responded that this definition of the MITT population is consistent with advice given to other sponsors and that it will be their risk if they do not take this into consideration.
- In response to the Division's question, the Sponsor confirmed that the two treatment trials will be done concurrently. The acute VVC studies will start by the end of the year and the recurrent VVC trial will start in the first quarter of 2019. The Division commented that if the trials were not run concurrently, the Sponsor might be able to assess if the dose selected was appropriate. The Sponsor acknowledged the comment but stated that other factors affect the timing of the trials. The Sponsor stated that clinicians are comfortable with the 300 mg BID single day dose. The Sponsor noted that adverse events were slightly higher with 3-day dosing than with a 1-day dose.

c. the proposed primary and secondary endpoints and analysis methods will support approval and labeling of the indication?

FDA Response: *The proposed primary and secondary endpoints and analysis methods in your draft protocol appear to be acceptable. We will likely have further comments for you when you submit the final protocol to the IND.*

d. the duration of follow-up is appropriate?

FDA Response: *The duration of follow-up appears appropriate to include a period of observation after completion of 20 weeks of study drug administration.*

Additional Meeting Discussion:

- Regarding Question 5, the Sponsor stated that they will provide the requested information. The Division asked if the Sponsor had collected metabolite data. The Sponsor responded that they did not collect pharmacokinetic (PK) data for metabolites in the Phase 2 study. The Division commented that they usually request clinical pharmacology/PK information on the major metabolite(s) in order to determine if the Sponsor's proposed QT study is adequate to replace a Thorough QT study. The Sponsor acknowledged the comments.
- The Sponsor stated that they are moving forward with development of the oral formulation and asked that the Division send comments regarding their recently submitted Aspergillosis protocol as soon as possible.
- The Sponsor stated that their development programs for rescue therapy for *Candida* and *Candida auris* (*C. auris*) are progressing; however, it is difficult to enroll subjects in the *C. auris* study. The Sponsor is not prospectively opening centers in the United States (U.S.) unless asked as it is difficult to predict cases of *C. auris* in the U.S. The Sponsor is opening centers for the *C. auris* study in India. Enrollment in the salvage therapy program for Candida infection is ongoing in the U.S.
- The Division acknowledged the summary results of the Sponsor's coagulation study in healthy adult volunteers that was included in the background package for the meeting. The Sponsor commented that the coagulation study demonstrated that measuring thrombin-antithrombin complexes (TAT) is not worthwhile as TAT values in healthy volunteers varied greatly even in screening. The Division noted that they will consult the Hematology Division and provide feedback to the Sponsor.
- The Division stated that the Sponsor should request a Chemistry, Manufacturing, and Controls (CMC) meeting soon. The Sponsor responded that they will probably request a CMC meeting in a few months.

ACTION ITEMS

- The Division will issue meeting minutes within 30 days.

ADDITIONAL IMPORTANT APPLICATION INFORMATION [not discussed at the meeting]

PREA REQUIREMENTS

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

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 after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start 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 on or 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.

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 https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

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.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf) and for more information.

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

ATTACHMENT

SPONSOR'S ORIGINAL QUESTIONS AND DIVISION'S PRELIMINARY RESPONSES SENT TO SPONSOR ON SEPTEMBER 14, 2018

8.1 Nonclinical

8.2 Chemistry, Manufacturing and Controls

A separate Chemistry, Manufacturing and Controls meeting will be requested.

8.3 Clinical Pharmacology/Biopharmaceutics

Question 2

SCYNEXIS has performed nonclinical *in vitro* assessment of interactions of ibrexafungerp with CYP enzymes and transporters, and clinical studies with ketoconazole, diltiazem, rosiglitazone, tacrolimus, and pantoprazole. The results of these evaluations are summarized Sections 9.7 and 9.11.14 Drug Interactions. In parallel to Phase 3 studies, SCYNEXIS is developing a physiologically-based pharmacokinetic (PBPK) modelling and plans to evaluate additional *in vivo* DDI studies as guided by the results of the PBPK modelling. As agreed previously with FDA, SCYNEXIS will conduct studies with digoxin or dabigatran, pravastatin and ritonavir.

Does the Division agree that the proposed approach could provide sufficient information to characterize clinically relevant drug interactions for labeling purposes?

