CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214429Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 110365

MEETING MINUTES

Sanofi US Services, Inc.
A SANOFI COMPANY
Attention: Michael Macalush, MS
Director, North America and Global Regulatory Affairs
50 Binney Street
Cambridge, MA 02142

Dear Mr. Macalush:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Fexinidazole Winthrop (HOE239) Tablets, 600 mg.

We also refer to the meeting between representatives of your firm and the FDA on September 20, 2019. The purpose of the Pre-NDA meeting was to reach agreement on the plans for a new drug application including the study pooling strategy and the format of the clinical datasets.

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

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 20, 2019, 9:00 AM – 10:00 AM
Meeting Location:	10903 New Hampshire Avenue, Silver Spring, MD 20903 Building 22, Room 1311
Application Number:	PIND 110365
Product Name:	Fexinidazole (b) (4) (HOE239) Tablets, 600 mg
Indication:	Treatment of first-stage (haemo-lymphatic) and second-stage (meningo-encephalitic) human African trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense* in adults and children ≥ 6 years old and weighing ≥ 20 kg
Sponsor Name:	Sanofi US Services, Inc.
Meeting Chair:	Sumathi Nambiar, MD, MPH
Meeting Recorder:	Alison Rodgers

FDA ATTENDEES

Division of Anti-Infective Products

Abimbola Adebowale, PhD, Associate Director for Labeling
Shukal Bala, PhD, Clinical Microbiology Reviewer
Philip Colangelo, PharmD, PhD, Clinical Pharmacology Team Leader
Maureen Dillon-Parker, MS, Chief, Regulatory Project Management Staff
Avery Goodwin, PhD, Clinical Microbiology Team Leader
Karen Higgins, ScD, Statistics Team Leader
Dmitri Iarikov, MD, PhD, Deputy Director
Abhay Joshi, PhD, Clinical Pharmacology Reviewer
Dorota Matecka, PhD, Product Quality Team Leader
Terry Miller, PhD, Nonclinical Team Leader
Owen McMaster, PhD, Nonclinical Reviewer
Shrimant Mishra, MD, MPH, Medical Officer
Sumathi Nambiar, MD, MPH, Director
Alison Rodgers, Regulatory Project Manager
Edward Weinstein, MD, PhD, Clinical Team Leader

SPONSOR ATTENDEES

Sanofi US Services, Inc.

Michael Macalush, MS, Director, North America and Global Regulatory Affairs
Don Gieseker, PharmD, US Regulatory Head, Primary Care
Catherine Castin-Vuillerme, PharmD, Global Regulatory Lead, Global Regulatory Affairs

*Guillermo Doll, MD, Neglected Tropical Diseases Program Head, Global Health Programs
*Alexia Letierce, PhD, Biostatistician Project Leader
*Eric Sultan, PharmD, Head of PK Group, Pharmacokinetics Dynamics and Metabolism
*Terence Appelqvist, PhD, Preclinical and Clinical Pharmacokinetics
*Elhadj Djeriou, MD, Global Safety Officer, Global Pharmacovigilance
*Christine Hamelin, MD, Therapeutic Area Team Leader, Global Pharmacovigilance
*Valérie Lameyre, MD, Neglected Tropical Diseases Medical Leader, Global Health Medical
*Michel Doubovetzky, DVM, DABT, Head of Nonclinical Safety
*Heinz Hänel, PhD, Preclinical Expert, Parasitologist, Global Development
*Philippe Neau, Head Project Management, Global Health Programs
*Alan Divanovic, Head Global Health Medical
*Anne Grandjacquot, Head of Regulatory Affairs Global Health and Portfolio
*Céline Beauchard, Neglected Tropical Diseases Project Leader, Global Health Programs

Drugs for Neglected Diseases Initiative (DND*i*)
Nathalie Strub-Wourgaft, MD, Medical Director
Bruno Scherrer, PhD, MBA, Statistician, Consultant to DND*i*
*Antoine Tarral, MD, Head of the HAT Clinical Program, DND*i*

**via teleconference*

BACKGROUND

On July 8, 2019, the Sponsor submitted a request for a Pre-NDA meeting. A briefing package was submitted on August 20, 2019.

The Division sent Preliminary Comments to the Sponsor on September 16, 2019. On September 19, 2019, the Sponsor communicated that they plan to discuss the Division's responses to Questions 2, 3, 4, 5, and 6, and the Microbiology comments during the meeting. Question 3 was however not discussed at the meeting.