FDA Response: *We agree that the proposed approach could provide sufficient information to characterize clinically relevant drug-drug interactions (DDI's). When available, provide the results and/or reports of the PBPK modeling and the rationale for conducting or not conducting additional in vivo DDI studies. Consult the recently updated Guidance for Industry on In Vitro Metabolism and Transporter-Mediated Drug-Drug Interaction Studies; Clinical Drug Interaction Studies Study Design, Data Analysis, and Clinical Implications; and Physiologically Based Pharmacokinetic Analyses – Format and Content:*

https://www.fda.gov/downloads/Drugs/Guidances/UCM581965.pdf, https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf, https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm531207.pdf

Question 3

Administration of the current tablet formulation of ibrexafungerp citrate with a high-fat meal to healthy subjects was associated with an increase in C_{max} by 50% and AUC by 70% (see Section 9.11.3 Pharmacokinetics). The effect of a more typical meal has not yet been determined. A Phase 1 study to evaluate the effect of high fat and a more typical meal with the to-be-marketed tablet is planned before the NDA.

Does the Division agree that a Phase 1 evaluation of the effect of a high fat and a more typical meal on the to-be-marketed tablet would provide appropriate information for labeling purposes?

FDA Response: *We agree with your plan to conduct a Phase 1 evaluation of the effect of a high fat and a more typical meal on the bioavailability of the to-be-marketed tablet. We recommend that you use the highest clinical dose (i.e. 300 mg as 2 x 150 mg tablets) in the food-effect study. Provide the full protocol of the proposed food-effect study, including the full description of the typical and high-fat meals both in terms of total calories and the nutritional breakdown of calories from fat, protein, and carbohydrate. We may have additional comments on your proposed food effect protocol. In addition, please consult the Food-Effect Bioavailability and Fed Bioequivalence Study Guidance for Industry for details on study design and specifically the composition of the FDA high-fat meal to be used in the study:*
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070241.pdf.

Question 4

In the Phase 2b study, SCY-078-204, dosing instruction was for ibrexafungerp to be taken 30 minutes before or 2 hours after food, to minimize variability of the pharmacokinetic results in this study. A previous Phase 2a study in VVC SCY-078-203 was conducted with ibrexafungerp administered with meals. Results of Study SCY-078-102, that compared administration of oral ibrexafungerp citrate tablets (500 mg) with and without meals, suggest a reduction of nausea when the product is administered with a meal. The proposed Phase 3 studies will include the recommendation that the study drug should be preferably administered with a meal, aiming to limit the potential for nausea.

Based on simulations from the current population pharmacokinetic model, the proposed dose of ibrexafungerp of 300 mg given orally twice for one day (2 doses total) is expected to provide a geometric mean AUC_{0-24} of 7.8 uM·hr with a corresponding geometric mean C_{max} of 476 nM. A previous food effect study (SCY-078-102) showed that when ibrexafungerp was administered with a high fat meal, AUC_{0-24} and C_{max} were increased by as much as 70% and 50%, respectively, and as noted above, less nausea. Such potential increases in the exposure from a 300 mg dose given twice would not result in a systemic exposure that would present any safety concern, based on both the existing pre-clinical safety experience, as well as the clinical safety experience where higher doses and exposures have already been explored in humans.

Does the Division agree there is low likelihood of safety concerns in the Phase 3 studies if patients take ibrexafungerp at the time of a typical meal?

FDA Response: *We agree that administering ibrexafungerp at the time of a typical meal would likely not pose a potential safety concern for the phase 3 development program.*

Question 5

SCYNEXIS is consolidating the available data from nonclinical and clinical studies with ECG monitoring and high precision QT analysis (see Section 9.11.2 Pharmacodynamics). No evidence of risk for QT prolongation is identified by this information. Additional ECG monitoring will be conducted for confirmation in future studies, particularly in Phase 1 studies with dosing likely to result in high C_{max}.

Does the Division agree that the information related to risk of QT prolongation is sufficient to support a waiver for conduct of a thorough QT study considering the dosing regimen for the VVC indication?

FDA Response:

The proposed concentration-QT analysis based on data from Part 1 of Study SCY-078-106 appears adequate to characterize the potential for your drug to prolong the QTc and can potentially serve as an alternative to the TQT study. Whether these data exclude a 10-ms mean QTc effect at the highest clinical relevant exposure will be a review issue when the data are submitted.

Additionally, we have the following comments for you to consider:

1) The adequacy of dose/exposure would be a review issue depending on the final choice of highest therapeutic dose and whether the selected doses would cover the highest clinically relevant exposure (worst case scenario exposure due to drug-drug interaction or organ impairment) of drug and any relevant metabolites for the therapeutic dose.

2) If your product is likely to increase or decrease the heart rate significantly (e.g., >10 bpm) in the study, you will need to consider the use of alternative methods for assessing changes in the QT interval, such as QTcI (individualized QT correction). For additional information, please see "Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects" (Garnett, C. et al., Am Heart J 2012;163(3):912-30).

In the absence of significant heart rate effects, we recommend the use of QTcF for the primary analysis.

3) For exposure-response analysis, we recommend the analysis and reporting of results follow the recommendations described in "Scientific white paper on concentration-QTc modeling" (Garnett, C. et al., J Pharmacokinet

Pharmacodyn 2017; doi 10.1007/s10928-017-9558-5) and "Correction to: Scientific white paper on concentration-QTc modeling" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6).

4) When you submit your QT study report, please include the following items:

a. Study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed

b. Study report

c. Statistical analysis plan

d. Clinical study protocol

e. Investigator's Brochure

f. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table

g. Annotated CRF

h. A data definition file which describes the contents of the electronic data sets

i. Electronic data sets as SAS.xpt transport files (in CDISC SDTM and ADAM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Please make sure that the ECG raw data set includes at least the following:
Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable).

j. Data set whose QT/QTc values are the average of the above replicates at each nominal time point

k. Adverse Event analysis using the MedDRA SMQ "Torsade de pointes/QT Prolongation" and include the preferred term "Seizure" by treatment and dose level.

l. Narrative summaries and case report forms for any

i. Deaths

ii. Serious adverse events

iii. Episodes of ventricular tachycardia or fibrillation

iv. Episodes of syncope

v. Episodes of seizure

vi. Adverse events resulting in the subject discontinuing from the study

m. Electronic copies of study reports for patch clamp experiments used to support the assessment of cardiac safety of your product together with the following information for each experiment:

i. Raw and unaltered electrophysiology records (e.g. no baseline subtraction or zero'ing of baseline). The file format for the raw electrophysiology records can be ABF or CSV, and contain at a minimum information about time, voltage and current signals (note specific units for these signals).

ii. An overview file, e.g. in CSV or txt, describing the experimental conditions for each of the raw electrophysiology records. The description should include at a minimum the name of the file, temperature of the recording, when drugs and at what concentrations were added, and other information relevant to interpret the results.

5) We are also interested in the effects of the test substance on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.

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

8.4 Clinical

Question 6

SCYNEXIS plans to conduct two identical Phase 3 randomized clinical trials of ibrexafungerp compared to placebo in women 12 years of age and older with acute VVC. The representative draft protocol is summarized in Section 9.14.1 and included in Appendix 3. The design of these studies is consistent with the July 2016 Draft Guidance. These two studies are proposed to support an NDA for the treatment of VVC.

Does the Division agree:

a. the dose regimen proposed for the Phase 3 studies in VVC is adequately supported by nonclinical and clinical data?

FDA Response: *The dose regimen appears to be acceptable for phase 3 clinical development.*

b. the intended population is appropriate?

FDA Response: *The intended population is acceptable.*

c. the proposed primary and secondary endpoints and analysis methods will support approval and labeling of the indication?

FDA Response: *The proposed primary and secondary endpoints and analysis methods in your draft protocol appear to be in alignment with our draft guidance document, Vulvovaginal Candidiasis: Developing Drugs for Treatment. We will likely have further comments for you when you submit the final protocols to the IND.*

Question 7

SCYNEXIS estimates that the safety database at the time of the NDA for acute VVC will include ~1200 total exposures to ibrexafungerp, including ~380 healthy subjects, ~220 women with VVC in Phase 2 studies and ~480 in Phase 3, and ~100 women in an ongoing study of rVVC. In addition, approximately 60 patients will be exposed to ongoing studies of invasive fungal infections at the anticipated time of submission of the acute VVC NDA.

Does the Division agree that the safety database at the time of NDA submission will be sufficient to support the safety of ibrexafungerp in the treatment of VVC?