The Sponsor's original questions and the Division's preliminary responses to Questions 2, 4, 5, and 6, and the Division's Microbiology comments are provided below followed by meeting discussion points. The remaining questions and the Division's responses are appended.

DISCUSSION

Question 2

Does the Agency agree (b) (4)

FDA Response: [redacted] we do not agree with [redacted] The primary analysis will consist of evaluation of the results of the studies individually, particularly the DNDiFEX004 study.

Meeting discussion:

- The Sponsor [redacted] The Division responded that the Sponsor should use only study DNDiFEX004 for comparative safety analysis as it is the only trial with a comparator arm. The Sponsor agreed and stated that pooled data from Studies 004, 005, and 006 would be used for exploratory analyses of infrequent adverse events. The Sponsor stated they will include the datasets in Module 5.3 of the eCTD.

- Regarding efficacy analysis, the Sponsor stated that the populations in Studies 005 and 006 are different so it was unclear why these studies should be pooled. The Division agreed that it would not be necessary to pool Studies 005 and 006, and that the studies should be submitted individually. The Division clarified that the efficacy assessment should be based on a comparative analysis, so Study 004 should not be pooled with Studies 005 and 006. The Division explained that for efficacy they will primarily review Study 004; Studies 005 and 006 will be supportive.

- Regarding historical controls, the Division requested that the Sponsor include in the NDA, a summary of the natural history of the disease; specifically, outcomes if patients had not received appropriate therapy. This will provide a basis to interpret Studies 005 and 006. The Sponsor agreed but stated that there might be some limitations to the data. The Division acknowledged the comment.

Question 4

The Sponsor proposes to include case report forms (CRFs) and patient narratives for deaths, SAEs, and AEs leading to study discontinuation for the studies listed in the background information of the briefing book. Does the Agency agree with the Sponsor's proposal?

FDA Response: We request that you submit a 10% sample of the CRFs from the Phase 3 trial DNDiFEX 004 with the NDA. When available, please submit datasets in SAS transport (.xpt) format containing the patient IDs and treatment codes that contains one row per patient for Trial DNDiFEX 004. We will then generate a 10% random sample and send the listing to you. You may submit these datasets whenever they are available, but with enough time so the requested CRFs can be submitted with the initial

NDA submission. Additionally, we recommend you submit the CRFs of all subjects who fled an area of armed conflict.

Meeting discussion

- The Sponsor asked how soon after they submit the datasets from study DNDiFEX 004 the Division would provide the 10% random sample. The Division responded that they would provide it within a few weeks, or sooner.

Question 5

Does the Agency agree with the selected studies, content and format of the electronic datasets to be provided in the NDA?

FDA Response: We agree. We note that analysis datasets for Studies 004, 005 and 006 are in legacy format. We recommend ADaM datasets be submitted for these three studies as well.

Meeting discussion:

- The Sponsor inquired if ADaM datasets are required. The Division responded that ADaM datasets are not required but are useful. The Division explained that the data must be in a format they can analyze. The Sponsor asked, and the Division agreed, that it would be helpful to submit sample datasets in advance of the NDA submission.

Question 6

Does the Agency agree that (b) (4)

FDA Response: No, we do not agree (b) (4) Considering this, we have the following recommendations:

1. Conduct a separate dedicated clinical DDI study to evaluate the effects of a strong CYP inducer (i.e., rifampin) on the pharmacokinetics and systemic exposure to fexinidazole and its M1 and M2 metabolites.

2. Conduct separate dedicated in vivo DDI study(ies) to evaluate the potential of fexinidazole and the M1 and M2 metabolites to inhibit CYP2D6 and CYP3A4. For examples of sensitive CYP2D6 and CYP3A4 index substrates, please refer to the FDA Drug Interaction Guidance.

3. Provide additional information to support your conclusion: (b) (4)

(b) (4) [redacted] The findings reported in a literature publication indicates that in vitro inhibition of multiple CYP enzymes could be of in vivo clinical relevance[1].

Isoherranen N, Lutz JD, Chung SP, Hachad H, Levy RH, Ragueneau-Majlessi I. Importance of multi-p450 inhibition in drug-drug interactions: evaluation of incidence, inhibition magnitude, and prediction from in vitro data. Chem Res Toxicol. 2012 Nov 19;25(11):2285-300.

Meeting discussion:

- The Sponsor stated that based on the Division's recommendation at a previous meeting, additional DDI studies have been conducted. The Sponsor also stated that they have compiled a list of potential concomitant medications that a patient with human African trypanosomiasis (HAT) might receive. The Sponsor suggested that based on available information, (b) (4) [redacted]

- The Division responded that they do not agree with the Sponsor's conclusion that (b) (4) [redacted] The Division commented that they were not able to locate the findings related to the time-dependent inhibition of CYP enzymes. The Sponsor responded that the completed in vitro studies included the assessment of time dependent inhibition of CYP enzymes.

- The Division acknowledged the comments and requested that the Sponsor provide details regarding the mechanistic modeling approach that was used. The Division recommended that the Sponsor evaluate the DDI potential using the mechanistic modeling approach listed in the FDA Drug Interaction Guidance Document. The Sponsor responded that their approach is similar to the approach in the guidance document and agreed to conduct additional analysis if notable differences are identified between these two approaches.

- The Division asked the Sponsor to submit this information prior to NDA submission to allow time for review and to determine if any additional in vivo DDI studies will be needed. The Division commented that avoiding the need for post-marketing DDI study(ies) is preferred.

- The Sponsor asked what data the Division would like the Sponsor to submit prior to NDA submission in addition to the time dependent information. The Division responded that they want to see detailed findings from in vitro and in vivo studies as well as the mechanistic modeling approach that relied on commercial software (PharmaPendium®). The Division also requested a list of potential concomitant medications that HAT patients may be taking with fexinidazole.

- The Division requested that the Sponsor provide all information and/or data that supports their position and commented that their recommendation to conduct further DDI studies stems from the fact that multiple CYP450 enzymes are involved in the metabolism of fexinidazole and its two metabolites and it is not clear how the potential for in vivo DDI's would be adequately characterized using a mechanistic modeling approach. Therefore, the need for DDI studies to determine the effect of a CYP inhibitor and a CYP inducer (e.g., rifampin) on the PK of fexinidazole and its metabolites, and vice-versa should be evaluated.

- The Sponsor stated that they understood the Division's request. The Division noted that they will need four to six weeks to review a submission. The Sponsor asked if it would be a filing issue if after reviewing the submission the Division still does not agree with the Sponsor's position. The Division responded that it would not necessarily be a filing issue.

- The Division also recommended that the Sponsor conduct a radiolabeled ADME study for oral fexinidazole which would inform whether or not renal and/or hepatic impairment PK studies would be needed. The Division stated that while concomitant medications may not be an issue, potential dosage adjustment in patients with renal or hepatic impairment may be needed. The Sponsor acknowledged the comments.

Additional comments:

Clinical Microbiology

Details of the parasitological methods used at baseline and follow-up visits should be included in the NDA. Some of the details that are of special interest are as follows:

- The method(s) to be used including the volume of blood and other body fluids examined for parasites.
- The quality control for parasitological examination and training of the microbiologists/microscopists.
- The number of microbiologists that perform slide reading and the results of each one of the readers.
- Video recordings.

Meeting discussion:

The Sponsor stated that two to three laboratory technicians viewed each sample, but that there are no slides available for the Division to review. The Division stated that the slides are not needed; however, individual microbiologist's readings would be of interest. The Sponsor responded that they will be included this in the NDA. The Sponsor also noted that the microscopists were not blinded.

The Sponsor stated that they have some video recordings, but these were started after the interim analysis. The Sponsor agreed to provide the video recordings in the NDA.

The Division requested that the nonclinical microbiology studies, if available, be submitted to the IND. The Sponsor agreed to provide these studies.

Additional meeting comments:

- The Sponsor inquired about plans for site inspections. The Division asked what materials would be available for inspection at DND*i* and at the sites. The Sponsor responded that DND*i* has the Drug Master File (DMF) and monitoring reports. The Division asked if the largest sites are in a stable area of the Democratic Republic of Congo (DRC). The Sponsor responded that the sites are in stable areas and could be inspected. The Sponsor asked if they could receive advance notice of inspections as they need to provide logistical support to the site. The Division responded that they will need to check with the Office of Scientific Investigations (OSI).

- The Division inquired as to the most common comorbidities seen in patients treated with fexinidazole. The Sponsor reported that there were no significant comorbidities other than malnutrition.