FDA Response: *Note that several of our guidance documents for treatment of indication-specific infectious diseases provide 700 subjects as being a sufficient sample size for a pre-approval safety database. Although our draft guidance for vulvovaginal candidiasis does not provide a specific number, your proposal for an overall size of the safety database appears to be acceptable, provided that no specific concerns are observed in the phase 3 safety database. If a safety signal is observed, a larger pre-approval safety database might be necessary.*

Question 9

SCYNEXIS estimates that the safety database at the time of the Supplemental NDA for recurrent VVC will include ~1400 total exposures to ibrexafungerp, including ~460 healthy subjects, ~220 women with VVC in Phase 2 studies and ~480 in Phase 3 acute VVC, and ~100 women in recurrent VVC. In addition, approximately 140 patients will be exposed to ongoing studies of invasive fungal infections. Considering the 20-hour half-life of ibrexafungerp, the dosing regimen of 300 mg BID for one day administered every 4 weeks represents a cyclic administration schedule of the same dose regimen used in the acute VVC trials. Therefore, the augmentation of the safety data in the acute VVC NDA with the results of recurrent VVC trial is expected to provide sufficient information on the safety of ibrexafungerp in recurrent VVC.

Does the Division agree that the safety database at the time of the Supplemental NDA submission will be sufficient to support the safety of ibrexafungerp in the prevention of recurrent VVC?

FDA Response: *Your proposal for an overall size of the safety database appears to be acceptable provided that no safety signals are observed in the phase 3 safety database. If safety signals are observed, a larger pre-approval safety database might be necessary.*

8.5 Pediatric Study Plan

SCYNEXIS intends to submit an initial Pediatric Study Plan (iPSP) within 60 days of the date of this meeting. The iPSP will include the rationale for including adolescent girls, 12 years of age and older, in the pivotal studies of VVC and a partial waiver request for girls 11 years of age and younger.

Question 10

The population PK model, summarized in Section 9.8.3 Pediatrics, supports a conclusion that adolescent girls 12 years of age and older will have similar exposure and exposure-response relationship as the adults evaluated in Phase 1 and in Phase 2 VVC trials. It is reasonable to conclude that VVC in adolescent girls will respond to ibrexafungerp in the same manner as adults.

Does the Division agree that adolescent girls 12 years of age and older can be included in the Phase 3 VVC and rVVC clinical trials?

FDA Response: *As noted in our draft guidance document, if appropriate you should include adolescent girls in your phase 3 clinical development program. All of the nonclinical final study reports, including the fertility and embryofetal development study reports, should be submitted for review before we can determine if it is safe to enroll the adolescent population.*

Please submit an initial pediatric study plan (iPSP) to your IND within 60 days following the end of phase 2 meeting. The iPSP should outline your plans for pediatric evaluation.

Question 11

Based on the epidemiology of VVC, it is unlikely that ibrexafungerp would be used in a substantial number of girls 11 years of age and younger for the treatment of VVC (see Section 9.8.3 Pediatrics).

Does the Division agree that a partial waiver under PREA is appropriate for girls ages 11 and under for the indication of VVC?

FDA Response: *In the iPSP, include your rationale to request a partial waiver for girls 11 years of age and younger.*

8.6 Regulatory

Question 12

The Division has granted Qualified Infectious Disease Product (QIDP) designation to ibrexafungerp for the treatment of vulvovaginal candidiasis (VVC) and prevention of recurrent vulvovaginal candidiasis (rVVC). SCYNEXIS would like to understand the implications and process for granting of GAIN exclusivity extension upon approval of an initial NDA for VVC with a subsequent efficacy supplement for rVVC.

Does the Division agree that GAIN Exclusivity Extension would be applied to approval of the treatment of VVC for a total of 10 years (New Molecular Entity Exclusivity plus GAIN Exclusivity)?

FDA Response: *In general, a new molecular entity is eligible for 5-years of exclusivity and a drug that has been designated as a QIDP is eligible for a 5-year extension of exclusivity, provided the indication approved is one for which QIDP has been designated. However, we are unable to comment on whether this application will receive 10 years of exclusivity as exclusivity is determined at the time of application approval.*

Additional Important Information:

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf
https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

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

/s/

SUMATHI NAMBIAR
10/19/2018