- The Division acknowledged that having an oral treatment option may provide benefit for the developing world but asked how the Sponsor plans to position fexinidazole for the U.S. population given that fexinidazole appears to be inferior to the standard-of-care.

- The Division inquired about the excess mortality observed in the fexinidazole treatment group in Study 004. The Sponsor responded that the difference in mortality was not significant and will be discussed in the NDA.

- The Division asked that the Sponsor provide, in the NDA, information regarding the psychological side effects and reasons for discontinuation of fexinidazole related to these side effects. The Sponsor agreed.

- The Division asked the Sponsor to include the label approved by the European Medicines Agency (EMA) in the NDA. The Sponsor agreed. The Division inquired as to the approved indication. The Sponsor responded that the approved indication is for the treatment of both first-stage (haemo-lymphatic) and second-stage (meningo-encephalitic) human African trympanosomiasis (HAT) due to

Trypanosoma brucei gambiense in adults and children ≥ 6 years old and weighing ≥ 20 kg.

- The Sponsor stated that they plan to submit the NDA in February or March 2020.

ISSUE REQUIRING FURTHER DISCUSSION

- Discussion of DDI in vivo studies may be needed.

ACTION ITEMS

- The Sponsor will submit the data format they plan to use prior to NDA submission with sample data.
- The Sponsor will submit datasets from the Phase 3 trial DNDiFEX 004. The Division will provide a 10% random sample after receiving the submission.
- The Sponsor will prepare an analysis of the natural history of HAT and submit the summary in the NDA.
- The Sponsor will submit comprehensive results from completed in vitro and in vivo studies as well as detailed information on their DDI analyses to support their position that no additional DDI studies are needed.
- The Sponsor will provide all available study reports for pharmacology/toxicology studies as well as microbiology studies prior to the NDA submission. The study reports can be submitted to the Pre-IND.
- The Division will issue meeting minutes within 30 days.

-END

Post-Meeting Note: This application is for a New Molecular Entity and per the requirements of PDUFA VI, this note documents that there are no agreed to late component submissions for the NDA. We do, however, note that a chemistry pre-submission meeting is scheduled for October 3, 2019. A summary of any agreements reached at that meeting (as applicable) will be documented in the respective meeting minutes.

OTHER IMPORTANT APPLICATION INFORMATION [NOT DISCUSSED AT THE MEETING

PREA REQUIREMENTS

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

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

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] 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

[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

ATTACHMENT

SPONSOR'S ORIGINAL QUESTIONS AND DIVISION'S PRELIMINARY RESPONSES SENT TO SPONSOR ON SEPTEMBER 16, 2019

A. CLINICAL

1. Question 1

Based on the safety and efficacy data available for fexinidazole, does the Agency concur that the studies (DNDiFEX004, DNDiFEX005, and DNDiFEX006) will be sufficient to support submission of an NDA for the proposed indication?

FDA Response: Based on the information provided in your briefing package, the proposed studies appear adequate to support an NDA submission. We note an imbalance in deaths in DNDiFEX004, 9/264 (3.4%) vs 2/130 (1.5%). This will be assessed in further detail during review of the NDA.

2. Question 3

To support the ISS and ISE requirement for an NDA:

- Sanofi is planning to present the summary text along with key tables and figures in Module 2.7.3 Clinical Summary of Efficacy (CSE) and Module 2.7.4 Clinical Summary of Safety (CSS) respectively and provide in Module 5.3.5.3 SAP, individual reports, tables/figures, datasets and appendices. Does the Agency agree with the Sponsor's proposal for the location of these sections in the initial NDA submission?
- Does the Agency agree with Sanofi's proposal for the studies to be covered in Module 2.7.3 and Module 2.7.4?

FDA Response: Provide individual study reports, datasets, protocols with amendments, and case report forms in Module 5.3.5.3. Provide summary primary analyses as well as exploratory pooled analyses in Modules 2.7.3 and 2.7.4.

3. Question 7

Does the Agency agree with the proposed studies to be included in the 120-Day Safety Update Report?

FDA Response: We agree.

B. REGULATORY/ADMINISTRATIVE

1. Question 8

Does the Agency agree with the proposed eTOC for the NDA?

FDA Response: We agree.

2. Question 9

Sanofi believes the 3 studies (pivotal and 2 plug-in studies for the proposed indication) meet the definition of being a covered study for the purposes of providing financial disclosure information in the NDA and summary level clinical site data to meet the BIMO requirements. Does the Agency agree? In addition, Sanofi plans to provide financial disclosure in the NDA for DNDi-CH-FEX-001 (Chagas) and FEXI VL 001 (Visceral Leishmaniasis) studies. Does the Agency agree?

FDA Response: Yes, we agree. 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 NDA (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in the submission in the format described, you can describe the 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.[4]

Additional comments:
Regulatory

We agree with your proposal to include a request for a tropical disease priority review voucher (PRV) in section 1.4.2. Please also identify in your cover letter that a request for a tropical disease PRV is included in the NDA. For your information, we remind you below of the eligibility criteria for a tropical disease PRV, including changes to the

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

criteria made with the enactment of the Food and Drug Administration Reauthorization Act of 2017 (FDARA).

For the tropical disease PRV program, under section 524 of the FD&C Act, a human drug application is eligible for a priority review voucher (PRV) if it:

(1) is intended for the prevention or treatment of a tropical disease, as defined in Section 524(a)(3),

(2) is deemed eligible by FDA for priority review,

(3) is approved by FDA for use in the prevention or treatment of a tropical disease,

(4) contains no active ingredient (including any salt or ester of the ingredient) that has been previously approved by FDA in an application pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act of section 351 of the Public Health Service Act,

(5) contains reports of one or more new clinical investigations (other than bioavailability studies) that are essential to the approval of the application and conducted or sponsored by the sponsor, and

(6) contains an attestation from the sponsor that such report(s) were not submitted as part of an application for marketing approval or licensure by a regulatory authority in India, Brazil, Thailand, or any country that is a member of the Pharmaceutical Inspection Convention or the Pharmaceutical Inspection Cooperation Scheme prior to September 27, 2007.

For further information about eligibility for the tropical disease PRV program, please see section 524 of the FD&C Act and the tropical disease PRV guidance.

Statistics:

- Please note that it will be important that you provide a justification for your noninferiority margin in your NDA submission. This justification should rely on an estimate of the treatment effect of the active control over placebo or inadequate treatment on the endpoint used in the clinical trial. The margin should be less than a conservative estimate of this treatment effect (i.e., the lower bound of the 95% CI of the difference). Additionally, you should discuss the clinical relevance of the noninferiority margin chosen.
- We do have some concerns regarding changes made to the sample size in this unblinded trial (DNDiFEX004). In the NDA submission, you should clearly outline exactly what methods were put in place to ensure that you remained completely

blinded to all ongoing study results summarized by treatment arms (including masked treatment arms, such as “arm a” and “arm b”). Additionally, please clearly state who had access to any information from the futility and interim analyses.

Nonclinical Pharmacology/Toxicology

- Please submit final study reports for the Pharmacology, Toxicology and Pharmacokinetics studies to the IND as soon as possible to allow additional time to review the large number of nonclinical studies. Standard pdf files are acceptable for submissions to the IND.
- For the NDA submission, nonclinical studies initiated after December 17, 2016, must be submitted in the data formats supported by FDA and listed in the FDA Data Standards Catalog.
- Please ensure that any relevant impurities are qualified or controlled according to ICH guidelines.
- Please include the levels of the genotoxic impurity, (b) (4) , and any other known impurities in the drug substance lots used for GLP toxicity studies and clinical trials.
- Please provide complete reports (not summaries) of any relevant QSAR evaluations to be submitted with the IND/NDA.

Clinical Pharmacology

Regarding the effect of hepatic impairment on fexinidazole PK, we note that you do not plan to conduct a dedicated hepatic impairment PK study using the Child-Pugh classification. However, you plan to rely on a population PK analyses which shows that liver test parameters tested, i.e., AST, ALT, ALP, total bilirubin, albumin, total protein, were not significant covariates. Provide additional information on the ranges of the following parameters tested: AST, ALT, ALP, total bilirubin, albumin, total protein in the patients/subjects used for the population PK analyses. In the absence of adequate information and/or data for impaired liver function parameters in your Pop PK analyses, you may need to conduct a dedicated hepatic impairment PK study since fexinidazole appears to be primarily eliminated from plasma via hepatic metabolism. Thus, it is critically important to know the effects of hepatic impairment on the PK exposure of fexinidazole and the M1 and M2 metabolites so that dosage adjustments may be made in such patients, if warranted by the results of the hepatic impairment PK study.

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
10/11/2019 04:30:22 PM